Depression and antidepressants in Australia and beyond
A critical public health analysis

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Certification

I, Melissa Raven, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Faculty of Arts, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

Melissa Raven

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List of acronyms

ABPI	Association of the British Pharmaceutical Industry	
ABS	Australian Bureau of Statistics	
ACCC	Australian Competition and Consumer Commission	
ADE	adverse drug event	
ADR	adverse drug reaction	
ADRAC	Adverse Drug Reactions Advisory Committee	
AHCPR	Agency for Health Care Policy and Research	
AIHW	Australian Institute of Health and Welfare	
AMA	American Medical Association Australian Medical Association	
ANZJP	Australian and New Zealand Journal of Psychiatry	
APA	American Psychiatric Association	
ASM	Australian Statistics on Medicines	
ATC	Anatomical Therapeutic Chemical	
BOIMHC	Better Outcomes in Mental Health Care	
CDHAC	Commonwealth Department of Health and Aged Care	
CDHFS	Commonwealth Department of Health and Family Services	
CPG	clinical practice guideline	
D/ART	Depression Awareness, Recognition, and Treatment (Program)	
DAJ	*Depression Awareness Journal*	
DDC	Defeat Depression Campaign	
DDD	defined daily dose	
DoHA	Department of Health and Ageing	
DSM	Diagnostic and statistical manual (of mental disorders)	
DSM-III	Diagnostic and statistical manual of mental disorders (3rd edition)	
DSM-IV	Diagnostic and statistical manual of mental disorders (4th edition)	
DTCA	direct-to-consumer advertising	
FDA	Food and Drug Administration	
GP	general practitioner	
HDRS	Hamilton Depression Rating Scale	
HRT	hormone replacement therapy	
ICD	International Classification of Diseases	

KOL	key opinion leader	
MAOI	monoamine oxidase inhibitor	
MHFA	Mental Health Foundation of Australia	
NAMI	National Alliance for the Mentally Ill	
NARSAD	National Alliance for Research on Schizophrenia and Depression	
NCS-R	National Comorbidity Survey – Replication	
NDAC	National Depression Awareness Campaign	
NDMDA	National Depressive and Manic-Depressive Association	
NICE	National Institute for Health and Clinical Excellence	
NIMH	National Institute of Mental Health	
NMHA	National Mental Health Association	
NPECCD	National Public Education Campaign on Clinical Depression	
NSMHW	National Survey of Mental Health and Wellbeing	
PBS	Pharmaceutical Benefits Scheme	
PhRMA	Pharmaceutical Research and Manufacturers of America	
PIHP	Partnerships in Health Promotion	
RACGP	Royal Australian College of General Practitioners	
RANZCP	Royal Australian and New Zealand College of Psychiatrists	
RCGP	Royal College of General Practitioners	
RCP	Royal College of Physicians	
RCPsych	Royal College of Psychiatrists	
ROI	return on investment	
RPBS	Repatriation Pharmaceutical Benefits Scheme	
SNRI	serotonin and noradrenalin reuptake inhibitor	
SSRI	selective serotonin reuptake inhibitor	
TCA	tricyclic antidepressant	
TGA	Therapeutic Goods Administration	
TMAP	Texas Medication Algorithm Project	
WHO	World Health Organization	
WPA	World Psychiatric Association	

Abstract

In Australia and most developed countries, depression has vaulted from an obscure affliction to a high-profile modern epidemic, accompanied by a significant escalation in antidepressant prescribing. A strong orthodoxy has developed that depression is common, serious, and treatable, and that the appropriate treatment is antidepressants. However, there are public health and social grounds for questioning this orthodox story. Vastly more people are being diagnosed with depression, and treated with antidepressants, now than several decades ago. Yet diagnosis of depression is subjective, and is based on highly criticised criteria. Furthermore, the evidence that underpins the orthodoxy is weak and biased, and this is compounded by biased interpretation and selective reporting, particularly in relation to clinical trials of antidepressants.

Two analytical approaches are used in this thesis. The first is critical analysis of the objective validity of specific claims and assumptions about depression and antidepressants, using a mixture of epidemiological analysis and critical appraisal skills from the evidence-based medicine field. The second approach is a broad analysis of strategies used by advocates of the orthodoxy. This includes an analysis of how claims about depression and antidepressants and related issues such as suicide are deployed in the depression arena, focusing on *what claims have been made, by which players, in which contexts, for which reasons, and with what impact*. Also analysed are pharmaceutical industry marketing strategies, and strategies used by other players such as psychiatrists and consumer organisations, all of which often utilise claims about depression and so on.

The orthodox story has been promoted by many players, including psychiatrists, pharmaceutical companies, marketing companies, health professional organisations, consumer organisations, governments and government agencies, and the media. These players interact in complex ways, based on overlapping and synergistic agendas.

Key players have strongly promoted the orthodox story, despite contrary evidence, systematically exaggerating the prevalence and severity of depression and the effectiveness and safety of antidepressants for both depression and suicide prevention. Pharmaceutical companies have played a key role in the establishment and maintenance of the orthodoxy, skilfully recruiting other players to their cause.

A detailed case-study analyses how key players, including prominent psychiatrists and consumer advocacy organisations and pharmaceutical companies, have succeeded in making depression a central focus of Australian mental health policy, fuelling the boom in antidepressant prescribing. Not only have antidepressants been remarkably successfully and profitably sold in Australia, but also depression has been reified and marketed as an all-purpose explanation for distress. As well as exposing many thousands of people to adverse effects of antidepressants, this has deflected attention from social determinants of well-being.

Publications in support of thesis

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[1] I am a member of the Healthy Skepticism *AdWatch* group and I was co-author of the two issues of *AdWatch* listed.

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Chapter 1
Introduction

1.1 INTRODUCTION

This thesis is a qualitative and quantitative critical analysis of the Australian depression and antidepressant arena. It examines depression, and its treatment – primarily via the prescription of antidepressants – in a much broader context and with a much more in-depth analysis than is usually the case. In the process, it illuminates how something as seemingly simple as a medical diagnosis can be profoundly influenced by social and commercial forces, and how a supposedly straightforward and effective treatment is based on questionable evidence and even more questionable marketing strategies.

In recent decades, in Australia and many other countries, depression has vaulted from being an obscure psychiatric diagnosis to a serious social issue, an epidemic, a blight (particularly on young people), the malady du jour, a common cop-out, and/or an over-used cliché, depending on one's perspective. Depression is the main condition for which antidepressants are prescribed, and it is diagnosed far more frequently now than throughout most of the twentieth century. Antidepressants dominate depression treatment (Norman 2006; Eccles et al. 1999), and their prescription and use has escalated commensurately with increases in depression diagnosis. In Australia, antidepressant utilisation nearly trebled between 1990 and 1998 (McManus et al. 2000), and has continued to increase (Department of Health and Ageing [DoHA] 2005, 2008). These developments have profound social and public health implications.

There are many players in relation to depression and antidepressants. They include: psychiatrists, general practitioners (GPs), medical researchers/academics, pharmaceutical companies, psychologists, other health professionals, hospitals and other health services, governments, journal editors, ghost writers, health insurance companies, health economists, consumer groups and community mental health organisations, individual consumers (both antidepressant users and patients more generally), parents, consumer

advocates, Scientology members, journalists, lawyers, and tax payers and insurance payers.

This thesis critically analyses the reasons for, the players in, and the discourses and empirical evidence deployed in the increasing prominence of depression and the escalating use of antidepressants. It also analyses the influence of interest groups on both the terms of the debates and the evidence available. I argue that key players – including pharmaceutical companies that manufacture and market antidepressants, and psychiatrists and consumer/community mental health organisations – have successfully developed and promoted a strong orthodox story about depression and antidepressants: that depression is a common and serious disease or illness[1] that requires treatment in the form of prescribed antidepressant drugs. This orthodox story is supported by a large body of clinical and epidemiological evidence, but much of that evidence is problematic. In particular, prevalence estimates of depression are inflated by flawed and biased survey instruments and methodologies, clinical assessment of individuals utilises problematic diagnostic criteria, and very powerful biases favour biological explanations and pharmacological solutions for depression.

Furthermore, I argue that this orthodoxy constitutes a network of interconnected belief systems supported by citation misrepresentation, and that espousal of these belief systems is beneficial to many players. In the case of pharmaceutical companies, there are very substantial financial benefits in promoting these belief systems in advertisements, continuing medical education, and other forums. For doctors, there are often direct financial benefits in the form of pharmaceutical company payments; however, there are also less tangible but often more important benefits in terms of publication and professional status and career advancement.

Distress is very common in contemporary society, as it probably has been in all human societies. What is significant is that depression and antidepressants have been very

[1] The terms disease and illness are used interchangeably in this thesis, as they are in many of the publications and other sources discussed. Although there are valid arguments for distinguishing between the two terms, with 'disease' denoting pathology and 'illness' denoting the experience of unhealth (Boyd 2000, pp. 9-10), that distinction is not important for the analysis in this thesis.

Common acronyms in this chapter: AIHW Australian Institute of Health and Welfare; APA American Psychiatric Association; BOIMHC Better Outcomes in Mental Health Care; CDHAC Commonwealth Department of Health and Aged Care; DoHA Department of Health and Ageing; DSM Diagnostic and statistical manual of mental disorders; PBS Pharmaceutical Benefits Scheme; RANZCP Royal Australian and New Zealand College of Psychiatrists; RPBS Repatriation Pharmaceutical Benefits Scheme; SSRI selective serotonin reuptake inhibitor

successfully sold as *the* problem and *the* solution respectively. Depression has been constructed in Australia and other developed countries as *the* explanation for distress, and antidepressants have been positioned as *the* treatment for depression.

Unquestionably, significant levels of distress constitute a social problem that requires attention. However, depression is only one possible interpretation; in other historical periods and in other cultures, other constructions have developed and have been socially useful. Yet depression has come to overwhelmingly dominate contemporary discourses about distress and unhappiness and dissatisfaction with life. Furthermore, the orthodox story about depression and antidepressants overshadows and overpowers alternative stories. This has greatly restricted investigation of alternative explanations and development and resourcing not only of alternative treatments, but also of alternative approaches to prevention and intervention. This thesis focuses primarily on the orthodox story, but it does briefly consider alternative stories and approaches where relevant, and it ends by recommending research, advocacy, social action, and policy reform that could facilitate more constructive ways of conceptualising and addressing distress.

Throughout this thesis, there is a major focus on depression and antidepressants in Australia. However, the Australian depression/antidepressant arena is also analysed in its global context, because there are many significant players and factors internationally, particularly in the US and the UK. In addition, there is a strong historical perspective, which helps to bring the orthodox story into question.

This thesis is multidisciplinary, drawing on (and frequently critiquing) the literature and methods of many disciplines, including psychiatry, psychology, epidemiology (particularly psychiatric epidemiology and pharmacoepidemiology), health economics (particularly pharmacoeconomics), evidence-based medicine/healthcare, sociology, and history. There are some brief comments about most of these disciplines in section 1.2 below. All of these disciplines are utilised to at least some extent by public health practitioners and academics, and at times I use 'public health perspective' as an umbrella term for the multidisciplinary perspective used in this thesis.

A public health perspective is much broader than a traditional biomedical perspective (discussed below). In particular, there is recognition of the influence of structural issues –

social, economic, and political factors – on health. Consequently, a public health perspective on depression and antidepressants would not only consider medical theories of depression, diagnostic issues, treatment strategies, prescribing patterns, antidepressant mechanisms, and so on, but would also consider social determinants of depression, social and economic influences on diagnosis, economic and political factors that influence the prescribing of antidepressants, social attitudes towards depression and the use of antidepressants, and so on.

However, of necessity, the discussion of sociocultural issues is limited, and some very interesting issues are beyond the scope of this thesis. For example, the public appetite for antidepressants can be viewed as a form of rampant consumerism. According to Das (2007), Prozac is 'the McDonald's of mental-health medication' and 'Not just a medicine, more an icon'. Also, according to Rose (2003), widespread use of antidepressants and other psychotropic drugs has profoundly influenced our conceptions of what it means to be a human being.

The main part of this chapter, after the brief comments about disciplines and perspectives, briefly outlines the orthodox story of depression and antidepressants, then briefly presents fifteen reasons why this dominant view warrants critique. Then the methodology of the thesis, primarily a combination of critical epidemiological and economic analysis and sociological analysis of the construction of depression as a social problem, is outlined. The chapter conclusion includes a brief outline of the content of the subsequent chapters.

1.2 DISCIPLINES AND PERSPECTIVES

Psychiatry is a medical specialisation that focuses on mental illness (which is often euphemistically referred to as 'mental health'). Psychiatrists in general are briefly discussed in chapter 3, because psychiatrists are key players in the use of antidepressants. Several particularly influential Australian psychiatrists are introduced there and discussed in more detail in later chapters, particularly chapter 9.

Common acronyms in this chapter: AIHW Australian Institute of Health and Welfare; APA American Psychiatric Association; BOIMHC Better Outcomes in Mental Health Care; CDHAC Commonwealth Department of Health and Aged Care; DoHA Department of Health and Ageing; DSM Diagnostic and statistical manual of mental disorders; PBS Pharmaceutical Benefits Scheme; RANZCP Royal Australian and New Zealand College of Psychiatrists; RPBS Repatriation Pharmaceutical Benefits Scheme; SSRI selective serotonin reuptake inhibitor

Psychology is the study of human behaviour. Psychologists are significant players in the conceptualisation of depression. Psychologists have also played a major role in the development of psychiatric epidemiology (discussed below), particularly in relation to population surveys and longitudinal outcome studies.

Epidemiology is the study of patterns of health, ill-health, and factors that affect health: 'The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems' (Last 2001, p. 62). It is a core strand of public health.

Epidemiology focuses on quantitative data, and is often considered to be much more objective than clinical medicine. Traditional epidemiological measures such as prevalence and incidence of disease are often considered to be valid and reliable indicators of the health of the population in Australia and other developed countries. However, epidemiology has many grey areas. Traditional epidemiology focused mainly on infectious diseases. However, it has increasingly broadened to include all health and disease states and both risk factors and protective factors. This has made epidemiology much more complicated, because many diseases have complex and poorly understood aetiology (causation). For example, many cases of cancer are of indeterminate origin.

Furthermore, epidemiology can have profound commercial ramifications (Pearce 2007) and political implications (Jackson et al. 1999). In addition, what epidemiological issues are investigated, and how, are strongly influenced by vested interests (Michaels 2008) and by methodological ideology (Pearce 2007, p. 714). Consequently it is naïve, even disingenuous, to suggest that epidemiological evidence is value-free.

Psychiatric epidemiology is the application of epidemiology to mental health and particularly mental illness. A key focus is on the prevalence of mental illness. A number of large-scale surveys have provided very useful information about the prevalence of depression (and other relatively common mental disorders) in the general population. Most relevant to this thesis are the National Comorbidity Survey – Replication (Kessler et al. 2005) and the Australian National Survey of Mental Health and Wellbeing (McLennan 1997; Andrews et al. 1999; Slade et al. 2009).

Pharmacoepidemiology is the study of patterns of use of medical drugs (both prescribed drugs and over-the-counter drugs, but primarily prescribed drugs), patterns of drug-related benefits and harms, and factors that influence drug use and the likelihood of harms and benefits. Patterns of drug use include who uses which drugs, how much they use, how often, and in what combinations. Factors influencing use include age, sex, socioeconomic status, gender roles, ethnicity, culture, education, availability of drugs, availability of alternative therapies, and so on. Patterns of benefits include recovery rates, remission rates, and survival rates, and rates of disease-specific outcomes (e.g. remission and recovery in depression). Patterns of harms include rates of adverse reactions and interactions with other drugs, and mortality rates (including suicide rates).

Psychopharmacoepidemiology is a term sometimes used to refer to the pharmacoepidemiology of psychotropic (psychoactive)[2] prescribed drugs such as antidepressants, anxiolytics (anxiety reducing drugs, particularly benzodiazepines) and antipsychotics.

Health economics is the application of economics (particularly economic evaluation) to health (and ill-health) and healthcare. It primarily focuses on healthcare supply and demand, but it also considers the value of health (and conversely the costs associated with ill-health) and factors that influence health (Williams 1987). In relation to depression, there have been a number of major studies focusing on costs associated with depression. Many of these have been funded by the pharmaceutical industry.

Pharmacoeconomics is a specialised area of health economics, focusing on the economic costs and benefits of pharmaceuticals. The most common methods are cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis. There have been a significant number of industry-funded studies analysing the economic impact of antidepressants.

[2] The terms psychotropic and psychoactive are used interchangeably in this thesis. The former is more often used in relation to medicinal drugs, particularly prescribed drugs, than nonmedicinal drugs.

Common acronyms in this chapter: AIHW Australian Institute of Health and Welfare; APA American Psychiatric Association; BOIMHC Better Outcomes in Mental Health Care; CDHAC Commonwealth Department of Health and Aged Care; DoHA Department of Health and Ageing; DSM Diagnostic and statistical manual of mental disorders; PBS Pharmaceutical Benefits Scheme; RANZCP Royal Australian and New Zealand College of Psychiatrists; RPBS Repatriation Pharmaceutical Benefits Scheme; SSRI selective serotonin reuptake inhibitor

Evidence-based medicine/healthcare: evidence-based medicine is a dominant force in contemporary medicine (although it is not universally accepted by clinicians). Probably the most commonly cited definition is:

> Evidence based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. This practice means integrating individual clinical experience with the best available external clinical evidence from systematic research. (Sackett et al. 1996, pp. 72-73)

However, evidence-based practice applies more broadly to health-care and welfare. It means basing practice on empirical (observable, factual) evidence, rather than belief, ideology, or tradition. It does not preclude intuition and creativity, but requires that strategies be evaluated rather than being adopted uncritically. A key method used in evidence-based practice is critical appraisal of published literature (and other sources of evidence), particularly reports of clinical trials. Critical appraisal is discussed in section 1.6.1, in the methodology section of this chapter, because it is a major component of the critical analysis methodology used in this thesis.

Sociology is the study of 'social life, social change, and the social causes and consequences of human behavior' (American Sociological Association 2005). Most relevant to this thesis is the sociology of the construction of social problems, particularly the concept of claims-making (Spector & Kitsuse 1977), which is discussed briefly in section 1.6.2, in the methodology section of this chapter.

Public health, unlike clinical medicine, focuses on the health of populations and other aggregate groups of people, not specific individuals.

Sometimes a distinction is made between traditional 'old public health' and 'new public health'. Old public health focuses primarily on the physical environment, particularly sanitation to prevent the spread of infectious diseases, and the availability and quality of food, air, and housing. Exposure to poisons and other hazards is another key focus. New public health also recognises the importance of the physical environment but particularly emphasises structural (social and economic) determinants of health. Baum (1998, p. 510) provided a useful definition of new public health, drawing on the Ottawa Charter for Health Promotion (World Health Organization 1986):

> The new public health is the totality of the activities organised by societies collectively (primarily led by governments) to protect people from disease and to promote their health. These activities occur in all sectors and will include the adoption of policies which support health. They will also ensure that social, physical, economic and natural environments promote health. The new public health is based on a belief that the participation of communities in activities to promote health is as essential to the success of those activities as is the participation of experts. The new public health works to ensure that practices of the government and private sector (including the health sector) do not detract from health and wherever possible promote health.

It also entails protecting people from injury. Generally these days, in Australia at least, the term 'public health' means something closer to new public health than old public health. That is how it is used in this thesis. Not surprisingly, given the scope of the above definition, public health is a multidisciplinary discipline.

Biomedical perspective: deterministic biomedical models dominate medicine, focusing on biological abnormalities that cause diseases and disorders and are theoretically amenable to physical intervention (primarily drug treatment, but also surgery and other clinical methods). In psychiatry, the biomedical model views mental illnesses as brain diseases.

Biopsychosocial perspective: psychiatry often claims to use a biopsychosocial model, in which biological factors interact with psychological factors and social contexts, jointly influencing mental health and illness. However, the emphasis on biology, particularly neurotransmitters, increasingly eclipses consideration of psychological and social factors (Read 2005). The term biopsychosocial usually reflects a hierarchical perspective, in which biological factors are considered to be by far the most important, with social factors being accorded little more than lip-service.

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1.3 DEPRESSION

Depression is common, serious, and treatable. (Ellis, Hickie, & Smith 2003, p. 34)

Depression is a psychological state characterised by sadness, lack of interest and pleasure in life (anhedonia), and other negative emotions that persist over a period of time (from weeks to decades). The primary focus in this thesis (and in most discussions of depression generally) is on *unipolar* depression, which is more straightforward than *bipolar* depression (manic depression), in which both negative and excessively positive (manic) states occur.

The above quote from Ellis et al.'s (2003) summary of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) (2004) clinical practice guidelines for the treatment of depression echoes the key message of the US National Institute of Mental Health's Depression Awareness, Recognition, and Treatment (D/ART) program, that depressive disorders are 'common, serious, and treatable' (Regier et al. 1988, p. 1351). Depression is now widely considered to be a major social problem, a product of its supposed high prevalence and substantial impact. However, inherent in the word 'treatable' is a claim that this social problem can be reduced by clinical intervention.

In the World Health Organization's landmark Global Burden of Disease study, unipolar major depression was calculated to be the fourth leading cause of disease burden in the world in 1990, and it has been projected to be the second leading cause in 2020 (Murray & Lopez 1996, p. 375) and the leading cause in developing countries (p. 377). Partly because of those projections, depression has been referred to as a 'Social and economic timebomb' (Dawson & Tyrer 2001). There have been similar projections about depression in Australia (Mathers et al. 2000). These projections have been widely used to argue for greater investment in depression treatment (Whiteford & Wells 1998; Commonwealth Department of Health and Aged Care [CDHAC] 2000, p. 5; Hickie, Davenport, Naismith, & Scott 2001, p. S4; Davies 2003, p. 1; Groom et al. 2003, pp. 4, 7).

Depression is considered to be a major cause of suicide. Indeed it is often taken for granted that people who kill themselves *must* be depressed. In the Global Burden of Disease study, all cases of suicide were attributed to depression (Murray & Lopez 1996, p, 250). Depression is also considered to be a factor in excess morbidity and premature

mortality from other causes, particularly cardiovascular disease. Traditionally, the risk of suicide has been the most powerful argument in favour of diagnosis, treatment, and prevention of depression, but in recent years there has been a substantial focus on its contribution to the burden of physical illnesses (Olver & Burrows 2007).

General practitioners[3] (GPs) are the main providers of treatment for depression (and other mental health problems) in many countries, including Australia (Australian Bureau of Statistics 2008, p. 23), New Zealand (Dew et al. 2005), and the UK (Lader 2007, p. 1657; Gilbody 2004, p. 80). However, many cases of depression are not detected by GPs and remain untreated (Goldman et al. 1999). GPs are being strongly encouraged to diagnose and treat more cases of depression (Hickie et al. 2001). In Australia, government concern about depression and suicide led to the establishment of *beyondblue: the national depression initiative*[4] (discussed in chapter 9), which has played a major role in the elevation of depression as a social problem in Australia.

There are multiple theories about the causes of depression. However, there has been wide acceptance of the serotonin hypothesis, the theory that depression is a brain disorder caused by a deficiency or imbalance of the brain neurotransmitter serotonin, and/or other neurotransmitter abnormalities (Leo & Lacasse 2008). This theory is congruent with the broader dominance of biological psychiatry that has emerged in recent years (Valenstein 1998). It underpins claims that depression requires treatment with antidepressants to correct a 'chemical imbalance' (e.g. National Alliance for Research on Schizophrenia and Depression 1995, reproduced in Valenstein 1998, p. 178; Weinstein 2004, p. 2).

Depression is discussed in more detail in chapter 2, and important debates about it are analysed in chapter 4. The relationship between depression and suicide is analysed in chapter 5.

[3] General practitioners in Australia are broadly the equivalent of primary care physicians (often referred to as 'family physicians') in the US.
[4] The official name is all lower-case italics, i.e. *beyondblue: the national depression initiative* (beyondblue 2011).

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1.4 ANTIDEPRESSANTS

Antidepressants are safe, effective and not addictive. (beyondblue 2008)

Antidepressants are psychotropic (mind-altering) drugs that affect mood and cognition and are used to alleviate depression. Usually the term 'antidepressants' is used to refer to mainstream *prescribed* antidepressants. These are the main focus of this thesis.

The most common type of antidepressant currently used is selective serotonin reuptake inhibitors (SSRIs). The most notable SSRI is fluoxetine (Prozac®), which first came on the US market in 1988[5] and rapidly eclipsed the older tricyclic antidepressants (TCAs) (McManus et al. 2000) as well as a few earlier SSRIs.[6] SSRIs are still sometimes referred to as 'newer antidepressants', but they are older than more recent 'newer' antidepressant types such as serotonin noradrenergic reuptake inhibitors (SNaRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), and noradrenaline reuptake inhibitors (NaRIs) (Kent 2000).

There has been a significant escalation in antidepressant use in recent years in Australia and elsewhere (Meijer et al. 2004; Mojtabai 2008). Between 1990 and 1998, antidepressant prescriptions dispensed through community pharmacies increased from 5.1 million to 8.2 million (McManus et al. 2000). Antidepressant use has continued to increase (Hawthorne et al. 2008), and in 2009, nearly 16.7 million prescriptions were dispensed, costing over $533 million (DoHA 2011a, pp. 165-166). Most are subsidised by the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS). [7]

It is generally believed that newer antidepressants are better than older ones, and that they are continuing to improve in terms of effectiveness, safety, and specificity (RANZCP and Society of Hospital Pharmacists of Australia 2001). A major reason for increased use of antidepressants is the increasing acceptance of the serotonin hypothesis. Furthermore, the idea that depression is a chronic relapsing disorder (Andrews 2001; Joiner 2000) supports claims that antidepressants are needed long-term to prevent relapse (Greden 2001), and

[5] Fluoxetine was approved by the Food and Drug Administration on 29 December 1987 (FDA 2008).
[6] Prozac is often referred to as the first SSRI, but it was preceded by several others (Healy 2004, p. 18-24).
[7] The PBS and RPBS are discussed in chapter 4.

thereby increases the likelihood of repeat prescriptions. It is commonly argued that treating depression with antidepressants not only improves health outcomes but also has net economic benefits, primarily through reducing other health-care costs.

The proportion of people in treatment diagnosed with depression who use antidepressant medications has increased significantly in recent years (Stafford et al. 2001), and the proportion who receive psychotherapy has declined (Olfson 2002). Indeed, antidepressants are often viewed as *the* treatment for depression: 'Antidepressants are the mainstay treatment of depression in primary care in the UK' (Eccles et al. 1999, p. 103); 'Antidepressant drugs represent the principal form of treatment for major depressive disorder' (Norman 2006, p. 394). Many journal articles about depression 'treatment' only discuss antidepressants, implying that the only *real* treatment is drug treatment.

GPs prescribe 86 per cent of subsidised antidepressants in Australia, most commonly for 'chronic mild depression', which is not an authorised indication (McManus et al. 2003). In the BEACH GP study, 71% of antidepressants prescriptions between April 2004 and March 2006 were for depression, 15% for other psychological problems, and 14% for other non-psychological problems (Charles et al. 2008, p. 201).

Antidepressants are also prescribed for anxiety disorders, smoking cessation, and, less commonly, a range of other disorders including bed-wetting (enuresis), problem gambling, and 'shopaholism'. Since the rapid decrease in the use of hormone replacement therapy, following the premature termination of the Women's Health Initiative trial because of increased risk of breast cancer (Chlebowski et al. 2003), antidepressants are also increasingly being used to treat menopausal symptoms (Kockler & McCarthy 2004). In this thesis, the primary focus is on antidepressant use for depression and, to a lesser extent, anxiety disorders.

Antidepressants are discussed in some more detail in chapter 2, and important debates about them are analysed in chapter 6.

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1.5 SIGNIFICANCE OF THE ISSUE

Given the authority of sources such as the RANZCP (2004) guidelines, the general agreement that it is important to treat depression, and the relatively high agreement among doctors that antidepressants are effective and safe, why is there reason to question the validity of those beliefs? There are important public health, social, and economic reasons, including:

1. Vastly more people are being diagnosed with depression, and treated with antidepressants, now than several decades ago.
2. The diagnosis of depression is problematic.
3. The epidemiology of depression is problematic.
4. Most of the evidence about the characteristics of and outcomes for people with depression comes from people in treatment for relatively severe depression. This evidence is inappropriately generalised to people in treatment for less severe depression, and even more inappropriately generalised to undiagnosed and untreated cases, which are generally much less severe.
5. Outcomes for people with untreated depression are under-researched. There is evidence of high rates of so-called spontaneous remission, but this evidence is generally ignored.
6. The postulated scientific basis of depression and antidepressant action (the serotonin hypothesis and similar theories) is questionable.
7. Personal and social problems, including depression, are inappropriately medicalised, partly influenced by the pharmaceutical industry.
8. Social causes of depression are under-researched.
9. The effectiveness of antidepressants is overstated.
10. The safety of antidepressants is overstated, and adverse effects downplayed.
11. A majority of the public believe that antidepressants are problematic.

12. Antidepressants are commonly prescribed for people who do not meet diagnostic criteria for depression.
13. The economic costs of antidepressants are substantial and increasing, and the economic benefits are over-stated.
14. The market for antidepressants has been, and continues to be, aggressively enlarged by the pharmaceutical industry.
15. Alternative treatments are under-researched and under-funded.

These reasons are very briefly discussed below. Most are discussed in more detail in other chapters, particularly in chapters 4 to 6.

1.5.1 Large numbers of people receiving depression diagnoses/treatment

> Depression has passed from being a rather obscure illness called melancholia, mainly seen in asylums to the number one cause of clinical disability in the world. (Shorter 2001, p. 1)

Diagnosis of depression has increased significantly, as has the number of people receiving treatment (Olfson et al. 2002). There is *some* equivocal epidemiological evidence that the prevalence of depression is increasing (Bland 1997; Lewinsohn et al. 1993), but not to the same extent as its diagnosis and treatment. However, other evidence suggests relative stability in prevalence (Murphy et al. 2000; Hawthorne et al. 2008). According to Parker (2007), Jacob (2009), and Bell (2005), among others, depression is significantly over-diagnosed.

Depression treatment has greatly increased in recent decades, with antidepressants increasingly dominating other treatment approaches. There are increasing concerns about over-prescribing of antidepressants (Jureidini & Tonkin 2006) and other psychiatric drugs, particularly to children (Safer 2006; Jureidini et al. 2004; Tonkin & Jureidini 2005) and older people (McLeod et al. 1997; Thapa et al. 1998).

Depression diagnosis and treatment are briefly discussed in chapter 2. Debates about depression and antidepressants are discussed in detail in chapters 4 and 6 respectively.

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1.5.2 Problems with diagnosis of depression

> physicians love to diagnose what they can treat and they can now treat depression successfully, but that does not automatically mean that a majority of their patients are depressed. Depression is indeed a common illness, but the irony is that the more successful the treatment, the commoner it becomes. (Shorter 2001, p. 25)
>
> if a discrete depressive syndrome exists in nature, the current DSM-IV criteria that we evaluated do not perform well in detecting it (Kendler & Gardner 1998, p. 176)

Psychiatric diagnosis and nosology (classification of diseases) is inherently contentious. Firstly, because there are very few definitive biochemical tests or genetic markers comparable to those for many physical illnesses (United States Department of Health and Human Services 1999, p. 72), diagnosis involves subjective assessments, in which inter-rater reliability (agreement among independent assessors) can be relatively low (Steinhausen & Erdin 1991; Llewellyn-Jones & Bird 2006). Secondly, for many disorders there are multiple sets of diagnostic criteria, agreement among which can be relatively low (Bertelsen 2004). Thirdly, diagnostic criteria have changed significantly over time and are sometimes very contentious, particularly when new diagnoses are introduced or existing diagnostic criteria are changed.

Depression diagnosis is contentious for several specific reasons (Kendler & Gardner 1998). The boundaries of depression have greatly broadened in recent years (Medawar, 2003, p. 12). Another issue is the debate about whether depression and anxiety are separate disorders or in fact variations of the same disorder (Shorter & Tyrer 2003).

The duration of many cases of depression is quite short (Patten 2001), yet the very influential DSM-IV (*Diagnostic and statistical manual of mental disorders* (4th ed.)) criteria (American Psychiatric Association [APA] 1994)[8] (appendix 1) only require two weeks' duration for a diagnosis for which long-term antidepressant treatment may be provided.

The pharmaceutical industry has exerted considerable influence on the diagnosis of depression. This is briefly discussed below (section 1.5.14). Depression diagnosis is

[8] A text revision of the DSM-IV (APA 1994), the DSM-IV-TR (APA 2000) has been published. However, the DSM-IV-TR criteria for major depressive disorder, depressive episode, and dysthymic disorder are exactly the same as the DSM-IV criteria, and most people continue to cite the 1994 DSM-IV criteria. DSM-5 is currently being developed, generating enormous controversy in the US, Australia, and many other countries (Dunlevy 2012).

discussed in more detail in chapter 2 and its significance in relation to the status of depression as a disease is discussed in chapter 4.

1.5.3 Problematic epidemiology of depression

As mentioned earlier, despite its focus on quantitative data, epidemiology has many grey areas. The epidemiology of psychiatric disorders is particularly complicated because diagnosis is problematic, particularly in relation to its subjectiveness (Jablensky 2002, p. 298). The epidemiology of depression has received considerable attention in recent years, particularly since the World Health Organization forecast that it would be the second leading cause of disability worldwide (Murray & Lopez 1996, p. 4). However, the methodology of that report has been challenged (Andrews et al. 2001; Ustun & Kessler 2002).

There is also criticism of depression epidemiology more generally (Murphy et al. 2000). Depression epidemiology is briefly reviewed in chapter 2 and claims that depression is common are critiqued in chapter 4.

1.5.4 Inappropriate generalisation of evidence about depression

As mentioned above, the majority of people who receive treatment for depression are treated by general practitioners. However, most of the research into the outcomes of depression has focused on people treated by psychiatrists, often in tertiary settings (psychiatric hospitals and psychiatric wards in general hospitals). Such people are unrepresentative of people with depression because they disproportionately include severe and chronic cases.

The prognoses (outcomes) reported from studies of such people are relatively pessimistic. They include high relapse rates (Solomon et al. 1997) and suicide rates of 15% (Guze & Robins 1970). Furthermore, the treatment regimes of patients treated by psychiatrists differ from those of people treated by GPs. Even if they are prescribed the same drugs, their treatment is likely to be significantly more intensive than that of people treated by GPs (McManus et al. 2003). It is not valid to generalise without qualification from patients in tertiary settings to those in primary settings (the majority of those treated for

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depression). Yet this frequently occurs in the medical literature. For example, the 15% suicide rate among clinical groups with unrepresentative severity is often inappropriately generalised to *all* people with depression (Blair-West et al. 1997). Depression outcomes are briefly discussed in chapter 4. Some key debates about suicide are discussed in detail in chapter 5.

1.5.5 Under-researched outcomes for untreated depression

There is little information about the prognosis of untreated depression. However, according to Patten (2001), 'many people with the syndrome of major depression may have quite brief episodes', and spontaneous remission is common (Parker 2000b). Outcomes of untreated depression are briefly discussed in chapters 4 and 6.

1.5.6 Questionable theories of depression and antidepressant action

> In pursuing the biochemical approach to mental disorders an enormous amount has been learned, but it is questionable how much has been learned about mental illness. We do not really know if a biochemical imbalance is the cause of any mental disorder, and we do not know how even the hypothesized biochemical imbalances could produce the emotional, cognitive, and behavioral symptoms that characterize any mental disorder. (Valenstein 1998, p. 138)

Despite widespread acceptance, theories of 'chemical imbalance', including the serotonin hypothesis of depression, have many critics. According to UK psychiatrist David Healy and colleagues, the idea that depression is the result of serotonin deficiency or a chemical imbalance 'had been discarded by the early 1970s but was resurrected with the marketing of the SSRIs – there is nothing to it other than marketing copy (Healy et al. 2012, p. 8). Valenstein (1998) argued that the serotonin hypothesis is reductionist, and that adherence to it has narrowed the scope of research. More recently, a pro-orthodoxy psychiatrist has disingenuously argued that 'In truth, the "chemical imbalance" notion was always a kind of urban legend – never a theory seriously propounded by well-informed psychiatrists' (Pies 2011), ignoring the fact that many in his profession have actively promoted the theory, which has been aggressively exploited by pharmaceutical companies (discussed in chapter 7). The validity of chemical imbalance theories is not discussed in detail in this thesis, but is well addressed by Lacasse & Leo (2005).

1.5.7 Medicalisation of personal and social problems

Medicalisation is the process of constructing an issue (often a problem) as something to be viewed with a medical lens and addressed with medical skills and technologies. The term usually has negative connotations – people who use the term are usually critical of the construction. Natural processes such as childbirth and death are well established targets of medicalisation (Conrad 1992); more contentious targets include personal and social problems such as shyness and sexual orientation.

There is such concern about inappropriate medicalisation of personal and social problems that the *BMJ* (previously the *British Medical Journal*) devoted a special issue to the topic (13 April 2002). The issues identified included old age, sexual behaviour, baldness, and anxiety and distress (Double 2002). Other critics of the medicalisation of distress include Heath (1999), Gardner (2003), Jacob (2009) and, in Australia, Fullagar & Gattuso (2002) and Bell (2005). Medicalisation of distress is discussed in chapter 4.

1.5.8 Under-researched social causes of depression

There is clear evidence that social deprivation is associated with higher levels of psychiatric disorders (Fryers et al. 2003; Cullen & Whiteford 2001; Hunter 1990). However, research focuses much less on social factors than on biochemical mechanisms. Furthermore, psychosocial research is paid little attention (Gardner 2003, pp. 118-119). Although the significance of gender is recognised, because women are more prone to depression than men, it is generally treated as a simple dichotomous variable (Fullagar & Gattuso 2002, p. 3), and analysed only in terms of sex differences. Further discussion of social causes of depression is beyond the scope of this thesis.

1.5.9 Overstated effectiveness of antidepressants

> There are no signs that the rapidly escalating use of antidepressants is reducing the burden of depressive disorders. (Moncrieff 2001, p. 288)
>
> Premarket trials are often carried out in restricted patient populations that inadequately represent the users of a drug once it is on the market. (Herxheimer & Mintzes 2004, p. 487)

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The medical literature abounds with claims of the effectiveness[9] of antidepressants, based on evidence from clinical drug trials. However, such claims are under increasing criticism, for several reasons. Firstly, there is increasing concern about the methodology and reporting of drug trials in general (Bhandari et al. 2004; Herxheimer & Mintzes 2004; Garland 2004), even randomised controlled trials, the 'gold standard' of clinical trials. Industry-funded drug trials generally have significant biases that favour funders' drugs (Jørgensen et al. 2006). Furthermore, pharmaceutical companies have until recently been under no obligation to report trials that demonstrate ineffectiveness, and they frequently suppress unfavourable findings.

There are significant concerns about the methodology of antidepressant drug trials. The main evidence about the effectiveness of antidepressants comes from industry-funded trials that are biased in favour of antidepressants (Angst, Kupfer, & Rosenbaum 1996; Bland 1997; Medawar 1997). A key source of bias is the use of selective exclusion criteria. According to Keitner et al. (2003), *most* people with depression who apply to participate in antidepressant trials do not meet eligibility criteria. People with comorbid psychiatric or physical disorders are routinely excluded (Posternak et al. 2002), despite the fact that comorbidity is arguably the norm in depression (Ellen et al. 1998, p. 19), as are people considered to be suicidal (Goldsmith et al. 2002, p. 8), despite the fact that antidepressants are promoted as the solution to suicide.

People with mild cases of depression are also sometimes excluded from trials. Because depression often takes a fluctuating course and because of the phenomenon of regression to the mean, which is responsible for much of the observed improvement in cases of depression (Smith 2006, p. 72; Flett et al. 1995), people with more severe depression may be more likely to improve significantly regardless of treatment.

Trials are further biased by the routine exclusion of 'placebo responders' – people who respond positively to placebo during the placebo run-in period, in which all participants are given placebo for days or weeks, before the trial proper begins. Some placebo responders are indeed responding to the placebo; others probably have short self-limiting

[9] The terms effectiveness and efficacy are sometimes used interchangeably, but efficacy means effects demonstrated in tightly controlled trials, whereas effectiveness means real-world effects (Gallo 1999; United States Department of Health and Human Services 1999, p. 72).

depressive episodes which would have resolved without any treatment. Exclusion of placebo responders eliminates people who would be more likely than others to respond to placebo during the trial. This makes it easier for significant difference to be found between the active drug and placebo.

The use of placebos in trials is controversial for reasons other than placebo run-in. Particularly relevant to antidepressant effectiveness is the fact that many trial participants can distinguish antidepressants from placebos on the basis of their side-effects; this 'unblinding' can result in bias in favour of antidepressants (Moncrieff et al. 1998). Despite this, there is some evidence that antidepressants are little more effective than placebos (Walsh et al. 2002).

Furthermore, according to Herxheimer & Mintzes (2004), SSRIs are largely ineffective in treating depression in children and adolescents. Antidepressant effectiveness is discussed in detail in chapter 6.

1.5.10 Overstated safety of antidepressants

> Deaths from antidepressants continue to account for a substantial proportion of drug-related deaths. (Cheeta et al. 2004)

There are mounting calls for changes in the reporting of drug trials generally, including mandatory reporting of adverse effects (McPherson & Hemminki 2004). Claims that antidepressants, particularly SSRIs, are safe are common in the medical literature. Such claims often contrast antidepressants with other prescribed psychotropic drugs, particularly benzodiazepines. However, there are significant concerns about the safety of antidepressants (Parker 2000b; Medawar 1997).

Until the last decade or so, whenever the risks of antidepressants have been discussed, there has tended to be a disproportionate focus on dependence (or addiction). The potential for dependence was constructed as a pivotal issue in the 1990s. Antidepressants have often been emphatically contrasted in relation to dependence with benzodiazepines and nonmedical psychotropic drugs such as heroin and other illegal opioids.

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A second key focus, which has increased in recent years, is on suicide, in terms of both the toxicity of antidepressants in overdose, and whether or not antidepressants can trigger suicide (Healy et al. 1999). Other risks, including heart attacks (Thorogood et al. 1992), and pulmonary embolism (Parkin et al. 2003), have generally received little attention.

There is particular concern about the safety of antidepressant use by children (Safer & Zito 2006). There is increasing evidence that SSRI use can cause suicidal behaviour in children and adolescents (Herxheimer & Mintzes 2004; Garland 2004). Furthermore, there is some evidence that exposure to antidepressants can increase the risk of bipolar disorder ('manic depression') (Cicero et al. 2003). There is also concern about risks to elderly people, including falls caused by side-effects such as dizziness (Thapa et al. 1998). Antidepressant safety is discussed in detail in chapter 6.

1.5.11 Public beliefs that antidepressants are problematic

> 78% [of lay people] regarded antidepressants as addictive.… patients should know that dependence is not a problem with antidepressants (Priest et al. 1996, p. 858)

A large proportion of the general public believe that antidepressants are addictive or otherwise problematic. In the UK in the 1990s, publications linked with the Defeat Depression Campaign of the Royal College of Psychiatrists and the Royal College of General Practitioners, for example Priest et al. (1996), publically challenged such beliefs, emphasising that antidepressants were not addictive (Medawar 2003, p. 27).

Similarly, in Australia, Jorm et al. (1997, p. 182) found that antidepressants were 'more often rated as harmful than helpful'. Public attitudes towards antidepressants are briefly discussed in chapters 6 and 8.

1.5.12 Antidepressant prescription outside diagnostic criteria

> A significant number of prescriptions for the newer antidepressants may not accord with the Pharmaceutical Benefits Scheme (PBS) restrictions for use. (McManus et al. 2003, p. 184)

In Australia and many other countries, antidepressants are approved for prescription to people who meet established diagnostic criteria such as DSM-IV (APA 1994). However, they are frequently prescribed for people who do not meet such criteria (McManus et al.

2003; Ornstein, Stuart, & Jenkins 2000). Often there is no formal assessment of patients prior to prescribing antidepressants.

One reason is the time pressure GPs experience. Many GP consultations are less than 10 minutes in length; as many as two-thirds end with the issuing of a prescription for one or more drugs (Audit Commission 1994, cited by Greenhalgh & Gill 1997). Antidepressant prescription is discussed briefly in chapter 2 and in more detail in chapter 6.

1.5.13 Substantial and increasing costs of antidepressants

> Antidepressants are the mainstay treatment of depression in UK primary care, with one million person-years of treatment provided annually. The purchase cost of these drugs is currently £160 million per year, although this is increasing dramatically as newer (and more expensive) antidepressants receive greater use. (North of England Antidepressant Guideline Development Group 1997)

The high expenditure on antidepressants in Australia was briefly discussed in section 1.4. Drugs have been the fastest growing component of health-care costs (Angell 2000b), and antidepressants have featured prominently in this growth. In 2003, drugs for depression and anxiety disorders accounted for 'the largest proportion by far of sales of psychiatric drugs' (Shorter & Tyrer 2003). In 1998, sertraline (Zoloft), one of a number of SSRIs subsidised by the PBS, was the eighth most expensive drug for the Australian Government, costing $45,174,008 for 1,455,271 prescriptions (CDHAC 1999a, p. 20, Table D).

Drug companies argue that antidepressants reduce health-care costs, because of the higher costs of untreated depression. Such arguments are often incorporated into industry-sponsored guidelines (e.g. Hirschfeld et al. 1997). However, many pharmacoeconomic studies of antidepressants are flawed (Conner et al. 1999; Baker et al. 2003). Antidepressant costs are discussed briefly in chapter 2.

1.5.14 Aggressive enlargement of the market for antidepressants

> Eli Lilly sells Prozac by promoting the broad notion of depression, rather than the drug itself. (Gardner 2002, 9)

> the escalating rates of use of antidepressants may have more to do with marketing imperatives than any benefits to mental health (Moncrieff 2003b)

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> as we spoke with research psychiatrists about writing an editorial on the treatment of depression, we found very few who did not have financial ties to drug companies that make antidepressants (Angell 2000a)

The pharmaceutical industry is one of the most profitable industries in the United States, ranking in the top five in terms of returns on revenues, assets, and shareholders' equity, according to *Fortune* magazine (2011). Its marketing budgets are much larger than its research and development costs (Angell 2000b). In recent years, serious concern has emerged in the medical literature about pharmaceutical industry tactics, including political lobbying and 'lavish spending' to influence doctors and researchers (Angell & Relman 2001) and bias in clinical trials (Bhandari et al. 2004).

Like many lucrative drug categories, antidepressants are heavily promoted. In addition to advertising antidepressants to doctors, drug companies also sponsor research, conferences, continuing medical education, and publications. Antidepressants are also advertised directly to consumers in countries that allow this. Other promotional strategies include funding of consumer/community mental health groups (Silverstein 1999), sometimes referred to as 'Astroturf lobbying' (Silverstein 1997). Perhaps the most important meta-strategy is marketing the concept of depression (Gardner 2002; Healy 1999) to both doctors and the public. Pharmaceutical industry strategies are discussed in 8. Chapter 9 presents a detailed case-study of how depression has been very successfully 'sold' in Australia by industry-funded initiatives, contributing substantially to the escalating prescription of antidepressants.

1.5.15 Under-research and under-funding of alternative treatments

Most depression treatment research focuses on neuroscience and patentable drug treatments, with less attention paid to alternative treatments such as cognitive-behavioural therapy (Gardner 2003, p. 106, note 4). A major reason for this is that most treatment trials are funded by pharmaceutical companies (Mulrow et al. 1999).

In Australia, access to alternative therapies funded by Medicare was very limited until the establishment of the Better Outcomes in Mental Health Care (BOIMHC) program in 2001. Although BOIMHC had increased the accessibility of counselling, for many people, the only real source of treatment is a GP who is far more likely to prescribe

antidepressants than to provide anything other than minimal counselling. The neglect of alternative treatments is briefly discussed in chapter 6.

1.6 METHODOLOGY

In this thesis, two major interrelated analytical approaches are used. The first approach is critical analysis of the objective validity of specific claims and assumptions about depression and antidepressants, using a mixture of epidemiological analysis and critical appraisal skills from the evidence-based medicine field. The second approach is a broad analysis of strategies used by advocates of the orthodoxy. This includes an analysis of how and by whom claims about depression and antidepressants and related issues such as suicide are deployed in the depression arena. Also analysed are pharmaceutical industry marketing strategies, and strategies used by other players such as psychiatrists and community mental health organisations, all of which often utilise claims about depression and so on.

Most antidepressants are prescribed by GPs, but diagnosis of mental disorders and prescribing of psychotropic drugs by GPs (and other doctors) is strongly influenced by psychiatrists. Consequently there is a major focus in this thesis, in both analytical approaches, on general practice and psychiatry. As mentioned in the introduction, the Australian depression/antidepressant arena is analysed in its global context, with a strong historical perspective.

1.6.1 Critical analysis of claims

The first major approach is critical analysis of the validity of players' claims against empirical evidence, using epidemiological analysis, and critical appraisal skills from the evidence-based medicine field (Greenhalgh, 1997b). A major component is questioning key claims and assumptions about:

- the epidemiology of depression
- the prognosis of depression

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- the impacts of depression, both treated and untreated, including the relationship between suicide and depression
- the evidence base of guidelines for treatment of depression
- clinical efficacy of antidepressants (in randomised controlled trials)
- clinical effectiveness of antidepressants (in real-world practice)

Most of the analysis involves assessing claims against published evidence. Some of the analysis uses methods derived from critical appraisal in the sense that that term is used in the evidence-based medicine literature. Critical appraisal is the process of systematically analysing research evidence to assess its validity, results and relevance to clinical practice (Hill & Spittlehouse 2001, p. 1). It draws strongly on epidemiology (particularly in relation to the methodology of clinical trials), but it also draws on health economics where relevant, in addition to general critical analysis skills.

In this thesis, the critical analysis of epidemiological claims utilises a number of large-scale population surveys, particularly the US National Comorbidity Survey – Replication (Kessler & Merikangas 2004; Kessler et al. 2004) and the Australian National Survey of Mental Health and Wellbeing (McLennan 1997; Andrews et al. 1999; Slade et al. 2009).

Prognostic claims in the literature are assessed mainly against evidence from key longitudinal studies of depression. The analysis of economic claims about both depression and antidepressants focuses primarily and critically on the methodology of industry-funded studies. The analysis of guidelines, many of which are also industry-funded, and claims about adherence to guidelines, largely involves assessing claims and assumptions against evidence from clinical studies. Claims about the pharmacoepidemiology of antidepressants are assessed mainly in relation to the methodological rigour of surveys and database studies. Claims about the efficacy and effectiveness of antidepressants are primarily assessed against evidence from randomised controlled trials and other clinical studies.

Important aspects of the analysis include the validity of generalisation from specific clinical and epidemiological samples to other clinical groups and populations more generally. Another important issue is the selection of citations to support claims.

Particular attention is paid to claims for which no evidence is cited; where possible, their sources and trajectories are investigated. The validity of interpretation and representation of cited evidence is another important focus of analysis.

As in the analysis of claims-making, the sources of material for analysis include academic literature (particularly journal articles but also books and conference proceedings etc.), treatment guidelines, education and training materials, and promotional materials produced and distributed by pharmaceutical companies.

This critical analysis allows objective analysis of the validity of claims made by players (particularly epidemiological claims, claims about the effectiveness of treatments, and economic claims). Furthermore, in tandem with the analysis of the influence of claims-making on policy and practice, it allows analysis of the relationships between particular types of evidence and policy and practice, and analysis of how these relationships are mediated by particular players.

Bridging the two approaches is investigation of the *provenance* and *trajectories* of factual and conceptual claims. Particular attention is paid to claims based on misleading representations of published evidence, particularly evidence in the psychiatric literature, which has considerable authority and is often accepted uncritically, both in primary publications and when cited elsewhere.

Unfortunately, citation misrepresentation (or citation distortion) – inappropriate use and representation of published evidence – is very common in the psychiatric literature (as it is in the medical literature generally), even in peer-reviewed academic journals. Furthermore, citation misrepresentation permeates far beyond journals, to textbooks and other teaching media, the grey literature, policy documents, pharmaceutical industry advertisements and websites and publications, consumer/community mental health organisation websites and publications, and the mass media. Often the grey literature serves as a bridge for citation misrepresentation to other domains, particularly the media.

I have publicly challenged multiple instances of citation misrepresentation in the depression arena (Raven 2010a; Raven 2005; Raven 2006; Jureidini & Raven 2012) and

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the broader mental health arena (Raven 2008a; Raven 2011; Raven & Jureidini 2010), and in other instances I have queried authors about problematic claims but not published anything about them. The misrepresentations I have challenged (a very time-consuming process, particularly if no sources have been cited) represent a tiny fraction of the cases of misrepresentation that I am aware of. Almost all misrepresentations remain unchallenged, and are often propagated.

Although some citation misrepresentation is due to carelessness, many of the cases considered in this thesis are strategic – particular misrepresentations are made by particular players in particular contexts for specific purposes. Two key purposes are to magnify the extent of a problem and to inflate the effectiveness of a solution. Such misrepresentations are often repeated and reinforced by people who are unaware of their problematic nature.

A strong spotlight has recently been cast on citation misrepresentation in the academic neurological literature by Greenberg (2009) in a key paper, the title of which warns that 'citation distortions create unfounded authority'. Greenberg analysed the claim that 'β amyloid, a protein accumulated in the brain in Alzheimer's disease, is produced by and injures skeletal muscle of patients with inclusion body myositis' (p. 1). This claim is widely accepted as fact, despite very weak evidence in support of it, and significant evidence to the contrary. The latter is largely ignored, despite being more rigorous. According to Greenberg, the β amyloid claim has gained unfounded authority and become a 'published belief system' (p. 210) via the influence of 'distorted persuasive citation' (p. 212).

The β amyloid claim is not an isolated case. Tatsioni et al. (2007) analysed the persistence in the medical literature of another claim despite strong contradicting evidence. According to two highly cited observational studies, vitamin E bestows major cardiovascular benefits. Subsequently most randomised trials have found no benefit; some have found *increased* mortality. Despite this, many journal articles have continued to cite the two observational studies, endorsing the claim. Often the contradictory randomised trials have not been cited. Tatsioni et al. concluded: 'The wish bias of

individuals, irrespective of topic, can be large and may also influence the interpretation of scientific results' (p. 2525).

A much less ambitious paper than Greenberg's (2009) and Tatsioni et al.'s (2007), by Williams (1977), also provides an example of a questionable claim that has gained unfounded authority, namely that preweaning handling of rodents always produces weight gain. As with the β amyloid and vitamin E claims, there is plenty of contrary evidence that is largely ignored. Also ignored are 'rather obvious' methodological problems in the supportive studies (p. 242). Williams used the preweaning handling example to illustrate how 'a "fact" can emerge from the science system and yet be fallacious, and that this can be the work of honest men [sic] with no intent to deceive' (p. 242). He argued that this is 'a direct result of the career/financial structure, of the need to publish, and of the need to produce significant findings with implications beyond the narrow limits of the experiment' (p. 243).

Greenberg also discussed the potential advantages of problematic claims. He referred to the β amyloid belief system as an 'information cascade', which he defined as 'an entity resulting when people perceive advantage in accepting the prevailing view over any private information they may have when making choices' (p. 213). Another term for this is 'bandwagon'.

Greenberg commented that 'there are incentives for generating and joining information cascades regardless of their soundness' (p. 213). Among the incentives is the fact that papers with positive findings (and fitting the prevailing zeitgeist) are more likely to be published. Similarly, funding applications with strong hypotheses based on current mainstream academic literature are more likely to be successful, and their results more likely to be published, reinforcing the power of information cascades. The fact that players who participate in information cascades benefit in terms of their professional status, which in turn enhances their credibility, is another self-reinforcing factor.

Information cascades are also convenient for people less centrally involved with research topics, who often uncritically utilise established facts. Williams commented that

'Publication of a finding enhances its status; it converts it to a "fact"' (p. 242), and he expressed concern that such 'facts' are often compounded by distortions in secondary publications:

> Each 'new fact' can be compared and contrasted with other such 'facts' to produce yet more 'newer facts'; and changes occur in this compilation rather like those found in serial reproduction of a drawing or the spread of a rumour. The most worrying example of this trend is in textbook production. With a general text (or worse still one for an adjacent subgroup, e.g. 'Psychology for Nurses') the author is rarely in a position to assess each area covered in detail – so he [sic] reads other texts and reviews. As each review is in itself a simplification, distortion is inevitable. (p. 242)

Although the β amyloid claim is itself of no relevance to the claims that are analysed in this thesis, Greenberg's paper provides a useful categorisation of types of citation distortion, which is used in a modified form in this thesis. For Greenberg, citation distortion encompasses three categories of inappropriate citation practice. The first category, 'citation bias', refers to systematic ignoring of papers that contradict a claim. Citation bias has been reasonably well documented in the literature (James Lind Library 2007).

Greenberg's second category of citation distortion is 'amplification': citation of papers without any primary data (often review papers), increasing the number of citations supporting a claim. He documented how four primary data papers from the same laboratory supported many thousands of citations endorsing the β amyloid claim (p. 2). One review paper was also very highly cited.

Greenberg's third category of citation distortion is 'invention'. This includes several forms of misrepresentation of content and sources. The primary form I focus on is what he referred to as 'citation diversion', which he defined as 'citing content but claiming it has a different meaning, thereby diverting its implications' (p. 8). However, I refer to this as *content misrepresentation*. This is my main point of departure from Greenberg's categorisation.

An extreme form of content misrepresentation is citation of a source that does not contain *any* relevant information. This is similar to Greenberg's 'dead end citation' – citation of papers that do not contain content relevant to a claim.

The main types of citation distortion discussed in this thesis, modified from Greenberg's classification, are:

- **citation bias**: selective citation of papers and other publications that support a claim, and non-citation of papers that contradict it.
- **amplification**: citation of reviews and other publications that do not add any primary data but bolster the credibility and authority of a claim.
- **content misrepresentation**: misrepresentation of the content of a cited source to support a claim that it actually does not support.
- **inappropriate abstract citation**: misrepresentation of abstracts as peer-reviewed papers,[10] and more generally citation of abstracts as authoritative sources.
- **hypothesis conversion**: conversion of a hypothesis into a putative fact by citing it authoritatively.[11]

Greenberg's analysis of different types of citation distortion and his concept of information cascades are very relevant to the analysis in this thesis. So too is William's (1977) concept of 'fallacious' facts.

For example, a finding from a review of suicide rates among people predominantly hospitalised for severe depression, a group very unrepresentative of people with depression, most of whom are never hospitalised – that an alarming fifteen per cent of them subsequently killed themselves (Guze & Robins 1970) – has been repeatedly misrepresented over several decades, both by authors citing the original study and in secondary citations, as being applicable to the broader population of people with depression, including untreated cases. Studies with contrary findings have been largely ignored.

The repeated misrepresentation of Guze & Robins' finding in a plethora of journal articles and other publications is an example of amplification. The non-citation of studies with

[10] Greenberg refers to this as 'back door invention'.
[11] Greenberg refers to this as 'citation transmutation'.

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contrary findings is an example of citation bias. The claim that fifteen per cent of depressed people kill themselves is a 'fallacious fact', and players who use this claim are participating in an information cascade.

I argue that citation distortions, fallacious facts, and associated information cascades are important constituents of the orthodox story about depression and antidepressants. Participating in such information cascades has been beneficial to many researchers and clinicians and consumer/community mental health organisations and other players. Incentives for academic players include research funding and publications, both of which contribute to career advancement. Commercial considerations play a major role: much of the published research and other literature that supports these information cascades is funded by the pharmaceutical industry. Another factor is people's 'wish bias' (Tatsioni et al. 2007, p. 2525), for example the desire to believe that an antidepressant is an effective treatment for depression. Political considerations are another influence. For example, it is politically expedient for governments to accept claims that suicide is caused by mental illness, rather than acknowledging the major contributions of social and economic factors amenable to interventions that do not fit with neoliberal ideology and would not be electorally popular (e.g. gun control).

Like other dominant discourses, the depression/antidepressant orthodoxy is resistant to challenge and has powerful inertia, not only because of vested interests, but also because of the utility and self-reinforcing nature of information cascades. This would not be of concern if the content was accurate. However, in this thesis, I attempt to demonstrate that this is not the case, and that the orthodox story has profoundly problematic effects.

1.6.2 Analysis of strategies of advocates

The second major methodological approach used in this thesis is a broad analysis of strategies used by advocates of the orthodox story. This includes analysis of how claims about depression and antidepressants and related issues such as suicide are deployed in the depression arena, focusing on *what claims have been made, by which players, in which contexts, for which reasons, and with what impact*. In other words, there is analysis of the debates from an external perspective (*who* is arguing *what* and *why*?, and *how successfully*?), and critical analysis of the *content* of the debates (how *valid* are the claims

being made?). Also analysed are more overt pharmaceutical industry marketing strategies (for example direct-to-consumer advertising), and strategies used by other players such as psychiatrists and consumer/community mental health organisations, including academic publications, education campaigns, media engagement, and political lobbying, all of which often utilise claims about depression and so on.

Many key pharmaceutical industries, including disease awareness campaigns, are discussed in chapter 7. Then depression awareness campaigns are discussed in detail in chapter 8, followed by an Australian case study in chapter 9.

This analysis draws on the sociology of the construction of social problems (Blumer 1969; Best 1989; Bacchi 1999), particularly the concept of claims-making (Spector & Kitsuse 1977), to analyse how and by whom depression has been constructed as a major public health and social problem, for which antidepressants have been constructed as the solution, by a range of players, particularly pharmaceutical companies, doctors, and consumer/community mental health organisations.

Among sociologists, analysis of the social construction of social problems has been common for several decades. In such analyses, Spector & Kitsuse's (1977) views have been very influential. According to them, definition of something as a social problem is a claims-making activity. Claims-making includes: 'demanding services, filling out forms, lodging complaints, filing lawsuits, calling press conferences, writing letters of protest, passing resolutions, publishing exposes, placing ads in newspapers, supporting or opposing some governmental practice or policy, setting up picket lines or boycotts' (Spector & Kitsuse 1977, p. 79, cited by Schneider 1985, p. 211).

Spector & Kitsuse argued that the sociology of social problems should focus on such claims-making activities, asking questions such as:

- Who makes what claims?
- Who do claims-makers represent?
- Whose claims are responded to?

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Spector & Kitsuse (1977) argued against analysing social problems as objective conditions; they argued that sociologists of social problems should not concern themselves with the *validity* of claims (Schneider 1985, p. 212). However, Best (1989/1985, p. 345) advocated a *contextual constructionist stance* according to which assessment of the validity of claims can be useful, in contrast to Spector & Kitsuse's *strict social constructionist* stance. This thesis draws on Best's *contextual constructionist stance*, analysing both claims-making processes and the objective validity of claims.

Best (1989/1985) outlined three tasks for constructionist analysis of social problems:

1. Claims: Locate examples of claims, and analyse their content, asking questions such as: 'What is being said about the problem? How is the problem being typified? What is the rhetoric of claims-making – how are claims presented so as to persuade their audiences' (p. 348).
2. Claims-makers: Identify the claims-makers, and ask questions about representation, affiliations, alliances, ideology, vested interests, and so on (pp. 348-349).
3. The claims-making process: Analyse the claims-making process, asking questions such as 'Whom did the claims-makers address? Were other claims-makers presenting rival claims? What concerns and interests did the claims-makers' audience bring to the issue, and how did those concerns or interests shape the audience's response to the claims? How did the nature of the claims or the identity of the claims-makers affect the audience's response?' (p. 349).

The analysis of claims-making in this thesis includes review and discourse analysis of academic literature (particularly journal articles but also conference abstracts and textbooks etc.) and a broad range of other publications, including reports and other grey literature, treatment guidelines, education and training materials, promotional materials produced and distributed by pharmaceutical companies, and media articles.

In Australia, claims-making activities have brought about a dramatic elevation of the status of depression as a social problem, particularly since the publication of *National Health Priority Areas 1998 Report, Mental Health: A Report Focussing on Depression*

(CDHAC & AIHW 1999) and the establishment of *beyondblue: the national depression initiative* in 2000. Prior to the latter, few people in the general population had much awareness of depression as a social issue. An earlier driver of the change in status was the industry-funded National Depression Awareness Campaign, established in 1994 by the Mental Health Foundation of Australia. A major claim of that campaign was that depression was a 'serious, common and treatable condition' (Burrows 1997d, p. 1). Another important contributor was the pharmaceutical-industry-funded SPHERE project (SPHERE: A National Depression Project), established in 1998 by Professor Ian Hickie, who subsequently became the inaugural Chief Executive Officer of *beyondblue*. The National Depression Awareness Campaign and its flagship publication, the *Depression Awareness Journal*, are discussed in a detailed case-study in chapter 9. The SPHERE project is also discussed in that chapter, but not in depth.

In the social sciences literature, there are some analyses of other social problems that are referred to in this thesis. Particularly relevant are several somewhat similar analyses of problems related to alcohol and other drugs, both medical and non-medical, and problem gambling. In the analyses of alcohol-related problems, the most significant issue is the promotion of the disease model of 'alcoholism'[12], which strongly parallels the orthodox story about depression.

One relevant analysis is Wiener's (1981) 'arena analysis' of the alcohol field in the US in the 1970s, published as the book 'The politics of alcoholism: Building an arena around a social problem'. Wiener explored how alcohol problems became highly visible and were constructed as a medical problem called 'alcoholism', which was defined as a serious hidden social problem, with diagnosed cases being only the tip of the iceberg. Simultaneously, a rapidly developing treatment industry (dominated by Alcoholics Anonymous's 'twelve-step' philosophy) was constructed as the solution.

[12] I use quotation marks around the term 'alcoholism' because I question the validity of the concept, which is heavily freighted with disease model and twelve-step (Alcoholics Anonymous) ideology that both medicalises the problem and locates it within the individual, who is constructed as powerless. Furthermore, neither the DSM-IV (APA 1994) nor the ICD-10 (International Classification of Diseases (10th ed.) (World Health Organization 1992) includes 'alcoholism' as a diagnosis. Instead, both refer to 'dependence' on alcohol (and other substances).

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Wiener explored how different stakeholders participated (some reluctantly, particularly the alcohol industry) in generating this collective definition and successfully advocating for major government funding. Her approach explicitly focused on 'problem perception rather than problem incidence' (p. 251).

Today the validity of the status of alcoholism as a social problem is almost unassailable in the US, where the treatment industry is frequently criticised but remains firmly entrenched in the health system. In Australia, there is less emphasis on alcohol *dependence* and more emphasis on intoxication and harmful and hazardous drinking (National Health and Medical Research Council 2009), and there is greater diversity in treatment approaches, but alcohol problems are firmly established as a major social problem and a range of treatment and prevention programs are regarded as the solution (albeit imperfect).

Wiener's use of the term 'arena' was derived from Strauss et al.'s (1964) concept of an arena as a place of action and contest, and she drew on their arena-negotiation model: 'the processes of bargaining, tacit understandings, and shared agreements that characterize organizational life' (Wiener, p. 13). Wiener also drew on Kitsuse & Spector (1975), citing their perspective as central to her own task:

> if the social problem of alcohol use has grown from an invisible social problem to one of heightened visibility, how, to use Kitsuse's and Spector's terminology, has its definition been "socially processed"?

Weiner used grounded theory (Glaser & Strauss 1967), which she referred to as 'a hypothesis-seeking strategy for generating substantive and formal theory' (p. 268). Rather than imposing theory on data, as in conventional social research, theory is elicited from the data.

The theory that emerged from Wiener's data was that: 'building an arena around the social problem of alcohol use entails increasing its visibility by *animating* the problem, *legitimizing* it, and *demonstrating* it' (p. 20) [italics in original]. These three processes overlapped; they were not sequential (p. 22).

Animating the problem includes (pp. 20-21):

- Establishing turf rights (e.g. the growth of relevant research activity)

- Developing constituencies (e.g. the establishment of advisory boards)
- Funneling advice and imparting skills and information (e.g. the establishment of the National Center for Alcohol Education)

Legitimizing the problem includes (p. 21):

- Borrowing prestige and expertise (selectively borrowing the expertise and status of academic disciplines such as economics and physiology; borrowing an eclectic range of treatment techniques including pharmacotherapies and psychotherapies)
- Redefining the scope (p. 89) (in particular, promoting the disease model of 'alcoholism' as an alternative to the moral model)
- Building respectability (e.g. public disclosure by prominent people identifying as alcoholics, and the establishment of a national institute)
- Maintaining a separate identity (e.g. distinguishing alcohol problems from mental health problems)

Demonstrating the problem includes (p. 22):

- Competing for attention (e.g. courting media and seeking funding); combining for strength (e.g. forming alliances)
- Selecting supportive data (e.g. cost-benefit analyses)
- Convincing opposing ideologists (in particular, there was intense debate about whether abstinence was the only viable treatment goal or whether controlled drinking was appropriate for some people)
- Enlarging the bounds of respectability (e.g. promoting career development in the alcohol arena, and developing prevention strategies)

Several of these strategies are discussed in this thesis in relation to the construction of depression as a major social problem in recent decades and the related construction of antidepressants as the solution. Demonstrating the problem – particularly selecting supportive data – is the most important process overall. There are some strong parallels,

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but also some significant differences, between the 'alcoholism' and depression/antidepressant arena-building enterprises. The role of evidence claims has been stronger in the latter, largely because of pharmaceutical industry funding of research. Consequently the role of ideology has been less central, but has nevertheless been important. In addition, the analysis in this thesis has a strong focus on *misuse* of supposedly supportive data.

As with alcohol problems, the epicentre in relation to depression/antidepressants has been in the US, but the shift towards the orthodox story has also occurred in many other countries, including Australia.

1.7 CONCLUSION

This chapter has briefly outlined the current prevailing view of depression as a common and serious medical problem, and thereby a major public health and social problem, for which antidepressants are the solution. It then briefly outlined fifteen reasons why this dominant view warrants critique. These reasons are related to the diagnosis, prognosis, epidemiology, and causation of depression, the prescribing, effectiveness, safety, and economic costs and benefits of antidepressants, the marginalisation of alternative treatments, the medicalisation of social problems, and promotional strategies used by the pharmaceutical industry.

Then the two components of the methodology of the thesis were outlined: firstly analysis of the construction of depression as a social problem and the players and strategies used in the claims-making process, and secondly critical epidemiological and economic analysis of the validity of claims, focusing primarily on published medical literature but also including mass media, pharmaceutical industry promotional materials and other less academic sources of information.

These analyses are central to chapters 4 to 6, which focus on debates about depression, suicide, and antidepressants respectively, and chapters 8 and 9, which focus on depression awareness campaigns. Chapter 8 analyses such campaigns generally, then chapter 9 focuses specifically on Australia, presenting a case-study about the selling of

depression and antidepressants via the National Depression Awareness Campaign, the *Depression Awareness Journal*, the SPHERE project, and *beyondblue*. This case-study illustrates how key players' claims-making activities, utilising problematic claims that have become information cascades, have profoundly influenced the Australian mental health arena.

In order to do justice to this case-study, this thesis provides a considerable amount of background information about depression, antidepressants, key players, and legislative and policy contexts, as well as an analysis of key debates about depression, suicide, and antidepressants. There is also a detailed discussion of the pharmaceutical industry and allied players, concentrating primarily on practices most relevant to the promotion of antidepressants. A key theme that emerges is the strategic value of relationships with other players. Several such relationships are featured in the two case-studies.

The structure of this thesis consists of several blocks of chapters. The next three chapters after this provide background information about depression and antidepressants (chapter 2) and about the key players involved (chapter 3). These are followed by chapters 4 to 6, which critically analyse debates about depression, suicide, and antidepressants respectively. Chapter 7 is a long chapter on the pharmaceutical industry. Chapter 8 discusses depression awareness campaigns in general, followed by the detailed Australian case-study of the National Depression Awareness Campaign and the *Depression Awareness Journal* in chapter 9. The conclusions in chapter 10 focus mainly on how problematic claims about depression, suicide, and antidepressants, along with pharmaceutical industry strategies, particularly depression awareness campaigns, have been used to successfully sell the orthodox story about depression and antidepressants in Australia and elsewhere.

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Chapter 2
Background: Depression and antidepressants

2.1 INTRODUCTION

This chapter presents more detailed information about depression and antidepressants, and outlines the current orthodoxy that promotes depression as a contemporary epidemic for which antidepressants are the cure. It also identifies some aspects of this orthodoxy that are challenged in subsequent chapters, particularly chapters 4 and 6, which analyse current debates about depression and antidepressants respectively.

The first major section of this chapter focuses on depression. There is a brief review of the history of depression and related concepts, followed by a brief discussion of first-hand accounts of the experience of depression. Then there is a very brief discussion of happiness, often considered the antithesis of depression.

Then the diagnosis, epidemiology, causes, and treatment of depression are briefly discussed. The current orthodoxy is that depression is an almost overwhelming public health problem that imposes an enormous burden on society as well as blighting the lives of millions of individuals, but it is very amenable to treatment. A common catchphrase is that depression is 'common, serious, and treatable' (Ellis, Hickie, & Smith 2003, p. 34). In addition, it is commonly claimed and accepted that depression is a brain disorder, specifically an imbalance of one or more neurotransmitters.

Antidepressants, which target neurotransmitters, are the focus of the second major section of this chapter, beginning with a brief review of the range of drugs with antidepressant properties, and the history of their use. Then the pharmacology of mainstream prescribed antidepressants is discussed in some detail, followed by the epidemiology of their prescription and use, the risks associated with their use, their effectiveness, and economic considerations.

According to the current orthodoxy, antidepressants are safe, effective, and cost-effective. It is also commonly claimed and accepted that newer antidepressants are safer and more effective and more cost-effective than older ones. Another important claim is that antidepressants are necessary when depression occurs. The mantra that depression is 'common, serious and treatable' is paralleled by the mantra that

antidepressants are 'safe and effective'; a variant is that they are 'safe, effective and not addictive' (beyondblue 2008). Claims that antidepressants are cost-effective are common in economic analyses, most of which are sponsored by pharmaceutical companies. Claims that antidepressants are necessary are often implicit, but are very powerful.

The orthodoxy about depression and antidepressants is widely accepted and promoted by many key players, particularly the medical profession, but there are some very outspoken critics of it. By outlining the orthodoxy about depression and antidepressants, this chapter lays a foundation for subsequent chapters, particularly chapters 4 to 6, which analyse key debates and challenge many aspects of the orthodoxy.

2.2 DEPRESSION

Depression is a psychological state related to unhappiness. It is characterised by sadness, lack of interest and pleasure in life (anhedonia), and other negative emotions that persist over a period of time (from weeks to decades). It is often referred to in medical and psychological literature as a 'mood disorder' or an 'affective disorder' (the noun 'affect' is a psychological term for mood or emotion). The term 'depression' is used to encompass a range of severity of negative mood. In common parlance, related terms such as 'depressed' and 'depressing' are often used to refer to relatively mild degrees of negativity that would not remotely warrant a clinical diagnosis (e.g. being 'depressed' because one's favourite sports team has lost a match).

2.2.1 History of depression

Depression has been documented for more than 2,000 years, under a variety of names including 'melancholy', 'melancholia' (Radden 2000, pp. 3), 'the vapours' (p. 168), 'acedia' (Solomon 2001, p. 293), and 'the blues'. These conditions have been defined in many different ways, overlapping to various extents, over time. Furthermore, these labels and the discourses about them have been strongly influenced by social and cultural factors (Solomon, p. 285).

Common acronyms in this chapter: ADE adverse drug event; ADR adverse drug reaction; AIHW Australian Institute of Health and Welfare; APA American Psychiatric Association; ASM Australian Statistics on Medicines; ATC Anatomical Therapeutic Chemical; CDHAC Commonwealth Department of Health and Aged Care; DDD defined daily dose; DoHA Department of Health and Ageing; DSM Diagnostic and statistical manual of mental disorders; ICD International Classification of Diseases; MAOI monoamine oxidase inhibitor; NCS-R National Comorbidity Survey – Replication; NIMH National Institute of Mental Health; NSMHW National Survey of Mental Health and Wellbeing; PBS Pharmaceutical Benefits Scheme; RPBS Repatriation Pharmaceutical Benefits Scheme; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant; WHO World Health Organization

At times, depression has been regarded as a sign of weakness (Jadhav 1996) – a moral failing. Such attitudes persist to some extent today (Hickie 2006), but depression is increasingly regarded as a legitimate psychiatric disorder (or mental illness) (Parslow & Jorm 2002; Goldney et al. 2005). Unfortunately, as discussed in chapter 4, the debate has generally taken for granted a false dichotomy that stipulates that depression must be *either* a moral failing *or* a medical disorder, without any other possibilities.

According to Radden (2000, pp. 22-24), around 1890 the term depression was used to refer to one symptom of melancholia, but by 1913 it was viewed as a symptom cluster or disease, and shortly thereafter it eclipsed melancholia as a diagnostic term. Surprisingly, from today's perspective, depression was considered a relatively rare disorder until about 1980 (Healy 2004, p. 4). However, a variety of emotional maladies such as 'anxiety disorders', 'nerves', 'nervous breakdowns' (p. 4), 'neurosis' (Tyrer et al. 2003), and 'suburban neurosis' (Manne 2003, p. 47) were commonly diagnosed during much of the twentieth century. These terms emphasise anxiety rather than depression. However, what was defined as anxiety disorders in previous decades would frequently be defined as depression today (Healy 2000). Furthermore, there is an ongoing debate about whether or not anxiety disorders and depression are separate entities (Pilgrim & Bentall 1999, p. 264; Shorter & Tyrer 2003). Consequently, historical conceptualisations of and attitudes towards anxiety disorders are relevant to the history of depression.

A turning point in depression's twentieth century trajectory was a 144-page hardback book, *Recognizing the depressed patient* (Ayd 1961), written by a prominent US psychiatrist, Frank J. Ayd. Fifty thousand copies of it were distributed world-wide by Merck, the manufacturer of a new antidepressant, amitriptyline (Healy 2004, p. 8). This was an early example of 'selling' a disorder in order to sell a drug. Depression diagnosis has escalated ever since, as have prevalence estimates (Bland 1997). Furthermore, depression has become a staple psychiatric diagnostic category, 'the common cold of psychopathology' (Seligman 1975).

In addition, depression has become remarkably prominent in the media and in the public domain more generally in recent decades. According to Macken (2006), among others, it is 'the malady du jour'.

2.2.2 Experiences of depression

The experience of depression is painful. It often includes feelings such as low self-esteem, guilt, lethargy, and suicidal ideation (thinking) (Ellis & Gordon 2004). Styron's (1992, p. 50) description of his pain and the resultant suicidal ideation is widely quoted:

> mysteriously and in ways that are totally remote from normal experience, the gray drizzle of horror induced by depression takes on the quality of physical pain. But it is not an immediately identifiable pain, like that of a broken limb. It may be more accurate to say that despair, owing to some evil trick played upon the sick brain by the inhabiting psyche, comes to resemble the diabolical discomfort of being imprisoned in a fiercely overheated room. And because no breeze stirs this caldron, because there is no escape from the smothering confinement, it is entirely natural that the victim begins to think ceaselessly of oblivion.

In a remarkably eloquent account of suffering, a member of an online depression support forum likened depression to 'emotional haemophilia' and 'a civil war of the self' (Cedric 2006):

> Depression, plainly put, is constant psychological pain. I think an accurate comparison can be drawn with haemophilia. Normal human beings are equipped with highly efficient physiological mechanisms to repair bodily injury, eradicate wounds and clot the blood. But our body is skilled at repairing emotional wounds, too. A crucial tool in this essential maintenance work is memory, for instance. People who have gone through deep trauma often do not remember at all what happened, simply because the brain has done its job of repairing the mental damage by erasing any memory of the event and facilitating the self-healing process. Rationalisation is another process at the disposal of the mind to cope with the uncopeable. In normal circumstances, people are duly equipped by their body with all the mental facilities necessary to "get on with it" and be able to unload most of life's frustrations, all the bruises and cuts of the emotional world. These are forgotten, or "gotten over", easily enough by depressive standards.
>
> Depressives, however, are devoid of this all-important healing mechanism. They cannot even begin to comprehend the meaning of "getting over" anything. The slightest (especially negative) event is ruthlessly recorded and replayed in the depressive's mind with maddening circularity. He [sic] is always left alone and at the mercy of his own festering feelings. Because of this relentless hurting, the mental equivalent of the tender and sore skin that forms on top of a raw wound, depressives develop an unusually heightened sensitivity and start monitoring everything without realising it. For depressives, there is no taking

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> for granted, no letting by-gones be by-gones, no putting things on the back burner, no end to the longing. Everything always firmly occupies the forefront of their thoughts, like a bullet in the brain. Depression is emotional haemophilia. Every single blow hurts deeply and the depressive just bleeds. And bleeds. Everything stays in his mind for weeks and becomes worse with every passing day. The wounds never heal. Depression is a civil war of the self. The depressive's life is a constant and desperate struggle, waged microsecond after microsecond, against the demons inside his head.

Depressed people commonly withdraw from the world, at least to some extent, both physically and emotionally. Karp (1996) interviewed fifty people who identified themselves as having been diagnosed with depression. His analysis, informed by symbolic interactionism, resulted in a rich description of diverse experiences. However, a key theme that emerged very consistently was that 'depression is an illness of isolation, a dis-ease of disconnection' (p. 15), a theme that accorded with Karp's own experience of depression (p. 7).

Often the isolation is actively sought as well as painfully experienced. An anonymous young Australian woman described her experience of wanting to withdraw from the world because of the aversive impact of the minutiae of daily life:

> My depression is like not having a skin. Anything and everything feels like an assault; loud noise, loud voices, too many people, everything just seems incredibly intense and overwhelming. You want everything to go away (Wilde 2006)

Some people use metaphors of living entities to describe depression, locating depression outside themselves. Winston Churchill famously referred to his depression as his 'Black Dog' (McKinlay 2005). Solomon (2001) referred to his as 'the noonday demon'. He also described it as a suffocating vine: 'a sucking thing that had wrapped itself around me, ugly and more alive than I. It had had a life of its own that bit by bit asphyxiated all the life out of me' (p. 18).

Many writers have described their experiences of depression through fiction. One classic is Charlotte Gilman Perkins' (1981 [1892]) novella *The yellow wallpaper*. The wallpaper of the title represented both depression and the stifling societal expectation that women would confine themselves to the domestic sphere. Gender is undoubtedly a key social dimension in relation to depression (Fullagar & Gattuso 2002), and a number of gender issues are briefly discussed in this and subsequent chapters, but a detailed analysis is beyond the scope of this thesis.

More recently, J. K. Rowling used the prison Azkaban and its loathsome guards, the Dementors, as metaphors for depression in her Harry Potter books:

> Her experience with depression made a lasting impact on her and inspired the Dementors that first appear in Prisoner of Azkaban. On depression, Rowling said, "It is that absence of being able to envisage that you will ever be cheerful again. The absence of hope. That very deadened feeling, which is so very different from feeling sad." (Linsenmayer 2002)

A classic depressed character in children's literature is A. A. Milne's (1926) Eeyore, the endearingly gloomy donkey (Shea et al. 2000). One of the characters in *Red Dwarf*, the British comedy science fiction television series, is a rather depressed cyborg, Kryten. Although both characters are humorous, it would not be surprising if they reflected some real life experience of their creators.

Depression often includes feelings of worthlessness and self-loathing. The 19th century English/Irish poet Gerard Manley Hopkins vividly expressed self-loathing in these lines in his poem 'I wake and feel the fell of dark, not day':

> I am gall, I am heartburn
> God's most deep decree bitter would have me taste; my taste was me.

Another of his poems, 'No worst, there is none', contains these lines, which describe a painful introspection that cannot be understood by someone who has not personally experienced it:

> O the mind, mind has mountains; cliffs of fall
> Frightful, sheer, no-man-fathomed. Hold them cheap
> May who ne'er hung there.

The theme that only people who have experienced depression can understand it has been stated by a number of prominent authors:

> Until one has experienced a debilitating severe depression it is hard to understand the feelings of those who have it. (Wolpert 1999, p. 1):

> Depression is a disorder of mood, so mysteriously painful and elusive in the way it becomes known to the self – to the mediating intellect – as to verge close to being beyond description. It thus remains nearly incomprehensible to those who have not experienced it in its extreme mode (Styron 1992, p. 7)

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This important claim is sometimes used to suggest that people who question the nature and impact of depression are ignorant because they have not personally experienced depression. Along with other criticisms of people who challenge the orthodoxy about depression, this is discussed in chapter 4.

Clearly, for some people, depression is a very negative state indeed. However, it is often relatively mild (Hegarty 2005, p. 8) and relatively brief (Patten 2001; Spijker et al. 2002), and self-limiting, in that most people recover relatively quickly (Kendler et al. 1997).

2.2.3 Happiness

Before concluding this discussion of what depression is, it is worth briefly discussing what is perhaps its antithesis, happiness. Until a few years ago, happiness had been researched much less than depression. However, there is now a rapidly growing literature on it (Veenhoven 2005).

It has been argued both that happiness and depression are polar opposites on the same continuum and, in contrast, that they are different entities that need to be measured separately (Joseph & Lewis 1998, p. 539). This debate is complex, and is beyond the scope of this thesis.

As an aside, Bentall (1992) provocatively suggested that happiness should be classified as a psychiatric disorder, because it is abnormal and it impairs rational judgement:

> It is statistically abnormal, consists of a discrete cluster of symptoms, there is at least some evidence that it reflects the abnormal functioning of the central nervous system and it is associated with various cognitive abnormalities – in particular, a lack of contact with reality. (p. 97).

Bentall's argument amusingly highlights the contestable and value-laden foundations of psychiatric diagnosis, which are discussed in chapter 4.

2.2.4 Depression diagnosis

In psychiatry, depression is currently formally defined by two main sets of diagnostic criteria: the *Diagnostic and statistical manual of mental disorders* (4th ed.) (DSM-IV) of the American Psychiatric Association (APA) (1994) and the *International Classification of Diseases* (10th ed.) (ICD-10) (World Health Organization (WHO) 1993). The ICD-10, which includes physical as well as mental disorders (unlike the

DSM-IV[1]), is the official classification system in Australia, but many psychiatrists use the DSM-IV instead (Andrews et al. 1999, p. 2). The two systems are structured similarly, but agreement between them is by no means perfect (p. 2). However, according to Stefanis & Stefanis (2002, p. 6), the ICD-10 and DSM-IV criteria can be used interchangeably in clinical practice, despite differences in terminology.

Many different types of depression have been identified over the years. There is ongoing confusion and debate about which types are valid (Kendell 1976; Kramer 2002; Parker 2000a). However, there is general acceptance of the most important distinction currently, between unipolar affective disorder (which is what most people mean when they mention depression) and bipolar affective disorder. Unlike unipolar depression, bipolar disorder, which until recent years was generally referred to as 'manic depression', is characterised by periods of excessively positive ('manic') states as well as periods of depressed mood. It is less common than unipolar depression (Jablensky et al. 2000, p. 221), and generally more debilitating (p. 222). Antidepressants are used much less often for bipolar disorder than for unipolar depression, and there is less evidence of their efficacy (Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Bipolar Disorder 2004, p. 287). Furthermore, some experts argue that antidepressant monotherapy is inappropriate for bipolar disorder because of the risk of inducing mania (Das et al. 2005, p. 956). Bipolar disorder is only peripherally considered in this thesis, which focuses on unipolar depression and antidepressants.

Another significant distinction is between endogenous (biological) depression (attributable to individual physiological characteristics, and generally considered to be genetically based) and exogenous (reactive) depression (caused by negative life events). This currently receives much less attention than the unipolar/bipolar distinction, and is dismissed by some psychiatrists as irrelevant (Kramer 2002). However, the distinction is championed by prominent Australian psychiatrist Professor Gordon Parker (2000a).

[1] The DSM-IV records physical illnesses on the third of its five axes, but does not diagnose them.

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The ICD-10 lists seven main types of depressive disorder: F30 Manic episode, F31 Bipolar affective disorder, F32 Depressive episode, F33 Recurrent depressive disorder, F34 Persistent mood (affective) disorders, F38 Other mood [affective] disorders, F39 Unspecified mood (affective) disorder (WHO 1993, pp. 89-107). All but the last have a number of subtypes. F32 Depressive episode and F33 Recurrent depressive disorder are the most relevant to this thesis.

The DSM-IV distinguishes 'depressive disorders' (dysthymic disorder, major depressive disorder, and depressive disorder not otherwise specified), which are centrally relevant to this thesis, from 'bipolar disorders' (bipolar disorder and cyclothymic disorder). The DSM-IV also allows for finer differentiations. For example, within major depressive disorder, distinctions can be made between recurrent and single episode and between severe with and without psychotic features.

These DSM-IV diagnoses are axis I disorders, which are clinical disorders. There are fourteen categories of axis I disorders: adjustment disorders, anxiety disorders, childhood disorders, cognitive disorders, dissociative disorders, eating disorders, factitious disorders, impulse control disorders, mood disorders, psychotic disorders, sexual and gender identity disorders, sleep disorders, somatoform disorders, and substance-related disorders. Some of these, particularly psychotic disorders and dissociative disorders, would be considered by almost everyone to be psychiatric disorders; the status of others, particularly sexual and gender identity disorders and adjustment disorders, is more controversial.

DSM-IV also includes axis II disorders (personality disorders mental retardation), axis III (general medical conditions), axis IV (psychosocial and environmental problems), and axis V (global assessment of functioning).

In this thesis, the major focus is on major depression and dysthymia (chronic mild depression), for which the most likely diagnoses would be: DSM-IV major depressive episode, major depressive disorder, and dysthymic disorder; and ICD-10 depressive episode and recurrent depressive disorder. The criteria for these disorders are given in appendices 1 and 2 respectively. Notably, only two weeks' duration of symptoms are required for a diagnosis of DSM-IV major depressive disorder,[2] which is increasingly constructed as a chronic disorder (Andrews 2001; Joiner 2000), despite the fact that

[2] In ICD-10, one two-week episode is required for a diagnosis of depressive *episode*; a second such episode is required for a diagnosis of recurrent depressive *disorder* (WHO 1993).

the duration of many cases is quite short (Patten 2001). Claims of chronicity are briefly discussed in chapter 4.

As discussed later in this chapter (section 2.3.4), many antidepressant prescriptions are for 'chronic mild depression' and other forms of depression that do not meet DSM-IV criteria for major depressive disorder (McManus et al. 2003, p. 188; Ornstein, Stuart, & Jenkins 2000). Partly for that reason, the term 'depression' is used in this thesis to include dysthymia as well as major depression. However, where relevant, distinctions are made between major depression and dysthymia.

Notably, depression was not listed as a specific diagnostic entity in the first two editions of the DSM (Hirshbein 2006, p. 188). The nearest equivalents were 'neurotic depressive reaction' and 'depressive neurosis' in DSM-I (APA 1952) and DSM-II (APA 1968, p. 40) respectively. The significance of diagnostic changes is discussed in chapter 4.

Standardised scales are often used to diagnose and assess depression. Prominent among these are the Beck Depression Inventory (Beck et al. 1961), the Hamilton Depression Rating Scale (Hamilton 1960), and the Montgomery-Asberg Depression Rating Scale (Montgomery & Åsberg 1979). These scales are commonly used in antidepressant trials – indeed some were developed specifically for that purpose (Demyttenaere & De Fruyt 2003). There has been considerable criticism of depression scales (Kurdyak & Gnam 2005; Bagby et al. 2004; Healy 2004; Levine 2007). This is discussed briefly in chapter 6.

2.2.5 Epidemiology of depression

Depression is a relatively commonly diagnosed psychiatric disorder (Kessler et al. 2003, p. 3095; Andrews et al. 1999, p. 7; Hickie, Davenport, Naismith, & Scott 2001, p. S4), and there is some evidence that it is becoming more common (Bland 1997; Lewinsohn et al. 1993). Anxiety disorders are also relatively common. Depression and anxiety disorders are sometimes referred to as high prevalence, low impact disorders (Webb 2001, p. 9), in contrast to much less prevalent disorders such as psychoses (including schizophrenia), which are generally more debilitating.

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In Australia, the second National Survey of Mental Health and Wellbeing (NSMHW) found 12-month prevalences of 6.2% for affective (mood) disorders and 14.4% for anxiety disorders, and lifetime prevalences of 15% and 26.3% respectively (Slade et al. 2009, p. 5), among adults aged 16-85. Affective disorders were defined as depressive episode, dysthymia, and bipolar affective disorder (p. xi). Women were more likely than men to experience affective disorders (7.1% versus 5.3%) and anxiety disorders (17.9% versus 10.8%), but men were more likely to have substance use disorders (7% versus 3.3%) (p. 5).

The first NSMHW had found that, among adults, the 12-month prevalence of affective (mood) disorders and anxiety disorders was approximately 5.8% and 9.7% respectively (Andrews et al. 1999, p. 7). Women had higher rates than men of both affective disorders (7.4% versus 4.2%) and. anxiety disorders (12% versus 7.1%).

The Child and Adolescent Component of the first NSMHW (which was not repeated as part of the second survey) found that the 12-month prevalence of depressive disorder among children and adolescents was 3.7% (Sawyer et al. 2000, p. 20).

In the US, a number of large-scale surveys have provided estimates of the prevalence of depression in the general population. Most significantly, the National Comorbidity Survey – Replication (NCS-R) (Kessler & Merikangas 2004; Kessler et al. 2004), reported a lifetime prevalence of 16.2% and a 12-month prevalence of 6.6% (Kessler et al. 2003, p. 3095).

Despite depression's lower impact than psychosis at an individual level, its impact at an aggregate level is claimed to be a substantial public health and economic issue. According to the WHO, unipolar major depression was the fourth leading cause of disease-burden (a single measure of premature death and years lived with disability) world-wide in 1990 (Murray & Lopez 1996, p. 4) and the leading cause of years lived with a disability (p. 21). Furthermore, it was projected that by 2020 unipolar major depression will be the second leading cause of disease-burden worldwide (p. 4). Partly because of that projection, depression has been referred to as a 'Social and economic timebomb' (Dawson & Tylee 2001).

There have been similar projections about depression in Australia. Mathers, Vos, & Stevenson (2000), using similar methods, found that depression was the fourth leading cause of disease burden in Australia in 1996, and the top-ranking cause of

non-fatal disease burden, causing 8% of the total years lost due to disability. Depression rose from the tenth most common problem managed in general practice in 1990-91 to the fourth most common in 1998-99 (McManus et al. 2000). It is also a significant cause of mortality through suicide, and in recent years it has been suggested that it is a significant contributor to heart disease, diabetes, and other physical diseases (Centers for Disease Control and Prevention 2005).

Such epidemiological and economic findings are widely used to support claims that depression is common and serious. Partly as a result of such findings, depression became a major focus of Australian mental health policy in the late 1990s (Australian Health Ministers, 1998, p. 11; Commonwealth Department of Health and Aged Care (CDHAC) & Australian Institute of Health and Welfare (AIHW) 1999; CDHAC 2000/2001).

The epidemiology of depression is discussed further and critiqued in chapter 4. The validity of many claims is analysed with reference to findings of population surveys, particularly the US NCS-R and the Australian NSMHW. Other relevant sources of evidence include some very significant epidemiological studies focusing specifically on depression, such as the NIMH Treatment of Depression Collaborative Research Program (Elkin et al. 1985).

2.2.6 Causal factors

Many causes of depression have been postulated and investigated. Some relationships have been found to be robust, others more equivocal. Depression is strongly linked to gender: women are significantly more likely to experience depression. This is usually attributed to biological sex differences, but this interpretation is disputed by some, including Fullagar and Gattuso (2002), who argue that sociocultural factors are very important (and neglected).

A significant body of research has demonstrated an inverse relationship between socioeconomic status and depression prevalence (Lennon et al. 2001, p. 40; Muntaner et al. 2004). There is also evidence of the importance of other social factors such as

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unemployment (Rodriguez, Frongillo, & Chandra 2001; Gilmer et al. 2005) and childhood adversity (Brown 2002).

However, in research and clinical practice, there is an increasingly dominant focus on biological causes of depression, typified by the serotonin hypothesis of depression (which is briefly critiqued in chapter 4). This is in keeping with the increasing hegemony of biological psychiatry (Ross & Pam 1995; Read 2005), according to which psychiatric disorders are disorders of the brain (and according to many advocates, they are genetically based). Despite its wide acceptance, biological psychiatry has been criticised for being reductionist (Herlihy & Gandy 2002), and because it is strongly linked to pharmaceutical industry profit agendas. Furthermore, it is highly compatible with neoliberal individualistic political ideologies (Moncrieff 2006). This deflects attention from social determinants of mental health and privileges medical treatment, particularly antidepressants, as the appropriate response

2.2.7 Treatment

General practitioners provide the majority of treatment for depression (McManus et al. 2003, p. 184) and other mental health problems (Regier et al. 1978, 1993; Keks & Burrows 1998; Andrews et al. 1999) but are often inadequately trained to do so (Department of Health and Ageing (DoHA) 2002, p. 154). Many people who suffer from depression (among other disorders) are undiagnosed, and their depression is not directly treated (Henderson et al. 2000, p. 197; Hickie et al. 2001; Olfson et al. 2002). In fact, a major theme of the depression treatment literature is that depression is seriously undertreated and there is an urgent need to encourage people to seek help. According to Hirschfeld et al. (1997, p. 333):

> There is overwhelming evidence that individuals with depression are being seriously undertreated. Safe, effective, and economical treatments are available. The cost to individuals and society of this undertreatment is substantial. Long suffering, suicide, occupational impairment, and impairment in interpersonal and family relationships exist.

The validity (and power) of such claims of undertreatment are analysed in chapter 4. Two reasons frequently given for undertreatment of depression are stigma and low mental health literacy, both of which discourage people from seeking treatment. These are also discussed in chapter 4.

The majority of people who do receive treatment for depression are prescribed antidepressants (AIHW 2004, p. 211; Wilson et al. 2003, p. 685; MacGillivray et al. 2003; North of England Antidepressant Guideline Development Group 1997). GPs prescribe 85% per cent of antidepressants in Australia (McManus et al. 2000, p. 458), and they prescribe the majority of antidepressants in many countries, including the US (Mojtabai & Olfson 2008) and Italy (Percudani et al. 2004). Consequently there is a major focus on GPs in this thesis.

Non-pharmacological treatments are less likely to be used, for a variety of reasons. Structural factors such as the Australian Medicare rebate system encourage prescribing psychotropics rather than offering non-pharmaceutical interventions such as counselling and cognitive behaviour therapy, let alone the social supports that are so often needed. However, this has changed in recent years in Australia, since the establishment of the Better Outcomes in Mental Health Care program (briefly discussed in chapter 3).

The prognosis (outcome) of depression is variable. Expert opinions range from very bleak (Joiner 2000) to relatively optimistic (Patten 2001; Zeiss & Lewinsohn 2000). There is disagreement about a range of prognostic issues, including the duration of depression, the risk of suicide (the most dramatic risk associated with depression), the impact of depression on physical health, and the impact of detection and treatment on outcome. There is considerable epidemiological evidence, particularly from longitudinal community studies, that challenges mainstream clinical opinion. Suicide risk is discussed in chapter 5; other prognostic issues are discussed in chapter 4.

2.3 ANTIDEPRESSANTS

Antidepressants are psychotropic (mind-altering) drugs that affect mood and cognition and are used to alleviate depression. They are sometimes referred to as 'happy pills' (Crompton 2003; Walsh 2004). Usually the term 'antidepressants' refers to mainstream *prescribed* antidepressants. These are the main focus of this thesis and are discussed in some detail below.

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However, historically, and across cultures, a wide variety of other drugs have also been used for their antidepressant properties, both as medically prescribed treatment and on a self-help basis. Physical treatments (e.g. acupuncture), lifestyle interventions (e.g. exercise), and dietary changes (e.g. sugar avoidance) are also used by significant numbers of people (Jorm et al. 2002). However, for many drugs and other interventions, there is little evidence of effectiveness (Jorm et al. 2002).

Nonmedicinal drugs (often referred to as 'recreational' drugs)[3] are frequently used for their antidepressant effects. Such drugs range on a legal continuum from over-the-counter remedies and licit recreational drugs (particularly alcohol and tobacco), to illicit drugs. The legal status of some drugs has varied over time, as discussed below.

Probably the earliest drug used as an antidepressant was alcohol, which has been used for many purposes by humans since prehistoric times (Mendelson & Mello 1986, p. 13). Despite its common use for entertainment and celebration, and its perceived stimulant effects, alcohol is actually a *depressant* drug (Bryant, Knights, & Salerno 2003, p. 367) and, in the medium to long term, excessive alcohol use often causes or exacerbates depression (Gilman & Abraham 2001; Lennane 1992, p. 110). However, alcohol can have short-term antidepressant effects, and it is often used as a coping mechanism by depressed people (Carpenter & Hasin 1999; Holahan et al. 2004; Jorm et al. 2002, p. S93). Alcohol *avoidance* is also used by some people as an antidepressant strategy (Jorm et al. 2002, pp. S92-S93), most commonly by people who have previously drunk excessively over an extended period of time.

Another licit recreational drug that can have antidepressant properties is nicotine (Klimek et al. 2001; Bech 2002), which is a stimulant. It is deliberately used as an antidepressant by some people (Niaura et al. 1999, p. 251), and it is well documented that many people with a history of depression become depressed (or more depressed) when they quit smoking (Wilhelm et al. 2006; Glassman et al. 2001). For people without a history of depression, nicotine's antidepressant action may become apparent in its absence, when they quit smoking and experience some degree of temporary depression (Pomerleau et al. 2000).

[3] I use the terms nonmedicinal and recreational interchangeably. Neither is entirely satisfactory. Many such drugs have medicinal properties (e.g. pain relief), and such drugs are used for many purposes other than recreation (e.g. wine in Communion).

Caffeine also has antidepressant effects (Bryant et al. 2003, p. 323). It was a key ingredient in the compound analgesics that were heavily promoted to Australian women from the 1950s to the 1970s as the solution to everyday stresses (Hennessey 1993). Like many other antidepressants, caffeine has significant dependence potential (p. 6).

Other over-the-counter (OTC) drugs continue to be used as antidepressants (among other purposes). Current legal but controversial OTC antidepressants include St John's wort (Mitchell 1999), which is discussed in chapter 6, and S-adenosyl-l-methionine (SAMe) (Bressa 1994).

Several drugs that are now illicit or very highly regulated in many western countries have long histories as antidepressants, including cannabis (Grinspoon & Bakalar 1997) and amphetamines (Breggin & Breggin, 1994, p. 104). In the nineteenth century and early twentieth century, then-licit opioids such as morphine and opium were commonly used to treat 'melancholia' (Feinberg, Pegeron, & Steiner 1982; Weber & Emrich 1988), both by doctors and by the general public, who used opioid-containing patent medicines (Healy 2002, pp. 34, 58). As recently as 1955, Skottowe, in *The Lancet*, recommended the use of opium (and amphetamines) for mild depression. The use of such drugs to alleviate depression continues (Abraham & Fava 1999; Weiss, Griffin, & Mirin 1992; Sbrana et al. 2005) despite their changed legal status. A much more recent illicit 'happy pill' is ecstasy (MDMA) which is pharmacologically similar to some prescribed antidepressants (*The Economist* 1996), but its potential use as an antidepressant is stymied by politics (Sessa & Nutt 2007).

The use of drugs other than prescribed antidepressants for mood enhancement is often referred to as 'self-medication'. Self-medication is sometimes effective, but it is often frowned upon to varying degrees (depending on drug choice). Often the disapproval takes the form of medicalisation (e.g. treating it as an 'addiction') and/or criminalisation.

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2.3.1 Pharmacology of antidepressants

Pharmacology is the study of the composition of drugs and how they act in living organisms. Most pharmacology focuses on medicinal drugs, particularly prescribed drugs. Classification of drugs is fundamental to pharmacology, but it is not as straightforward as might be expected, because it can be approached from many different perspectives (Bryant et al. 2003, p. 13). This complexity is not particularly relevant to this thesis, for the purposes of which the following clinically based classification (adapted from Diamond 1998, pp. 2, 15-17) is useful. From this clinical perspective, the main types of prescribed psychotropic drugs are:

1. antipsychotics (neuroleptics, major tranquillisers): traditional antipsychotics (e.g. chlorpromazine), atypical antipsychotics (e.g. Zyprexa® (olanzapine), Seroquel® (quetiapine), and Risperdal® (risperidone))
2. side-effect medications (antiparkinsonian medications): anticholinergics (e.g. benztropine), diphenhydramine, amantadine
3. antidepressants: selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, newer antidepressants
4. mood stabilisers: lithium, carbamazepine, valproic acid, newer anticonvulsants
5. anti-anxiety medications (anxiolytics) and sleeping pills: benzodiazepines (e.g. Valium® (diazepam)), buspirone, meprobamate, barbiturates

There are also miscellaneous other prescribed psychotropics, including beta-blockers, stimulants, and pharmacotherapies for alcohol and other drug-related problems (particularly dependence) (e.g. methadone, naltrexone, nicotine patches).

Many other drugs used for non-psychotropic purposes also have some psychotropic effects, which are generally regarded as undesirable side-effects. For example, many prescribed drugs can cause dizziness (Anderson et al. 1995).

Until the middle of the 20th century, prescribed psychotropics were used primarily for sedation. Then the first specific psychotropic, lithium, was found to be effective for mania (one pole of what is now called bipolar affective disorder) (Bryant et al. 2003, p. 293).

Specificity has become a very important issue in psychotropics generally, including antidepressants. Most psychotropic drugs are intended to target one or more

neurotransmitters (brain messenger chemicals, e.g. serotonin, the focus of the dominant serotonin hypothesis of depression), acting to increase or decrease the activity of the neurotransmitter(s). The most important neurotransmitters are acetylcholine, dopamine, epinephrine (adrenalin), norepinephrine (noradrenalin), and serotonin (Diamond 1998, p. 17).

The main focus in this thesis is of course on the third category in Diamond's classification, antidepressants. However, prior to the development of the first mainstream antidepressants in the 1950s, several other types of prescribed psychotropic drugs, including bromides and barbiturates, were used extensively for the treatment of anxiety and other common forms of psychological distress (Healy 2004, p. 4). Benzodiazepines became prominent in the 1960s and 1970s (p. 5), and by 1985 were commonly used for patients with a diagnosis of depression (Johnson 1985). Therefore historical benzodiazepine use is relevant to antidepressant use, just as historical conceptualisations, diagnosis, and treatment of anxiety disorders are relevant to depression.

The use of benzodiazepines for depression is much less common currently, mainly because of awareness of the dependence potential and other risks of these drugs (Committee on Safety of Medicines 1988) and because of the promotion of antidepressants. In contrast, antidepressants are increasingly being used for the treatment of anxiety disorders (Arikian & Gorman 2001, p. 112), partly related to the expiry of patents for antidepressants used for depression.

Atypical antipsychotics such as olanzapine are now commonly marketed as 'mood stabilisers' and promoted as treatment for bipolar affective disorder, despite not being included in Diamond's (1998) mood stabiliser category. They are also increasingly being promoted for unipolar depression (CL Psych 2007; Healy 2009). This development, which is also related to loss of patent protection for mainstream antidepressants, is worrying but is beyond the scope of this thesis.

Common acronyms in this chapter: ADE adverse drug event; ADR adverse drug reaction; AIHW Australian Institute of Health and Welfare; APA American Psychiatric Association; ASM Australian Statistics on Medicines; ATC Anatomical Therapeutic Chemical; CDHAC Commonwealth Department of Health and Aged Care; DDD defined daily dose; DoHA Department of Health and Ageing; DSM Diagnostic and statistical manual of mental disorders; ICD International Classification of Diseases; MAOI monoamine oxidase inhibitor; NCS-R National Comorbidity Survey – Replication; NIMH National Institute of Mental Health; NSMHW National Survey of Mental Health and Wellbeing; PBS Pharmaceutical Benefits Scheme; RPBS Repatriation Pharmaceutical Benefits Scheme; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant; WHO World Health Organization

Classification of mainstream antidepressants is not straightforward, and many different classes are mentioned in the literature. However, Diamond's (1998, p. 16) four classes are widely recognised by key stakeholders:

- selective serotonin reuptake inhibitors (SSRIs), e.g. Prozac® (fluoxetine) and Zoloft® (sertraline)
- miscellaneous 'new generation' antidepressants, e.g. Desyrel® (trazodone), Serzone® (nefazodone), and Wellbutrin® (bupropion)
- tricyclic antidepressants [TCAs], e.g. Norpramin® (desipramine) and Pamelor® (nortriptyline)
- monoamine oxidase inhibitors (MAOIs), e.g. Nardil® (phenelzine) and Parnate® (tranylcypromine)4

Less commonly mentioned are tetracyclic antidepressants (e.g. mianserin) and reversible monoamine oxidase inhibitors (e.g. moclobemide).

The Pharmaceutical Benefits Scheme[5] (PBS) *Schedule of pharmaceutical benefits* (DoHA 2011b) uses the WHO's Anatomical Therapeutic Chemical (ATC) classification (WHO 2006), with one exception: lithium carbonate is included as an antidepressant in the PBS classification but as an antipsychotic in the ATC classification. Antidepressants are classified as psychoanaleptics (stimulants), and divided into five classes somewhat different from Diamond's categories (pp. 386-395):

- Non-selective monoamine reuptake inhibitors [TCAs]: including Endep® (amitriptyline), Anafranil® (clomipramine), Prothiaden® (dothiepin), Sinequan® (doxepin), Tofranil® (imipramine), Allegron® (nortriptyline)
- Selective serotonin reuptake inhibitors [SSRIs]: including Cipramil® (citalopram), Lexapro® (escitalopram), Prozac® (fluoxetine), Luvox® (fluvoxamine), Aropax® (paroxetine), Zoloft® (sertraline)
- Monoamine oxidase inhibitors, non-selective [MAOIs]: Nardil® (phenelzine) and Parnate® (tranylcypromine)

[4] Not all of these antidepressants are or have previously been available in Australia.
[5] The PBS subsidises many prescribed drugs for Australians. It is briefly discussed in chapter 3.

- Monoamine oxidase type A inhibitors [reversible MAOIs, often referred to in the literature as RIMAs (reversible inhibitors of monoamine-oxidase-A)]: moclobemide only
- Other antidepressants (newer antidepressants plus lithium carbonate): including Cymbalta® (duloxetine), Lumin® (mianserin), Avanza® (mirtazapine), Edronax® (reboxetine), Efexor® (venlafaxine)

Every drug in the ATC classification has a 7 letter/number code. For example, sertraline's code is N06AB06. N represents the nervous system group, 06 represents psychoanaleptics, A represents antidepressants, B represents SSRIs, and 06 is sertraline's specific number (it is listed sixth out of ten SSRIs). In addition, every commercial formulation of every drug listed in the PBS Schedule has a unique item number[6]. For example, in 2009, the item numbers for sertraline were 2236Q, 2237R, 8836C, and 8837D (DoHA 2011a, p. 166).

Antidepressant classes are based on mechanisms of action. Different classes of antidepressants have different mechanisms, but most act on one or more neurotransmitters at brain synapses. The 'scientific' rationale for their use is the serotonin (or monoamine or catecholamine) hypothesis of depression: 'depression is due to a deficiency in one or other of three biogenic monoamines, namely serotonin, norepinephrine (noradrenaline) and/or dopamine' (Stahl 2000, p. 3). These neurotransmitters are cyclically released and reabsorbed, and it is argued that in depression too little is released and/or too much is reabsorbed. This hypothesis is critiqued in chapter 4.

Antidepressants supposedly act by boosting the activity of one or more of these neurotransmitters at brain synapses, by blocking their reuptake and/or inhibiting enzymes that inactivate them (Bryant et al. 2003, p. 306). TCAs block reuptake of both serotonin and norepinephrine (Stahl 2000, p. 34). SSRIs, as their name suggests, supposedly selectively inhibit the reuptake of serotonin (p. 41). MAOIs inhibit

[6] Prescription data can be accessed from the Pharmaceutical Benefits Schedule Item Reports page (https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml) of the Pharmaceutical Benefits Scheme website using these item numbers.

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monoamine oxidase, which inactivates several neurotransmitters. Newer antidepressants act somewhat differently to boost the activity of one or more neurotransmitters. Stahl (1998) outlined seven different mechanisms of action, all related to neurotransmitters.

MAOIs were the first contemporary antidepressants, developed in the 1950s. The first, iproniazid, was developed as a tuberculosis drug, but its antidepressant properties were soon noticed and utilised (Robie, 1958; Bech 2002, p. 90).[7] MAOIs are still used today, but usually only as second- or third-line antidepressants because of their adverse reaction and interaction profile (Bryant et al. 2003, p. 310).

TCAs were developed in the late 1950s. They dominated the market in the 1970s and 1980s. SSRIs, introduced in the early 1980s, now far outsell TCAs (Newton 2006).

Newer antidepressant classes such as serotonin and noradrenaline reuptake inhibitors (SNRIs or SNaRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs) (Stahl 2000, p. 85) are also increasingly being used, and newer classes again are being developed.

2.3.2 Antidepressant epidemiology

Antidepressants are commonly prescribed drugs in many countries. Furthermore, they have dominated psychotropic prescribing in recent decades, dwarfing sales of drugs for all other psychiatric disorders, according to Shorter & Tyrer (2003). In the US, the rate of antidepressant prescribing increased more than four-fold between the early 1990s and the early 2000s (Mojtabai 2008).

The Australian Government Department of Health and Ageing's (DoHA's) *Australian Statistics on Medicines* (ASM) series provides a huge amount of quantitative information about drugs prescribed in Australia since 1997, based primarily on PBS data. This provides useful trend data as well as annual data.

ASM uses the same five classes of antidepressants as the PBS Schedule (DoHAb 2011), except that lithium carbonate is classified as an antipsychotic (as is the case in the WHO ATC classification, which the ASM uses), rather than being included in the 'other antidepressants' category. ASM 2009 (DoHA 2011a) is the most recent volume.

[7] Such serendipitous discoveries are not uncommon. A particularly notable example is Viagra (sildenafil), which was originally developed for treatment of high blood pressure and angina, but its effectiveness in treating erectile dysfunction became apparent in trials (Kling 1998).

Table 1 below, drawing on the ASM series, shows the number of antidepressant prescriptions in the community (i.e. excluding hospitals) and costs (to both the Commonwealth Government and patients) of PBS-listed antidepressants from 1997 to 2008, both aggregate and broken down into the five classes.

Table 1. Antidepressant prescriptions and costs, 1997-2009

	1997	1998	1999	2000	2001	2002
Total scripts	7,504,599	8,242,199	9,054,262	10,005,572	10,897,015	11,577,456
Total costs ($)	200,354,387	234,327,831	269,175,853	315,181,233	360,117,869	390,929,049
TCA scripts	3,833,063	3,443,762	3,266,025	3,163,413	3,051,209	2,895,413
TCA costs ($)	42,071,369	26,542,841	25,127,620	24,218,085	23,831,499	23,342,114
SSRI scripts	2,756,417	3,510,890	4,312,340	5,170,280	5,955,729	6,474,867
SSRI costs ($)	115,273,280	143,544,437	173,248,412	208,888,503	241,716,038	257,644,593
MAOI scripts	48,582	42,612	42,907	39,814	38,332	29,739
MAOI costs ($)	921,461	836,815	863,291	815,259	801,224	611,669
MAOAI* scripts	611,630	611,810	562,424	485,409	410,172	343,266
MAOAI costs ($)	35,202,167	34,364,399	29,780,485	25,561,131	21,397,067	17,018,717
Other** scripts	254,907	633,125	870,566	1,146,656	1,441,573	1,834,171
Other costs ($)	6,886,110	29,039,339	40,156,045	55,698,255	72,372,041	92,311,956

*MAOAI = monoamine oxidase type A inhibitors (moclobemide only)

**Other = other antidepressants (newer antidepressants)

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Table 1. Antidepressant prescriptions and costs, 1997-2009 (continued)

2003	2004	2005	2006	2007	2008	2009
12,330,604	13,221,539	13,478,147	14,162,741	15,290,455	16,021,618	16,695,975
427,895,835	467,969,664	463,348,097	476,307,873	514,609,851	526,088,279	533,473,585
2,777,016	2,758,678	2,675,947	2,637,311	2,656,280	2,670,740	2,651,050
22,382,915	22,332,639	22,615,639	22,884,178	23,838,789	25,050,692	26,082,130
6,910,409	7,443,693	7,602,424	7,983,057	8,534,947	8,807,008	8,839,732
274,893,699	295,366,836	282,126,759	282,781,734	289,165,663	281,022,153	262,171,128
24,738	26,623	26,369	25,164	24,764	25,485	24,516
726,313	1,281,120	1,377,825	1,839,468	1,835,026	1,950,627	2,078,204
288,095	251,104	216,254	195,327	185,745	173,670	153,427
12,860,835	11,212,960	9,300,150	7,748,120	6,238,485	5,525,695	4,493,858
2,330,346	2,741,441	2,957,153	3,321,882	3,888,719	4,344,715	5,027,250
117,032,073	137,776,109	147,927,724	161,054,373	193,531,888	212,539,112	238,648,265

NB: Sertraline scripts were incorrectly categorised as selective monoamine reuptake inhibitors rather than SSRIs in ASM 2009 (DoHA 2011a, p. 164). It is correctly included in SSRI prescriptions and costs in this table.

Total antidepressant prescriptions increased from 7.5 million to nearly 16.7 million (122% increase) between 1997 and 2009. Their cost increased from $200 million to $533.5 million (167% increase) over the same period.

TCA scripts and costs and MAOI scripts declined significantly between 1997 and 2007. SSRI scripts and costs increased 210% and 151% respectively. Scripts and costs of 'other antidepressants' increased most dramatically, partly because newer antidepressants are usually more expensive (this is true of most drug classes (Shireman et al. 2005)) but partly because the number of these antidepressants in the market increased between 1997 and 2003.

It is worth noting that nervous system (primarily psychiatric) drugs generally are the second most frequently prescribed group of PBS/RPBS[8] subsidised drugs in Australia.

[8] Repatriation Pharmaceutical Benefits Scheme: as discussed in chapter 4, the RPBS is closely related to the PBS, but it provides free pharmaceuticals exclusively to ex-service (military) personnel.

In 2007, there were 36 million prescriptions for nervous system drugs (more than 15 million of them being antidepressants), This represents 19% of the 186 million total prescriptions (DoHA 2009a, p. 22). Only cardiovascular drugs (63 million prescriptions) were more frequently prescribed.

Sertraline, an SSRI marketed in Australia by Pfizer as Zoloft, is particularly commonly prescribed and used. In 2004-2005, it was the tenth most commonly subsidised drug in Australia (Australian Prescriber 2006). In 2007, it was the seventh most commonly used drug (DoHA 2009a, p. 24). Both figures are based on defined daily doses per 1000 population per day (DDDs/1000/day). A drug's DDD is based on its assumed average daily dose drug when used for its main indication (medical condition) by adults (DoHA 2009a, p. 7). DDDs are much more accurate measurement units than prescriptions, which can vary in dose and quantity.

Another key source of information about antidepressant use in Australia is a series of studies by McManus and colleagues, many of whom were members of the Antidepressants Working Group convened in 1998 by the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee, in the Department of Health and Aged Care. This group included academics and industry representatives as well as DHAC employees.

The first study published (McManus et al. 2000) investigated patterns of antidepressant use in Australia between 1990 and 1998 and compared them with patterns in similar developed countries. The number of prescriptions increased 61%, from 5.1 million to 8.2 million prescriptions (p. 458). More importantly, the use of antidepressants in terms of defined daily doses (DDDs/1000/day) in Australia trebled between 1990 and 1998, mainly due to rapid uptake of the more expensive selective serotonin reuptake inhibitors, which tend to be prescribed more closely in line with DDDs (p. 461). There was a decrease of only 25% in the use (DDDs/1000/day) of tricyclics (p. 458). McManus et al. attributed the rapid uptake of new antidepressants to 'increased awareness, together with the availability and promotion of new therapies' (p. 458). The Royal Australian and New Zealand College of Psychiatrists and Society of Hospital Pharmacists of Australia 2001) attributed the increase in antidepressant

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prescribing to 'a greater awareness of depression, the availability of drugs with fewer side effects and improved acceptance of medication as a therapeutic option'.

The increase in antidepressant prescribing has been accompanied by a decrease in benzodiazepine prescribing, which fell from 33.96 DDD/1000/day in 1990 (Mant et al. 1993, p. 345) to just over 25 DDD /1000/day in 1998 (CDHAC 1999a, p. 249). The displacement of benzodiazepines by antidepressants, and TCAs by SSRIs, conforms to a well established historical pattern of psychotropic succession that is discussed in chapter 6.

Antidepressant use has also escalated significantly in England (Middleton et al. 2001; Double 2002, p. 900), Canada (Hemels et al. 2002), the United States (Pirraglia et al. 2004; Olfson et al. 2002), Italy (Ciuna et al. 2004), and the Netherlands (Meijer et al. 2004), among many other countries.

2.3.3 Reasons for prescribing antidepressants

Not surprisingly, antidepressants are used primarily to treat depression (McManus et al. 2003; Loosbrock et al. 2002). However, they are also used for other indications. According to Patten et al. (2007), approximately a third of antidepressant recommendations by Canadian office-based physicians are for reasons other than depression. SSRIs in particular are increasingly being used for psychiatric disorders other than depression, including anxiety disorders (Pfizer Australia 2006, p. 7). SSRIs and non-selective MAOIs are sometimes prescribed for 'social phobia' or 'social anxiety disorder' (Scott 2006, p. 138), as is the reversible MAOI moclobemide (Moynihan et al. 2002, p. 888). SSRIs are prescribed for 'shopaholism' (Lee & Mysyk 2004, p. 1713). Other uses of antidepressants include treatment of premature ejaculation (Tignol et al. 2006), irritable bowel syndrome (Mikocka-Walus et al. 2006), enuresis (bed-wetting) (Rushton et al. 2000), and pathological gambling (Hollander et al. 1998).

Antidepressants are also prescribed for problems affecting women exclusively, including premenstrual syndrome (National Prescribing Service 2004), the status of which as a psychiatric disorder is controversial (Caplan 2004). They are also prescribed for menopause: in the wake of the premature termination of the Women's Health Initiative study, which found that hormone replacement therapy (oestrogen plus progestin) increased women's risk of invasive breast cancer, coronary heart

disease, stroke, and other adverse outcomes (Rossouw et al. 2002), antidepressants are increasingly being used as an alternative treatment for menopausal symptoms (McIntyre et al. 2005).

One particular antidepressant, bupropion (Zyban), has been approved in Australia for smoking cessation and is subsidised. However, both its use and its subsidisation are controversial (ABC 2001).

In addition to these myriad diagnoses, antidepressants are also sometimes advocated for *undiagnosable* conditions. The title of a paper by O'Malley et al. (1999) is significant: 'Antidepressant therapy for unexplained symptoms and symptom syndromes', as is their recommendation that: 'Physicians caring for patients with unexplained symptoms should focus their efforts on developing a therapeutic relationship, thoroughly exploring and treating any underlying depressive or anxiety disorder, and considering antidepressant therapy *even if a depressive disorder is not evident* [italics added]' (p. 988).

This recommendation is underpinned by the concept of somatisation – the somatic (physical) expression of psychological problems (Hickie, Davenport, Hadzi-Pavlovic et al. 2001; Sharpe 2002, p. 501). Somatisation is a significant current theme in psychiatry, with major implications for antidepressant prescribing.

Prophylactic (preventive) antidepressants are also increasingly being advocated and used to prevent depression in people with physical illnesses such as stroke (Jorge et al. 2003), people receiving interferon treatment (which can cause depression) for hepatitis C (Musselman et al. 2001), and more generally people requiring hospitalisation (Niculescu 2000).

Use of antidepressants for many of these indications is 'off-label', i.e. not authorised by regulatory bodies such as the FDA in the US, or the TGA (for safety) or the PBS (for subsidisation) in Australia. In the US, antidepressants are commonly prescribed for conditions other than those approved by the FDA (Streator & Moss 1997; Tabarrok 2000; Chung 2005). Ornstein et al. (2000, p. 68) reported that more than 40% of primary care (general practice) patients who were prescribed antidepressants

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had never been diagnosed with depression. Off-label use may cause significant unnecessary health care expenditure (Chung 2005).

In Australia, many PBS-subsidised antidepressants are listed for major depressive disorder only (DoHA 2005, pp. 276-280). None are listed for dysthymic disorder or mild depression. However, many antidepressant prescriptions are for 'chronic mild depression' and other forms of depression that do not meet DSM-IV criteria for major depressive disorder (McManus et al. 2003, p. 188). This is a form of off-label prescribing (prescribing for unapproved indications).

Prescription to certain types of patients, particularly children, is often off-label. In Australia, no SSRIs have been approved for children, but such off-label prescriptions are relatively common and are subsidised by the PBS (Davies 2008).

Antidepressants are also sometimes prescribed to animals, particularly dogs and cats. However, they are generally prescribed for anxiety disorders and behavioural problems rather than depression (Aiello 1998; Walsh 2004).

2.3.4 Likelihood of antidepressant prescription after depression diagnosis

As noted earlier in this chapter (section 2.2.7), people who are diagnosed as suffering from depression have a high chance of being prescribed antidepressants (AIHW 2004, p. 211; Wilson et al. 2003, p. 685), generally by GPs (McManus 2000, p. 458). A five-year follow-up study of Australian GP patients found that 93.6% of patients diagnosed with depression received an antidepressant at some time during the study period (Wilson et al. 2003, p. 685). The authors commented that 'diagnosis of depression is almost routinely followed by the prescription of an antidepressant at some stage' (p. 688). Similarly, van Weel-Baumgarten, van den Bosch, Hekster, van den Hoogen, & Zitman (2000) reported that, in a 10-year follow-up study in the Netherlands, 94% of patients who had recurrences of depression were prescribed antidepressants at some point.

Often antidepressants are prescribed very quickly. Ornstein et al. (2000) reported that 49% of patients newly diagnosed with depression were prescribed antidepressants, mostly (81%) SSRIs, within five days.

2.3.5 Duration of antidepressant use

The duration of antidepressant use can be many years, but is more often relatively short (Wilson et al. 2003; Pomerantz 2003). Gasquet et al. (2004) reported rapid early discontinuation (21% of people in 1-15 days, 8% in 16-30 days). However, 42% of people used them for more than six months. McManus et al. (2004, p. 450) reported that only 40 per cent of people who were prescribed an antidepressant continued to be prescribed one 6-8 months later. Meijer et al. (2004) found that both initiation and duration of use increased in the Netherlands over the period 1992 to 2001. Almost 30% of people who were prescribed antidepressants became long-term users (12 months or more).

Short-term use is sometimes due to short-term prescription (Pomerantz 2003), but is often due to discontinuation related to side-effects, or non-compliance related to reluctance to use antidepressants (Byrne et al. 2006).

Pomerantz (2003), among others, has expressed concern about short-term use, which is contrary to many clinical guidelines. Recommended duration is discussed in chapter 6, along with other issues related to guidelines.

2.3.6 Who uses antidepressants?

Although antidepressants are used by a wide range of people, there are some population groups that are more likely than others to use them. Hansen et al. (2004, p. 51) succinctly summarised some key factors:

> The 1-year incidence rate of antidepressant prescription (1.7%) increased with age. It was higher in people who were female, less educated, unemployed, those receiving old-age or disability pension, low-income groups, and singles.

It is not surprising that gender is a significant factor. Like benzodiazepines (and many other prescribed psychotropics), antidepressants are disproportionately prescribed to women (McManus et al. 2000, p. 460; Currie 2005; Stewart 1998). This raises questions about gender bias in prescribing and diagnosis. More generally, the association of both depression and antidepressant use with disadvantage and

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marginalisation raises questions about the conceptualisation of depression, and the appropriateness of pharmacological interventions.

Ethnicity has a complex relationship with antidepressant prescribing. People from ethnic minority groups are generally more likely to be poor, but there is some US evidence that they are less likely to be prescribed antidepressants (Sirey et al. 1999).

Elderly people have high rates of antidepressant use (Mamdani et al. 2000; Mort & Aparasu 2000). Antidepressant use is a contributory factor to falls caused by side-effects such as dizziness (Thapa et al. 1998). Furthermore, because elderly people use significantly more prescribed drugs than younger people (NHMRC 1994, p. 18), they are at greater risk of adverse drug interactions. Another issue is the differences in the pharmacokinetics (absorption, distribution, protein binding, and elimination) and pharmacodynamics (responsiveness to a given drug level) of drugs in the elderly (NHMRC 1994, pp. 4-9; McLeod, Huang, Tamblyn, & Gayton 1997), which can significantly influence the effects of drugs. Despite these differences, elderly people are often excluded from clinical trials (Bartlett et al. 2005, Van Spall et al. 2007). These factors make elderly people a particularly important demographic in relation to antidepressants.

Antidepressant use by children and teenagers has increased dramatically in recent years (Zito et al. 2002; Delate et al. 2004). Children have historically been largely excluded from clinical trials, although in recent years the US FDA has instituted incentives for paediatric trials (McKinney 2003). The appropriateness of prescribing antidepressants to children and teenagers is a key current debate (Boseley 2003), and is discussed in chapter 6.

Evidence has emerged in recent years that there is significant nonmedical use of antidepressants by polydrug users (people who use multiple drugs, both licit and illicit, for nonmedical purposes)[9] (Darke & Ross 2000). This is not surprising, given the pharmacological similarities between SSRIs and the illicit drug ecstasy (*New Scientist* 2002).

[9] Use of multiple non-medical drugs, and/or misuse of multiple medical drugs, is commonly referred to as 'polydrug use'. In contrast, doctor-authorised use of multiple prescribed drugs is referred to as 'polypharmacy'.

2.3.7 Antidepressant risks

Antidepressants, particularly SSRIs, have been vigorously promoted as safe (Berk & Dodd 2005; beyondblue 2008). Antidepressant advocates sometimes emotively contrast antidepressants favourably with historical treatments that are today considered barbaric and/or dangerous, including long-term confinement in grim asylums, psychosurgery, and insulin shock. However, antidepressants, like all drugs, can have undesirable effects, some of which are very aversive and/or dangerous.

In relation to prescribed drugs, the term 'side-effects' is often used in common parlance; in the medical literature, the terms 'adverse drug reactions' (ADRs) and 'adverse drug events' (ADEs) are more often used. ADRs impose a significant burden on the health system (Roughead 2005). Many hospital admissions are the result of ADRs, some of which are fatal. Roughead, Gilbert, Primrose, and Sansom (1998) estimated that 81,000 public hospital admissions in Australia in 1994-1995 would have been related to prescribed drugs. Many ADRs are acute, resolving rapidly when medication is reduced or discontinued. However, there are also long-term risks such as the increased incidence of cancer associated with hormone replacement therapy (Rossouw et al. 2002).

A major issue is the risks associated with 'polypharmacy' – the use of multiple medical drugs – which is particularly common among elderly people (Bolton et al. 2004, p. 78). The risk of ADRs increases as the number of medications rises (Pillans & Roberts 1999; Veehof et al. 1999). Furthermore, prescribed drugs can also interact with alcohol, tobacco or other nonmedicinal drugs, and many foods (Corrigan 2002).

Psychotropic drugs account for a significant proportion of ADRs. According to unpublished AIHW data, 12.67% of female drug-poisoning hospital admissions in Australia in 1994-1995 were related to the use of tranquillisers, antidepressants, analgesics, hypnotics, and sedatives (Williams 1997, p. 43). For males, the equivalent figure was 4.87%.

In an Australian study of community-dwelling elderly people (Roughead et al. 2004), nervous system drugs were second only to cardiac drugs in causing ADRs.

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Antidepressants and psycholeptics (anxiolytics and antipsychotics) were the most commonly implicated nervous system drugs. In a Canadian study of drug-related mortality, Mittmann et al. (1997, p. 165) reported that nervous system drugs were the most commonly reported drugs in ADRs, and they dominated non-suicidal cases as well as suicide reports.

It is often claimed that SSRIs have a lower side effect profile, which increases compliance relative to TCAs and MAOIs. However, the evidence is questionable (Brambilla et al. 2005), and there is increasing concern about a range of risks, which range from troublesome but non-serious 'side effects' to potentially fatal ADRs (Trindade et al. 1998; Spigset 1999).

Reviews of antidepressant ADRs have produced long lists of symptoms and syndromes across a range of categories. Spigset (1999), analysing reports to the Swedish Adverse Drug Reactions Advisory Committee, found that the most commonly reported ADRs were neurological symptoms, psychiatric symptoms and gastrointestinal symptoms. Dermatological symptoms and 'general symptoms' were also common.

One of the most well documented ADRs is sexual dysfunction. Male erectile dysfunction (Rothschild 2000) has received by far the most attention, but women also frequently experience SSRI-induced sexual dysfunction (Damis et al. 1999; Michelson et al. 2000). Viagra and similar drugs are sometimes prescribed for male erectile dysfunction caused by antidepressants (Taylor et al. 2005).

Two potentially serious ADRs are cardiac disturbances and serotonin syndrome (potentially fatal serotonin toxicity) (Burggraf 1997). The relative toxicity (particularly cardiotoxicity) of TCAs in overdose has been emphasised as an argument in favour of SSRIs, but deaths also occur with SSRIs (Cheeta et al. 2004). There is also weak evidence that antidepressants may increase the risk of breast cancer (Steingart et al. 2003).

Two other risks in particular have received significant attention and generated considerable controversy: the risk of dependence[10], and the potential to trigger suicide

[10] Although some people argue that dependence and addiction are different (e.g. Beers et al. 2005), both have been defined in many different ways that overlap greatly. At the core of both concepts is compulsion experienced by users to continue using a drug (or to continue a behaviour), which is

(and to a lesser extent homicide). These risks, and the overall safety of antidepressants, are discussed in detail in chapter 6.

2.3.8 Effectiveness of antidepressants

According to the dominant orthodoxy, antidepressants are effective treatments for depression, with evidence of effectiveness from both scientific trials and clinical practice (Ellis, Hickie, & Smith 2003). It is also claimed that they are effective in reducing suicide rates (Angst et al. 2005; Hickie 2004); this is discussed in chapter 6. A contrary view is that antidepressants are relatively ineffective, offering little more benefit than placebos (Moncrieff & Kirsch 2005).

One aspect of the debate relates to the distinction between effectiveness and efficacy. Efficacy refers to effects demonstrated in tightly controlled trials, effectiveness to real-world effects (Department of Health and Human Services (United States) 1999, p. 72; Nathan & Gorman 2002b, p. 644). Trials of antidepressants (and medicinal drugs generally) are not representative of everyday clinical practice for a number of reasons, including exclusion criteria that result in biased samples that favour the performance of antidepressants over placebos (Posternak et al. 2002), and more intensive treatment than normal clinical practice. Therefore results from clinical trials should not be uncritically generalised to everyday clinical practice, but this limitation is routinely ignored.

Another unresolved debate is about the relative effectiveness of TCAs, SSRIs and newer antidepressants. It is often claimed that newer antidepressants are more effective than their predecessors; however, the evidence is questionable (Williams et al. 2000). In addition, many industry-funded studies are used to support claims that a particular antidepressant is more effective than one or more other antidepressant (of the same class or a different class, particularly a TCA), but again the evidence is questionable (Hansen et al. 2005). Debates about antidepressant effectiveness and about clinical trials more generally are discussed in chapters 6 and 7 respectively.

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relevant to this discussion. In this thesis, the more scientific and less pejorative term, dependence, is used except when referring to sources that use the term addiction.

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2.3.9 Economics of antidepressants

Antidepressants are one of the most costly categories of drugs in many countries, and in Australia they impact significantly on the Pharmaceutical Benefits Scheme. As noted in section 2.3.2, nearly 16.7 million subsidised antidepressant prescriptions were dispensed in Australia in 2009 costing the Government and patients a total of over $500 million (DoHA 2011a, pp. 165-166). Prescriptions increased 122% between 1997 and 2009, whereas their cost increased 167%.

Sertraline (Zoloft) was the tenth most costly drug to the Australian Government in 2001 (DoHA 2004a, p. 25), having been the eighth most costly drug in 1998 (CDHAC 1999a, p. 20). In 2002, it dropped to thirteenth place (p. 25), but still cost the Government and patients more than $94 million (DoHA 2004a, p. 286). From 2006 to 2007, venlafaxine (Efexor), a newer antidepressant, was the eighth most costly drug, costing over $119 million in 2006 (DoHA 2008, p. 25), over $135 million in 2007 (DoHA 2009a, p. 25), and over $153 million in 2008 (DoHA 2010, p. 26).

Antidepressants consume significant economic resources in many other countries. A frequently cited study by Greenberg et al. (2003) estimated that US$10.4 billion was spent on antidepressants in the US in 2000. According to Hollinghurst et al. (2005, p. 999), nearly £400 million was spent on antidepressants in the UK in 2002.

Like most new classes of drugs, SSRIs and newer antidepressants are significantly more expensive than their predecessors (Shireman et al. 2005). There have been a significant number of pharmaceoeconomic studies on antidepressants, primarily funded by pharmaceutical companies. Such studies have repeatedly been used to argue that, despite being more expensive upfront, SSRIs and newer antidepressants may reduce other treatment costs (Croghan 2001). However, many such studies are flawed (Conner et al. 1999; Baker et al. 2003).

2.4 CONCLUSION

Depression is a negative psychological state, and a relatively commonly diagnosed psychiatric disorder. However, many depressed people are not diagnosed and do not seek treatment for their depression; those who do are mainly treated by GPs, and the most common form of treatment is antidepressants.

In the psychiatric and broader medical literature, depression is increasingly regarded not only as common, serious, and treatable (Regier et al. 1998; Ellis et al. 2003), but also as underdiagnosed, and undertreated, with significant negative public health consequences (Murray & Lopez 1996). Partly because of such claims, depression became a major focus of Australian mental health policy in the late 1990s (Australian Health Ministers, 1998, p. 11; CDHAC & AIHW 1999; CDHAC 2000/2001).

Depression is increasingly considered to be a brain disorder, specifically a disorder of serotonin and/or other neurotransmitters. Not surprisingly, therefore, it is seen as amenable to treatment with drugs that target neurotransmitters. However, there is substantial debate about what causes depression and how it should be treated.

Many different types of drugs are and/or have been used to treat depression, including prescribed and over-the-counter drugs, legal nonmedicinal drugs, and illicit drugs. In medical contexts, prescribed antidepressants dominate, particularly SSRIs. In Australia, among other countries, antidepressant prescriptions and costs have been increasing steadily for nearly two decades. Most antidepressants are prescribed by GPs, often for non-approved indications.

As with depression, there is an orthodoxy about antidepressants that is strong but is increasingly questioned. According to this orthodoxy, antidepressants are a scientific treatment for depression because they help to restore normal activity and metabolism of neurotransmitters such as serotonin. Antidepressants, according to this orthodoxy, are safe and effective in both relieving depression and reducing the risk of suicide. They have some side-effects, it is admitted, but the newer (more expensive) antidepressants are purportedly less problematic than the older ones. The biggest challenge for clinicians and governments, it is argued, is to increase the number of depressed people who are treated with antidepressants.

Many aspects of the orthodoxy about depression and antidepressants are challenged in this thesis, particularly in chapters 4 and 6 respectively. The key players involved in the development and maintenance of the orthodoxy are discussed next, in chapter 3.

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Chapter 3
Players

3.1 INTRODUCTION

Following the discussion of depression and antidepressants in chapter 2, this chapter discusses the many players involved in the depression/antidepressant arena, the 'constituencies for depression' (Horwitz & Wakefield 2005).

Among the most obvious players are: people who have depression and/or consume antidepressants (in some cases for disorders other than depression, particularly anxiety disorders); doctors who diagnose depression and prescribe antidepressants and/or other treatments; pharmaceutical companies that manufacture and market antidepressants; and governments that regulate antidepressants, and in some cases subsidise them, and more generally play a major role in the structure and function of the health care system. Other players include: other health professionals, including psychologists, social workers, pharmacists, and nurses; medical and other health professional bodies; consumer/community mental health organisations; a range of academics and researchers including epidemiologists and health economists; medical journals; health insurance providers; lawyers; journalists and media companies; and marketing and advertising agencies.

The orthodox beliefs about depression and antidepressants discussed in chapter 2 are accepted by, and beneficial to, most groups of players, some of whom vigorously champion them. The question of whether the orthodoxy is beneficial to people who have depression and/or consume antidepressants is a crucial question that subsumes many debates, for example whether medicalisation of distress is beneficial and whether antidepressants can trigger suicidal behaviours. Many of these debates are discussed in chapters 4 to 6, about depression, suicide, and antidepressants respectively.

Some players have direct financial interests that are served by the orthodoxy. In particular, the orthodoxy helps pharmaceutical companies to sell antidepressants and other psychotropic drugs. The common beliefs that depression is a disorder of brain chemistry amenable to chemical intervention and that antidepressants are a safe and

effective and cost-effective treatment for depression are used by pharmaceutical companies to persuade doctors to prescribe antidepressants, and to persuade governments and health insurance providers to fund or subsidise them. The belief that depression is common, serious, and treatable boosts the income of psychiatrists. It can also financially benefit general practitioners, who prescribe the majority of antidepressants, pharmacists who dispense them, and psychologists and other health professionals who provide non-pharmacological treatments.

These beliefs also financially benefit advertising and marketing agencies that develop promotional campaigns, and medical journals that run many of the advertisements. Debates about players financially benefitting from the orthodoxy are discussed primarily in chapter 7, which focuses on the pharmaceutical industry and its strategies, including alliances with a range of players.

Even without any direct financial benefits, many players, particularly health professionals, benefit from simply accepting the orthodoxy and the roles it affords them. Others gain status by actively promoting it. Not surprisingly, players who challenge the orthodoxy tend to be challenged themselves.

Governments also benefit from the orthodoxy, even governments that pay for or subsidise large amounts of antidepressants. The focus on depression deflects attention from other social problems such as inequality. Similarly, antidepressant advocates deflect attention from broader interventions that might be more effective in reducing distress in the population (for example, wealth redistribution strategies that reduce inequalities) but are not politically palatable.

The main categories of players are briefly discussed in this chapter, starting with consumers. Key players such as the pharmaceutical industry and psychiatrists and general practitioners are then discussed in more detail in other chapters in relation to specific issues and debates.

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3.2 CONSUMERS

People with depression, whether or not they are users of antidepressants, are of course central players in the depression/antidepressant arena. In fact, the largest group of players is potential sufferers and users – anyone who *might* experience depression and *might* be prescribed antidepressants.

Women are over-represented among actual and potential sufferers and users. They are more likely to consult doctors about psychological problems (Bland et al. 1997; Johnson 1988), more likely to be diagnosed with depression (Kessler 2003), and more likely to be prescribed antidepressants (Currie 2005). Considerable Australian evidence supports this. In 2001-2002, 67.9 per cent of depression problems managed by GPs involved female patients (Australian Institute of Health and Welfare [AIHW] 2004, p. 210). Between 1990 and 1998, women were the patients in two-thirds of encounters in which antidepressants were prescribed (McManus et al. 2000, p. 460). In 2006-2007, 61.3 per cent of patient encounters in which a psychiatric medication was prescribed involved female patients (AIHW 2009, p. 126); antidepressants were by far the most commonly prescribed such medication (p. 15). Similarly, in the US in 2001, nearly 65% of all selective serotonin reuptake inhibitors (SSRI) prescriptions were written for women (Stewart 2001).

Most antidepressants are prescribed for some sort of depressive disorder, although in many cases the disorder does not meet diagnostic criteria. Sometimes antidepressants are prescribed without any diagnosis, but most antidepressant users have been diagnosed, rigorously or otherwise, with depression. Such diagnosis can have social and occupational implications, both adverse and beneficial.

People experiencing distress can generally choose whether or not to consult a doctor about it. Many such consultations are triggered by disease awareness campaigns, which are discussed in chapters 8 and 9. Some people explicitly request antidepressants, partly as a result of direct-to-consumer advertising (discussed in chapter 7).

People who are diagnosed with depression usually have some choice about whether or not to accept the diagnosis and its implications (which can include special treatment in the workplace and elsewhere). Some embrace the diagnosis of depression and the standard solution of antidepressants. Many are ambivalent about either or both. People

who have been prescribed antidepressants generally have the power to decide whether or not to get the prescription dispensed (although some people, particularly in the US, do not even have that choice because of the prohibitive cost), and then whether or not to consume the antidepressants (some people, particularly children and institutionalised people, lack this choice, but they are the minority[1]).

Children who are diagnosed with depression and/or prescribed antidepressants are a small but growing group of consumers. The rate of prescribing of antidepressants for under-20-year-olds increased three- to five-fold in the US between 1988 and 1994 (Zito et al. 2002). However, emotive public debates in recent years about the risk of suicide, and resultant regulatory restrictions in a number of countries, have somewhat slowed the growth of antidepressant prescribing to children (see chapter 6).

Chapter 2 included a brief review of people's reported experiences of depression. There has been little investigation of the experiences of antidepressant users. A notable exception is a study by Chur-Hansen and Zion (2006), which examined the experiences of five young university students and found that overall they were unhappy with their treatment (p. 28).

Few consumers publicly comment about depression and antidepressants. They are generally reluctant to do so, largely because of stigma and lack of credibility. However, a number of high-profile celebrities have 'outed' themselves as suffering from depression, a strategy for 'building respectability', part of Wiener's (1990) 'legitimizing the problem' (p. 21). Notable in Australia is actor Gary McDonald, a *beyondblue* ambassador (Hollingworth 2009). In the US, Johns Hopkins University Professor Kay Redfield Jamison has published and spoken extensively about her experience of bipolar affective disorder ('manic depression') (Jamison 1995). Ex-actor Brooke Shields (2005) has written about her experience of postnatal depression, endorsing the value of antidepressants. Wurtzel (1994) has also written positively about antidepressants, becoming famous in the process. Beddoe (2007), on the other

[1] Mandatory treatment is much more common with antipsychotics than antidepressants, because most mandatory treatment is for schizophrenia (AIHW 2009, p. 95), and antipsychotics dominate schizophrenia treatment (AIHW 2005, p. 228).

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hand, was very negative about antidepressants. She was also critical of her diagnosis of postnatal depression.

3.3 HEALTH PROFESSIONALS AND PROFESSIONAL ORGANISATIONS

3.3.1 Doctors

Doctors are key players because they frequently diagnose depression, and they can prescribe antidepressants, which other health professionals cannot do, except in a very small number of jurisdictions. To practise medicine legally in Australia, doctors must be registered medical practitioners. Registration occurs at a state/territory level, with uniform minimum requirements for registration and mutual recognition of registration (Australian Medical Council n.d.). Registration requires firstly a primary medical degree from an accredited medical school after completion of either a four-year graduate entry medical course or a five- to six-year undergraduate medical course, and secondly a twelve-month internship. Doctors who wish to become specialists (e.g. psychiatrists) must complete further years of training. All doctors are required to undertake periodic post-registration continuing medical education (CME). As discussed in chapter 7, most CME is funded by pharmaceutical companies, as is much research conducted by doctors, which can create significant conflicts of interest.

General practitioners

General practitioners (GPs) are by far the largest group of doctors, and they are key players because they diagnose most cases of depression and prescribe the vast majority of antidepressants in Australia: 86% of subsidised antidepressants in 2000 (McManus et al. 2003, p. 184), and 88% in 2007-2008 (AIHW 2009, p. 122). They also prescribe most psychotropic drugs generally (Raven & Parry 2012, pp. 512-513).

There were approximately 22,954 GPs in Australia in 2006 (AIHW 2008, p. 5). For some years, new GPs have been required to have post-registration qualifications, although there are still many who became GPs prior to this requirement.

GPs prescribe a lot of drugs: in 2007-2008, 82 scripts per 100 encounters (Britt et al. 2008, p 58). Many patients expect to receive at least one prescription when they consult their GP.

GPs are the main providers of mental health services, treating the majority of people with mental disorders who receive any treatment. This is the case in Australia (Australian Bureau of Statistics 2008, p.23), New Zealand (Dew et al. 2005), and many other countries (Wang et al. 2007, p. 841). Furthermore, it is argued that GPs are ideally placed to diagnose and treat depression (Henderson, Andrews, & Hall 2000, p. 202).

However, structural constraints make it difficult for GPs to offer consultations lengthy enough and comprehensive enough to provide optimal management of mental health issues, or to refer patients elsewhere for counselling. Consequently, antidepressants are often the only treatment provided by doctors who actually value counselling (Wilson & Read 2001).

Psychiatrists

There were approximately 3,258 psychiatrists employed in Australia in 2006, representing 5.2 per cent of all employed medical practitioners (AIHW 2009, p. 144). Although they are much less numerous than GPs, they have significantly more status and influence. In Australia, becoming a psychiatrist requires undertaking a five-year specialist training program after registration as a medical practitioner (Royal Australian and New Zealand College of Psychiatrists (RANZCP) 2003b).

Psychiatrists have dominated the development of the orthodoxy about depression, although in recent years general practitioners (particularly academics) have played a more substantial role than previously. Most diagnostic criteria have been determined by psychiatrists, as have most guidelines. Both are powerful influences on clinical practice. Most major prevalence and outcome studies have been led by psychiatrists. Such studies have had a significant impact on policy development.

Psychiatrists have been closely involved in the development and promotion of antidepressants, and most psychiatrists in clinical practice frequently prescribe them. In Australia in 2007-2008, 944,228 antidepressant prescriptions (8%) were written by psychiatrists (AIHW 2009, p. 122). There is some evidence that psychiatrists tend to

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prescribe higher doses than GPs do (Kerr 1994; Isacsson et al. 1996) and tend to prescribe newly marketed antidepressants sooner (Ward et al. 2008, pp. 270-271). Although a small minority of psychiatrists are strongly critical of antidepressants (e.g. Healy 1997; Glenmullen 2000; Jureidini et al. 2004; Moncrieff 2001), many psychiatrists are in favour of increasing use of antidepressants (Druss et al. 2000; Katz et al. 1998; Hickie 2001).

Psychiatrists (like other specialists) are often cultivated by the pharmaceutical industry as 'opinion leaders' or 'key opinion leaders' (KOLs) to influence other doctors (RANZCP 2003a; Relman & Angell 2002; House of Commons 2005, p. 55), particularly GPs. Many opinion leaders also have a public profile, being frequently quoted in the media. Furthermore, psychiatrists often have financial interests in the promotion of antidepressants. According to Angell (2000a):

> as we spoke with research psychiatrists about writing an editorial on the treatment of depression, we found very few who did not have financial ties to drug companies that make antidepressants…. The problem is by no means unique to psychiatry. We routinely encounter similar difficulties in finding editorialists in other specialties, particularly those that involve the heavy use of expensive drugs and devices.

One very significant psychiatrist and prominent KOL in the Australian depression arena has been Graham Burrows, Professor of Psychiatry at the University of Melbourne from 1983 to 2008. He was also Chairman of the Mental Health Foundation of Australia (MHFA) since its inception in 1981, President of the Mental Health Foundation of Victoria, since 1972 (Balshaw 2007, p. 44), and Chairman of the Australian National Association for Mental Health from 1980 to 1988 (p. 45), and arguably the most influential psychiatrist in Australia in the 1990s. Burrows and the MHFA established the National Depression Awareness Campaign (NDAC) in 1994. The NDAC and its flagship publication, the *Depression Awareness Journal*, are discussed in detail in chapter 9.

The most prominent psychiatrist in Australia in more recent years, until the appointment of Patrick McGorry as Australian of the Year (Attard 2010), has been Professor Ian Hickie, inaugural CEO of *beyondblue: the national depression initiative* from 2000 to 2003 (and Clinical Advisor from 2003 to 2006) (Hickie 2010). Hickie established SPHERE: a national depression project in 1998, which was promoted in

Burrows' *Depression Awareness Journal*. As mentioned in chapter 1, *beyondblue* has played a major role in the elevation of depression as a social problem in Australia.

Contemporary psychiatry is dominated by biological psychiatry, according to which mental disorders are caused by abnormalities in the brain; this is discussed in chapter 4. Also powerful is neo-Kraepelinian psychiatry, according to which mental disorders are manifestations of brain pathologies, distinct from normality (Horwitz & Wakefield 2007, pp. 75-78).

Psychiatrists who challenge these dominant perspectives tend to be marginalised within the profession. One particularly significant such psychiatrist is Thomas Szasz, co-founder (with the Church of Scientology) of the Citizens Commission on Human Rights (discussed in section 3.10.4). Szasz led the negative team in a lengthy televised debate called 'Is depression a disease?' (Szasz et al. 1998), in which many key issues related to the depression/antidepressant orthodoxy were argued.

In Australia, two psychiatrists who have repeatedly challenged the orthodoxy about depression and antidepressants are Jon Jureidini[2] and Yolande Lucire. The former has been publicly criticised by peers, including Hickie and McGorry (McGorry et al. 2008), and the latter has faced disciplinary action related to her controversial views about psychotropic drugs and her prescribing practices (King 2010).

Non-psychiatrist specialists

Depression is also diagnosed, and antidepressants are also prescribed, by non-psychiatric specialists, such as paediatricians and obstetricians and gynaecologists (Raven & Parry 2012, p. 513). In Australia in 2007-2008, 391,091 antidepressant prescriptions (3.9%) were written by non-psychiatrist specialists (AIHW 2009, p. 122).

[2] I have published a number of papers jointly with Jureidini, including Raven et al. (2005), Mansfield et al. (2006), Jureidini et al. (2008), Isacsson et al. (2010), and Raven & Jureidini (2010).

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3.3.2 Medical professional organisations

GPs and psychiatrists are represented by various professional bodies. These include national medical associations and royal colleges. Some of these bodies provide guidelines on antidepressant prescribing and other relevant issues. They are also key consultants in the formation of government policy, and they attract significant media attention.

In Australia, the key medical bodies in relation to depression and antidepressants are the Australian Medical Association (AMA), the Royal Australian College of General Practitioners (RACGP), and the Royal Australian and New Zealand College of Psychiatrists (RANZCP). The Australian Divisions of General Practice (now called the Australian General Practice Network) also plays a significant role.

The AMA is the peak Australian organisation representing doctors. It publishes the *Medical Journal of Australia*, many articles from which are cited in this thesis. The AMA has a strong track record of rejecting claims that doctors are inappropriately influenced by the pharmaceutical industry (Hingston 2006; AAP 2008). Several such instances are included in chapter 7.

A very different organisation, the Doctors Reform Society (DRS), focuses on 'supporting health care reforms to ensure justice, equity and quality care' (DRS n.d.). It is critical of the pharmaceutical industry, and is frequently at odds with the AMA and other mainstream medical organisations. The DRS publishes a journal, *New Doctor*, and local newsletters.

Many GPs are members or fellows of the RACGP. Membership requires approved experience or qualifications. Fellowship has further requirements. The RACGP publishes an important GP journal, the *Australian Family Physician*. It also oversees and delivers many education and training events. Such events are routinely sponsored by pharmaceutical companies.

Approximately 85 per cent of Australian psychiatrists and over 50 per cent of New Zealand psychiatrists are fellows of the RANZCP (RANZCP 2003c). The RANZCP publishes a monthly peer-reviewed academic journal, the *Australian & New Zealand Journal of Psychiatry*. It has developed guidelines for the treatment of depression (RANZCP 2004b). It has also released statements about depression and antidepressants, including one (RANZCP & Society of Hospital Pharmacists of

Australia 2001), saying that they 'strongly endorse the appropriate use of antidepressant drugs as a contribution to managing depressive illnesses'. It also organises annual conferences and education and training events, which are sponsored by pharmaceutical companies.

The British counterparts of the AMA, the RACGP, and the RANZCP are the British Medical Association (BMA), the Royal College of General Practitioners (RCGP), and the Royal College of Psychiatrists (RCP). The RCP's Defeat Depression Campaign is discussed in chapter 8.

In the US, the key bodies are the American Medical Association and the American Psychiatric Association (APA). The APA is enormously influential, not only in the US but also in many other countries, including Australia. A major mechanism of influence is 'the DSM': the *Diagnostic and Statistical Manual of Mental Disorders*, currently in its fourth edition (American Psychiatric Association (APA) 1994), with a text revision (APA 2000).[3] The APA has been strongly criticised for its links to the pharmaceutical industry, including individual ties of members of committees developing DSM, and very substantial sponsorship of conferences. This is discussed in chapter 7.

Internationally, the World Psychiatric Association (WPA) plays a prominent role in psychiatry, convening major international conferences and undertaking educational and advocacy programs. The RANZCP, RCP, and APA are among the many members. The WPA also has strong links to the pharmaceutical industry and, according to Medawar (2003), it is an important channel via which the industry influences the World Health Organization in relation to mental health and illness.

[3] As mentioned in chapter 1, a text revision of the DSM-IV (APA 1994), the DSM-IV-TR (APA 2000) has been published. However, the DSM-IV-TR criteria for major depressive disorder, depressive episode, and dysthymic disorder are exactly the same as the DSM-IV criteria, and most people continue to cite the 1994 DSM-IV criteria. DSM-5 is currently being developed, generating enormous controversy in the US, Australia, and many other countries (Dunlevy 2012).

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3.3.3 Psychologists and other therapists/counsellors

Non-medically qualified health professionals such as psychologists and social workers deal with many people experiencing distress, which they often define as depression. They often provide alternative psychological treatment modalities such as cognitive behavioural therapy. They have lower status and influence than doctors. They are generally not closely involved in relation to antidepressants, which in almost jurisdictions they are not permitted to prescribe, although some do have a strong interest. Some (e.g. Kirsch et al. 2008) are strongly critical of the widespread use of antidepressants.

Some psychologists, particularly in the US, are advocating for the right of psychologists to prescribe antidepressants (and other psychotropics) (Williams-Nickelson 2000). However, some psychologists vehemently oppose it (Albee 2002), as, predictably, does the American Psychiatric Association (Mulligan 2002). In the US in the 1990s, ten military psychologists were trained and licensed to prescribe psychotropics (Dittman 2003). Then in 2002, in landmark legislation, psychologist prescribing rights were granted in New Mexico (American Psychological Association 2002), and other states are being lobbied to follow suit.

In Australia the Australian Psychological Society, the peak organisation for psychologists, has close links with *beyondblue* and has representation on a number of other key entities. However, it is a far less significant player than the medical organisations discussed above.

3.3.4 Pharmacists

Although they are sometimes regarded as little more than retail dispensers of medications, pharmacists can also give advice about prescribed and over-the-counter drugs, and potential adverse reactions and interactions. They are also increasingly involved in formal interventions to promote safe and effective use of medications. For example, they can conduct Home Medicines Reviews, in which they visit people – usually elderly people, many of whom use antidepressants (Hubbard et al. 2003) – at home and review all prescribed and over-the-counter medications, liaising with GPs to address any problems (Commonwealth Department of Health and Aged Care [CDHAC] 2001). Pharmacists are also sometimes involved in interventions to increase compliance (Pharmacy Guild of Australia 2008).

3.3.5 Nurses

Although nurses cannot prescribe antidepressants, they commonly dispense them to hospital patients and institutional residents. Apart from that, they are involved in the treatment of relatively few people with depression, for example by providing counselling in community health agencies. Nursing journals sometimes publish papers about depression and antidepressants, generally echoing the orthodoxy.

3.3.6 Researchers and academics

Health researchers come from a wide variety of academic disciplines. Researchers and academics with medical qualifications, particularly professors of psychiatry or pharmacology, have significant status and influence in relation to depression and antidepressants (and in the mental health arena more generally). They play a key role in the education of medical students, and are often involved in continuing medical education. Some are employed by universities in positions that are funded by pharmaceutical companies, and some are directly employed by pharmaceutical companies. More generally, most academics participate in teaching activities sponsored by pharmaceutical companies.

Among non-medical professionals, health economists (a few of whom also have medical qualifications) tend to have more influence than others, partly because they are few in number, but primarily because of the power of economic arguments in health systems that consume significant proportions of developed countries' gross domestic products. Even rarer are pharmacoeconomists, health economists who focus on prescribed drugs. Many pharmacoeconomists are employed by pharmaceutical companies.

Another relatively small group is epidemiologists, who focus on patterns of health, ill-health, and relevant factors in populations. Some are medically trained, others not. Pharmacoepidemiologists are a select group of epidemiologists who focus on the epidemiology of prescribed drugs. Psychiatric epidemiologists, a particularly rare

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breed, focus on the epidemiology of mental disorders and sometimes also the epidemiology of prescribed psychotropics.

3.4 THE PHARMACEUTICAL INDUSTRY

Pharmaceutical companies are powerful players with strong incentives to maximise sales and profits. They employ large numbers of sales staff ('drug reps' or 'detailers') whose job it is to persuade doctors, particularly GPs (because they constitute the majority of the medical workforce), to prescribe their specific company's drugs, including antidepressants. Pharmaceutical companies also employ other relevant staff, including researchers from disciplines such as medicine, pharmacology, and health economics, and lawyers. In addition, they spend huge sums of money on work outsourced to advertising and marketing and public relations companies and lobbyists.

The pharmaceutical industry is one of the world's largest industries (Industry Commission 1996, p. 7). US pharmaceutical companies dominate internationally: the US pharmaceutical market constitutes approximately half the global pharmaceutical market in terms of sales (Vernon et al. 2009, p. 797).

The pharmaceutical industry is a very large player in the US economy. It was estimated by the Minnesota Attorney General's Office (2003, p. 1) that expenditure on prescription medications represented almost 18 percent of health care costs, which in turn accounted for approximately 15 percent of gross national product. Angell (2005, p. 3) described the US industry as 'The $200 Billion Colossus'. It is one of the most profitable industries in the US, ranking in the top five in terms of returns on revenues, assets, and shareholders' equity, according to *Fortune* magazine (2011). Its marketing budgets are much larger than its research and development costs (Angell 2000b). The Pharmaceutical Research and Manufacturers of America (PhRMA) (www.phrma.org) has a high profile in the media and spends hundreds of millions of dollars lobbying Congress and state legislatures (Pear 2003).

The pharmaceutical industry is also one of the biggest industries in the UK (House of Commons 2005, p. 3), with strong links to government (Abraham 2002). The Association of the British Pharmaceutical Industry (ABPI) (www.abpi.org.uk) represents most UK pharmaceutical companies.

Australia has a relatively small pharmaceutical industry (Messinis 2002, p. 25), but it is significant economically, employing about 40,000 people and turning over approximately $18 billion in 2006-07, and exporting approximately $3.9 billion of products in 2007 (Department of Innovation, Industry, Science and Research 2008). Significantly, its importance is recognised in Australian medicinal drug policy: one objective of the *National Medicines Policy 2000* (CDHAC 1999b) is 'maintaining a responsible and viable medicines industry' (p. 1).

The main public voice of the Australian pharmaceutical industry is the peak body, Medicines Australia (www.medicinesaustralia.com.au) (formerly the Australian Pharmaceutical Manufacturers Association). Medicines Australia spokespeople are frequently quoted in the media, often criticising the Australian Government and associated entities (particularly the Pharmaceutical Benefits Advisory Committee and the Therapeutic Goods Administration, both of which are discussed below). Medicines Australia also administers a controversial industry code of conduct for marketing prescribed drugs (discussed in chapter 7).

Most Australian pharmaceutical companies relevant to antidepressants are subsidiaries of multinational corporations based in the US or Europe. They tend to use similar marketing strategies to those of their parent companies. Consequently, there is considerable discussion in this thesis of antidepressant marketing in other countries, particularly the US.

3.5 GOVERNMENTS

Governments play a major role both in how psychiatric disorders such as depression are addressed, and in how prescribed drugs such as antidepressants are used. They do this overtly through regulation and policy, but also more subtly through funding decisions, committee appointments, and so on.

Governments play a very significant role in relation to all prescribed drugs, regulating the availability (and sometime the price) of prescribed drugs. Not surprisingly,

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different countries have different agencies and systems regulating and funding prescribed drug use. An overview of these arrangements in Organisation for Economic Co-operation and Development countries is provided by Jacobzone (2000).

Governments also powerfully influence the lenses through which social problems are viewed. Many governments have mental health policies; most such policies espouse compassion but reinforce the orthodoxy that locates mental health problems firmly within individuals and locates solutions firmly within the health system rather than society more broadly. When social problems are identified, governments need to be seen to be doing something about them. In many countries, the orthodoxy about depression and antidepressants fits with prevailing neoliberal agendas that allow governments to deflect responsibility for addressing social determinants of mental health and capitalise on populist sentiments that depression is a major social problem that requires increased resources for medical intervention.

3.5.1 US governments

US governments play a major role in the depression/antidepressant arena. In relation to depression, the most important agency has been the National Institute of Mental Health (NIMH), which is influential in psychiatry internationally. After the 1990s were designated 'The Decade of the Brain' by President George Bush, the NIMH and the Library of Congress jointly promoted a neuroscience agenda that reinforced the dominance of biological psychiatry.

In relation to depression specifically, in 1988 the NIMH, in collaboration with many mental health organisations, launched its Depression Awareness, Recognition, and Treatment Program (D/ART) (Regier et al. 1988), a landmark in the global depression arena. D/ART, which was funded by pharmaceutical companies, is discussed in chapter 8. In 2001 the NIMH convened nine scientific workgroups to review the evidence about mood disorders and make recommendations about how to address them. In 2003 the resultant influential report, *Breaking ground, breaking through: The strategic plan for mood disorders research* (NIMH 2003), was published.

More broadly, a landmark report by the Surgeon General, *Mental health: A report of the Surgeon General* (US Department of Health and Human Services 1999), released at the end of The Decade of the Brain, emphasised that psychiatric disorders are real

illnesses that are relatively common, a serious burden, but treatable. Not surprisingly, it strongly endorsed the claim that psychiatric disorders are brain disorders.

Subsequently US President George W. Bush established the controversial President's New Freedom Commission on Mental Health, which investigated the US mental health system. The final report, *Achieving the promise: Transforming mental health care in America* (New Freedom Commission on Mental Health 2003) emphasised: 'mental disability is not a scandal — it is an illness. And like physical illness, it is treatable, especially when the treatment comes early' (p. 2).

Some US state governments also play an important role in psychiatry. Most notable is the Texas Medication Algorithm Project (TMAP), a collaboration between the Texas Department of State Health Services, several Texas universities, and several pharmaceutical companies. The project developed algorithms for the management of psychiatric disorders, including depression, within Texas's publicly funded mental health care system, and has influenced the policies of other state governments. In a recent court case linked to TMAP, Johnson & Johnson agreed to pay $158 million to settle a lawsuit brought by the Texas Attorney in relation to illegal promotion of the antipsychotic Risperdal® (Silverman 2012).

The US Federal Government plays a major role in the regulation of drugs both domestically and internationally. Of particular importance to antidepressants is the Food and Drug Administration (FDA), which is the world's most important regulator of medicinal drugs. It is extremely influential in many countries, including Australia. The FDA, which administers the Federal Food, Drug, and Cosmetic Act, regulates more than just food and drugs. According to the 'What We Do' statement on its website (FDA 2010):

> FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
>
> FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and

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> by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.
>
> Finally, FDA plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

One of the FDA's triumphs was its non-approval of the sedative Thalidomide®, which in other countries (including Australia) caused thousands of babies to be born with limb malformations in the early 1960s (Horton 2001; Harvey & Murray 1995, p. 254). More recently, however, the FDA has attracted considerable criticism for not adequately protecting public health, partly because of its relationships with the pharmaceutical industry (Furberg et al. 2006). This is briefly discussed in chapter 7.

However, the FDA has been criticised by antidepressant advocates for *excessive* caution, namely issuing advisories warning of the potential for antidepressants to trigger suicidal behaviours (Nemeroff et al. 2007). After the first FDA advisory was issued, the Australian TGA issued a similar warning (TGA 2004), as did the New Zealand Medicines Adverse Reactions Committee, Health Canada (the Canadian counterpart of the FDA), the National Institute for Health and Clinical Excellence (NICE, which regulates prescribed drugs in Britain), and regulatory agencies in other countries (Citizens Commission on Human Rights 2006). The relationship between antidepressants and suicide and suicidal behaviours is a key debate. This is discussed in detail in chapter 6.

Two key issues in relation to antidepressants are the controversial FDA public health advisories issued since 2003, warning about increased risk suicidal behaviour associated with SSRI use by children and teens (discussed in chapter 6) and the influence of the pharmaceutical industry on the FDA (discussed in chapter 7).

3.5.2 Australian governments

Australian governments play a major role in the depression/antidepressant arena, as they do in the broader health arena. This includes regulation and funding of health services, health professionals, and drugs of all kinds. In addition, depression is now a key focus of national mental health policy. There was relatively little discussion of depression in early Australian mental health policy documents, but this has changed

significantly since 1997, when depression was identified as a focus of the National Health Priority Areas initiative (AIHW & Commonwealth Department of Health and Family Services 1997). This was further consolidated in the *Second National Mental Health Plan* (Australian Health Ministers 1998), which emphasised the societal burden related to depression (p. 11). Depression now features very prominently in core Australian mental health policy, as well as having its own *National Action Plan for Depression* (CDHAC 2000/2001). Furthermore, this policy focus has resulted in major investment by Australian governments in programs to address depression and mental disorders more generally. The most important programs are briefly discussed here.

beyondblue: the national depression initiative

Established by Commonwealth and state governments in 2000, *beyondblue: the national depression initiative* (www.beyondblue.org.au) dominates the Australian depression/antidepressant arena. Based in Melbourne, it is a national, independent, not-for-profit organisation working to increase awareness of depression and related disorders. It has a very high media profile. Few other countries have equivalent organisations. The background to *beyondblue* is discussed in chapter 9 in relation to the National Depression Awareness Campaign.

Better Outcomes in Mental Health Care

In July 2001 the Commonwealth Government launched the Better Outcomes in Mental Health Care (BOIMHC)[4] initiative, which both recognises and supports the role of GPs in mental health care. BOIMHC has evolved since its inception. Currently it has five major components (Fletcher et al. 2009, pp. 30-31):

- Education and training for GPs: 3 levels: familiarisation training (to familiarise GPs with the BOIMHC program); level 1 training, focusing on use mental health plans; level 2 training, preparing GPs to deliver Focussed Psychological Strategies.

[4] Initially referred to as the Mental Health: More Options, Better Services Initiative. The acronyms BOiMHC and BOMHC are sometimes used.

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- The GP Mental Health Care Plan: three new Medicare items for GP mental health care (preparation and subsequent review of a mental health care plan, and mental health consultations). It was formerly the 3 Step Mental Health Process (assessment of patient, preparation and subsequent review of plan).
- Focussed Psychological Strategies: Medicare rebates for psychological therapies delivered by GPs who have completed level 2 training.
- Access to Allied Psychological Services (ATAPS): Focussed Psychological Strategies delivered by allied health professionals (primarily psychologists).
- Access to Psychiatrist Support: two sub-components: Medicare rebates enabling psychiatrists to organise or participate in case conferences; and the GP Psych Support service, which allows GPs to consult psychiatrists via phone, fax, and email.

Whereas GP mental health care plans, Focussed Psychological Strategies, and psychiatrist case conferences attract Medicare rebates, the other components have a range of funding mechanisms. ATAPS is delivered through projects coordinated by the Australian General Practice Network (previously the Australian Divisions of General Practice) as fund-holder, and the Royal Australian College of General Practitioners is funded to run GP Psych Support.

GP education and training is overseen by the General Practice Mental Health Standards Collaboration (GPMHSC), which is funded by the Commonwealth Department of Health and auspiced by the Royal Australian College of General Practitioners. The GPMHSC sets standards for training and certifies the eligibility of GPs to access Medicare entitlements. It is a joint collaboration of the Australian College of Rural and Remote Medicine, the Royal Australian College of General Practitioners, the Mental Health Council of Australia, the Australian Psychological Society, and the Royal Australian and New Zealand College of Psychiatrists (Australian Divisions of General Practice 2007, pp. 28-29). Some training is funded and/or provided by pharmaceutical companies. This is briefly discussed in chapter 7.

A key aspect of BOIMHC is its emphasis on counselling as an alternative and/or complement to drug treatment. A study by Ryan et al. (2005) of the impact of BOIMHC on GP treatment of depression found greater use of cognitive and behavioural treatments and increased referral to psychologists, However, the amount of time available for GPs to deliver non-pharmacological treatments was an ongoing problem.

Funding for BOIMHC was controversially reduced in the 2011 Federal Budget, and heated debate about it is ongoing in both the media and the medical literature. However, discussion of this is beyond the scope of this thesis.

Better Access to Psychiatrists, Psychologists and GPs through the Medicare Benefits Schedule program

The *Better Access to Psychiatrists, Psychologists and General Practitioners through the Medicare Benefits Schedule* (Better Access) initiative commenced in November 2006. It is funded by the Commonwealth Government as part of the Council of Australian Governments mental health package.

The *Better Access* initiative complements BOIMHC (Fletcher et al. 2009, p. 2). Both programs include mechanisms enabling GPs to refer patients to psychologists and other health professionals for approved non-pharmacological treatments. Whereas BOIMHC does this through *Access to Allied Psychological Services* projects run by the Australian General Practice Network (previously the Australian Divisions of General Practice, the *Better Access* initiative operationalises it through Medicare rebates (Bassilios et al. 2008, p. 2). Both initiatives also increase access to GP and psychiatrist services. As its name suggests, the *Better Access* initiative does this solely through Medicare rebates, whereas BOIMHC also funds programs delivered by relevant organisations such as the Royal Australian College of General Practitioners.

As with the BOIMHC, pharmaceutical companies have been involved in training related to the *Better Access* initiative. Eli Lilly Australia and the Australian General Practice Network jointly developed an education and training module to help GPs prepare mental health care plans (Australian General Practice Network 2008).

In Australia, responsibility for health services is split between the Commonwealth (Federal) Government[5] and state and territory governments (Dartnell 2001, p. 5). This creates many problems, including the fact that the Commonwealth funds GPs

[5] The terms 'Australian Government', 'Commonwealth Government', and 'Federal Government' are often used interchangeably. In this thesis, the term 'Commonwealth Government' is generally used, except when citing sources whose official names include 'Australian Government'.

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(primarily through Medicare) and nursing homes, but states and territories fund most hospital expenditure, along with community health centres and other community-based services. This creates barriers to coordinated health care, and also creates substantial inefficiencies, particularly related to cost-shifting.

The split also includes funding of prescribed drugs. The Pharmaceutical Benefits Scheme (PBS) subsidises many prescribed drugs for Australians, as does the Repatriation Pharmaceutical Benefits Scheme (RPBS) for military veterans and war widows. The PBS is the principal mechanism for ensuring access to prescribed drugs and, according to Duckett (2004, p. 64), it is 'the envy of many other developed countries'. Most GP prescriptions attract PBS or RPBS funding. However, a significant minority of prescriptions are written by hospital doctors and dispensed by hospital pharmacies, to inpatients and sometimes also outpatients. Consequently, they are funded by state and territory governments rather than the PBS. This can cause problematic cost-shifting (Dartnell 2001, p. 7), particularly when patients are discharged from hospitals with inadequate supplies of drugs.

In Australia, regulation of prescribed drugs is both a Commonwealth and a state/territory responsibility. However, the Commonwealth Government dominates, playing multiple roles in the depression/antidepressant arena. Most importantly, the Department of Health and Ageing funds GP and psychiatric treatment, subsidises antidepressant prescriptions, and funds approaches to 'mental health' that are congruent with the current orthodoxy. The most relevant Government agencies, committees, and programs are briefly discussed below. Some committees include pharmaceutical industry representation. Collaboration with the pharmaceutical industry is enshrined in national medicinal drug policy (CDHAC 1999b, p. 1), so this is generally considered appropriate.

Therapeutic Goods Administration

The Therapeutic Goods Administration (TGA) (http://www.tga.gov.au/) oversees the quality, safety, efficacy and timely availability of therapeutic goods, including medicines and medical devices (e.g. syringes, dialysis equipment, pacemakers). Therapeutic goods also include more mundane products such as sunscreens and nutritional supplements, which are included in the definition of medicines (TGA 2004, p. 5).

Australian Drug Evaluation Committee

Until 2010, the TGA sought independent scientific advice about prescribed drugs from the Australian Drug Evaluation Committee (ADEC) (DoHA 2009a, p. 5). ADEC advised on:

- the quality, risk-benefit, effectiveness and access within a reasonable time of any drug referred to it for evaluation
- medical and scientific evaluations of applications for registration of prescription drugs (e.g. new chemical entities, new forms of previously registered drugs and therapeutic variations to registered drugs). (www.tga.gov.au/docs/html/adec/adec.htm 15 February 2004)

Most antidepressants available in Australia were approved before 2010, and have therefore been subjected to scrutiny by ADEC prior to registration.

Advisory Committee on Prescription Medicines

In 2010, ADRAC was replaced by the Advisory Committee on Prescription Medicines (DoHA 2011, p. 5).

Adverse Drug Reactions Advisory Committee

Until December 2009, the Adverse Drug Reactions Advisory Committee (ADRAC), a subcommittee of the ADEC, was responsible for post-marketing surveillance (monitoring of drug safety after drugs have been released on the market) in Australia (DoHA 2009a, p. 5). It reported to ADEC. It collected and evaluated spontaneous reports of adverse drug reactions (ADRs), and published information about them in the *ADRAC Bulletin*, which was distributed free to doctors and pharmacists (Harvey & Murray 1995, p. 255). In 1998, ADRAC issued a warning about the antidepressant nefazodone (ADRAC 1998). Nefazodone is discussed in chapter 9. In 2004, ADRAC released two statements (the second replacing the first) giving guidelines on the use of SSRIs in children and adolescents (ADRAC 2004). This is discussed in chapter 6.

Advisory Committee on the Safety of Medicines

In 2010, ADEC was replaced by the Advisory Committee on the Safety of Medicines, which has 'an increased focus on the safety aspects of medicine regulation and the

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detection, assessment, understanding and prevention of adverse effects' (DoHA 2011, p. 5).

National Drugs and Poisons Scheduling Committee

Until 30 June 2010, the National Drugs and Poisons Schedule Committee (http://www.tga.gov.au/archive/committees-ndpsc.htm) decided how medicines (and poisons) should be scheduled (classified) (Moulds 1997), which influences their regulation in state and territory legislation. Antidepressants are classified as S4 (prescription only medications).

Advisory Committee on Medicines Scheduling

Scheduling of medicines is now undertaken by the Secretary to DoHA (or the Secretary's delegate), with advice and recommendations from the Advisory Committee on Medicines Scheduling (http://www.tga.gov.au/about/committees-acmcs.htm).

Pharmaceutical Benefits Scheme

The Pharmaceutical Benefits Scheme (PBS) (http://www.pbs.gov.au/info/about-the-pbs) provides subsidised drugs for all Medicare-eligible people (primarily Australian and New Zealand citizens). Most but not all antidepressants available in Australia are subsidised by the PBS. There are several different PBS committees, including:

- the **Pharmaceutical Benefits Advisory Committee** (PBAC), which evaluates effectiveness and cost-effectiveness relative to other alternatives (usually other drugs subsidised by the PBS), and recommends to the Minister whether or not a drug should be listed on the PBS and subsidised for specific indications (DoHA 2011, p. 4).
- the **Drug Utilisation Sub-Committee** (DUSC), which focuses on: collection, analysis, and interpretation of data on drug utilisation; identification of potential problems and benefits, evaluation of policy and other interventions; and other functions related to drug utilisation (DoHA 2011, pp. 4-5). DUSC assists the PBAC in making recommendations for PBS listings. DUSC produces (approximately annually) a key publication, *Australian Statistics on Medicines*, which provides valuable information on prescribing and associated

costs. In 1998, DUSC convened a working group to review trends in antidepressant use in Australia (McManus et al. 2000, p. 458).

- the **Economics Sub-Committee** (ESC) (http://www.health.gov.au/internet/main/publishing.nsf/content/health-pbs-general-listing-escmembership.htm), which reviews and interprets economic analyses of drugs required for drugs to be listed on the PBS and advises the PBAC on technical aspects of economic evaluations.

All subsidised antidepressants in Australia have therefore been subject to considerable scrutiny. However, much of the evidence used is derived from industry-funded trials which are subject to considerable bias. This is discussed in chapter 7, as is 'leakage' – prescribing for patients without indications for which drugs have been approved.

Pharmaceutical Benefits Pricing Authority

The Pharmaceutical Benefits Pricing Authority (PBPA) negotiates prices with drug companies (DoHA 2011, p. 3). It receives advice from the PBAC about the cost-effectiveness of drugs. It includes pharmaceutical industry representation (p. 4).

National Medicines Policy Committee and Executive

Australia's national medicinal policy (CDHAC 1999b) is supported by the National Medicines Policy Committee and National Medicines Policy Executive (DoHA 2011, p. 6). The third entity in the three-level advisory structure is the annual National Medicines Policy Partnerships Forum, first convened in June 2009. Similar roles were previously performed by the Australian Pharmaceutical Advisory Council (APAC) and the Pharmaceutical Health and Rational use of Medicines (PHARM) Committee (DoHA 2009a, p. 6).

National Prescribing Service, Australian Prescriber, and the Australian Medicines Handbook

The National Prescribing Service (www.nps.org.au) was established by the Commonwealth Government in 1998 to provide support to health practitioners to improve quality prescribing through education and prescriber feedback. The NPS has

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produced several publications related to antidepressants. In addition, the *Australian Prescriber*, which was outsourced to the NPS in 2002, has published many articles and letters about antidepressants.

Government funding has also been provided for the *Australian Medicines Handbook* (www.amh.net.au), an independent source of expert drug information intended to promote good prescribing. There are also some state government funded prescribing education organisations (Moulds 2003). In part, funding of these organisations is an attempt to counter the influence of pharmaceutical industry advertising and marketing. However, their resources are negligible compared with those of the industry.

Medicare Australia

Medicare Australia (http://www.humanservices.gov.au/customer/information/welcome-medicare-customers-website?utm_id=9) (previously the Health Insurance Commission) came into operation on 1 October 2005. Medicare administers the Pharmaceutical Benefits Scheme and other Commonwealth Government health programs.

Department of Innovation, Industry, Science and Research

As mentioned above, the pharmaceutical industry is important to the Australian economy. The Department of Innovation, Industry, Science and Research (www.innovation.gov.au) (previously the Department of Industry, Tourism and Resources) actively fosters the industry through a number of mechanisms.

3.6 WORLD HEALTH ORGANIZATION

The World Health Organization (WHO) has a strong ongoing mental health program (www.who.int/mental_health/en/index.html). A major focus is mental health in developing countries, but WHO is also a key player in psychiatry in developed countries. As mentioned in chapter 2, the official classification system for psychiatric disorders in Australia and many other countries is the *International Classification of Diseases* (10th ed.) (ICD-10) (WHO 1993), although many psychiatrists use the DSM-IV instead (Andrews et al. 1999, p. 2).

Together with the World Bank, WHO oversaw the Global Burden of Disease study, according to which unipolar depression was the fourth leading cause of disease-

burden in 1990, and will be the second leading cause of disability worldwide by 2020 (Murray & Lopez 1996, p. 4). However, some aspects of the methodology of the study have been criticised, including inappropriate modelling of severity and duration and comorbidity. This is briefly discussed in chapter 4.

3.7 MEDICAL JOURNALS

Medical journals are a major source of information for doctors (and others) about depression and antidepressants (and prescribed drugs more generally). They publish a huge volume of reports of clinical research. Journals also include many advertisements, revenue from which is essential for their financial viability. Most advertisements are for drugs; hence journals are financially dependent on the pharmaceutical industry.

In recent years, serious concern has been voiced about the implications of this dependence. Angell (2000a) baldly asked, 'Is academic medicine for sale?'. There have been cases of suppression of articles for fear of losing advertising revenue (Dyer 2004). Journal supplements are often paid for by pharmaceutical companies to promote new drugs. They often contain articles that have not been peer-reviewed (Fava 2001; Bero et al. 1992).

Other important issues include the use of ghost-writers – professional writers, paid by the pharmaceutical industry, who write papers that are published in the name of influential clinicians and/or academics (Sharp 2000). A particularly relevant example is GlaxoSmithKline's (2000) *CASSPER: Case Study Publications for Peer Review* program, which was used to encourage key opinion leaders to put their names to ghost-written publications favourable to Paxil® (paroxetine). This is discussed in chapter 7, along with relationships between pharmaceutical companies and medical journals more generally. One specific medical journal that has played an important role in Australia, the *Depression Awareness Journal*, is discussed in detail in chapter 9.

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3.8 LAWYERS

Lawyers are sometimes involved in cases in which depression features, for example when it is claimed that workplace conditions have caused depression, or that depression is a mitigating circumstance in a criminal prosecution. Interestingly, a *beyondblue* study (Beaton Consulting 2007) found high rates of depression among lawyers.

Lawyers play a much larger role in relation to antidepressants. Many lawyers are employed by pharmaceutical companies, and others act for governments, health insurance organisations, and so on, in cases related to prescribed drugs, including antidepressants. Many industry lawyers focus on intellectual property and patent protection issues. Pharmaceutical companies frequently sue other companies over such issues. As discussed in chapter 7, the stakes can be extremely high, particularly for 'blockbuster' drugs, and the industry has developed very sophisticated methods for extending the life of patents.

In addition, industry (and other) lawyers are involved in litigation against pharmaceutical companies. Many cases involve people who claim to have been harmed by prescribed drugs, or by relatives of people supposedly harmed (for example when children commit suicide while taking antidepressants). Defence lawyers are usually provided by medical defence organisations that provide malpractice insurance. Lawyers acting on behalf of plaintiffs are usually in private practice. The US firm Baum Hedlund has taken on many cases related to antidepressants, sometimes with assistance from Australian psychiatrist Jon Jureidini (Jureidini & McHenry 2009, p. 200).

In addition, there have been several high-profile trials in which defence lawyers have argued that antidepressants have caused defendants to commit crimes, including murder (Rosack 2001). Most such cases have occurred in the US but one was in Australia (Blood et al. 2003).

3.9 CONSUMER GROUPS AND COMMUNITY ORGANISATIONS

Consumer groups and community organisations play a significant role in the health field. In Australia, the Consumers Health Forum (www.chf.org.au) is the most prominent consumer organisation. Its members are consumer organisations representing a broad range of health consumers. It provides consumer representation on health-related committees, including Commonwealth Government committees, and generally advocates on consumer health issues.

Many other consumer/community organisations, on the other hand, focus on one particular health problem (or a relatively narrow range of problems) and are primarily composed of people with that problem, and/or their relatives. Commonly included in their major roles are consumer representation, advocacy for improved access to treatment, information sharing, and mutual support.

Mental health consumer/community organisations have traditionally had a relatively low profile, for several reasons, including the stigma associated with mental illness. Another reason is the fact that most such organisations have focused on one or more of the more severe disorders, particularly schizophrenia. Most participants have been relatives rather than sufferers.

More recently, consumer/community organisations for less severe psychiatric disorders such as depression have become more prominent. Many have a website; for many it is their main interface with the public. Many advocate for greater access to and/or choice of treatment. Combating stigma is another key theme. These organisations usually endorse the orthodoxy. Many accept pharmaceutical industry funding.

Overlapping with such consumer/community organisations are advocacy organisations that focus on mental health issues but have few if any consumers involved, and do not have consumer representation at the forefront. Instead, they are generally run by professionals and/or community entrepreneurs, and they are more likely to focus on fundraising and awareness raising.

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One particularly important such organisation in the Australian depression/anxiety arena is the Mental Health Foundation of Australia (MHFA), which has very strong ties with pharmaceutical companies. The MHFA is discussed in detail in chapter 9. Relationships between consumer/community mental health organisations and the pharmaceutical industry more generally are discussed in chapter 7.

3.10 OTHER ORGANISATIONS

A range of other organisations also play a role in the depression/antidepressant arena. Several independent organisations in the health field aim to promote evidence-based treatment and good prescribing in all areas of medicine. Among the most notable are the Cochrane Centre, Healthy Skepticism, and No Free Lunch. The latter two have a major focus on countering inappropriate promotion.

3.10.1 Cochrane Centre

With the increasing shift towards evidence-based healthcare (Sackett et al. 1996), the Cochrane Centre (www.cochrane.de), an international non-profit organisation, has become a dominant and respected source of systematic reviews of healthcare interventions. It has produced a number of reviews of the efficacy of antidepressants, and more generally the treatment of depression.

3.10.2 Healthy Skepticism

The Australian-based international non-profit organisation, Healthy Skepticism (www.healthyskepticism.org), aims to improve health by reducing harm from misleading drug promotion and misleading health information more generally.[6] A majority of members are doctors or pharmacists.[7] Healthy Skepticism conducts education and research, the majority of which is unfunded, and it engages in advocacy. It investigates and challenges many forms of promotion, including medical journal advertisements, gifts to doctors, sponsorship, pharmaceutical representatives, and direct-to-consumer advertising. Healthy Skepticism is very critical of the promotion of antidepressants, among many other drug types. Several Healthy

[6] I am a member of Healthy Skepticism, and I have previously been a member of its Management Group.
[7] Healthy Skepticism's identity statement: www.healthyskepticism.org/about/identity.php (11 September 2009).

Skepticism publications critical of antidepressant marketing and marketing more generally are briefly discussed in chapter 7.

3.10.3 No Free Lunch

No Free Lunch (www.nofreelunch.org) is a New York based organisation of doctors and other healthcare providers who believe that pharmaceutical promotion is frequently biased and that accepting gifts from drug companies – even small items such as pens – creates conflicts of interest that adversely influence clinical practice, particularly prescribing.

In April 2011, Healthy Skepticism announced that No Free Lunch was merging with it (Healthy Skepticism 2011). However, the No Free Lunch website is still online.

3.10.4 Church of Scientology/Citizens Commission on Human Rights

A few organisations are stridently opposed to any use of antidepressants and other prescribed psychotropics. Most prominent is the Church of Scientology, which regards psychiatric drugs as harmful: 'Except for antibiotics or other prescribed medical drugs by a medical doctor . . . . Any other drug use, such as the use of street drugs or psychiatric mind-altering drugs, is forbidden' (Church of Scientology International 2003, p. 38). In 1969, the Church of Scientology, together with Thomas Szasz, established the Citizens Commission on Human Rights (CCHR), which is based in the US but also has offices elsewhere, including Australia, and is extremely critical of psychiatry, even referring to it as 'An Industry of Death' (CCHR 2006). As discussed in chapter 6, critics of antidepressants (and other psychiatric drugs) are often erroneously accused of being Scientologists or at least being influenced by Scientology.

3.11 THE MEDIA

Journalists and media companies are another significant group of players. Most journalists accept the depression/antidepressant orthodoxy, and many uncritically report relatively simplistic industry-promoted messages, for example that depression

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is a biochemical disease for which ever better pharmaceutical cures are available and that destigmatisation of mental illness is crucial.

However, a few journalists in Australia have published more critical articles. In 2001 Peter Ellingsen made an important contribution to public discourse in Australia about depression with a series of articles that raised concerns about aspects of the orthodoxy, including the dominance of antidepressant treatment (Ellingsen 2001b). Julie Robotham has published articles analysing the politics of the Australian depression/antidepressant arena, including the animosity between Ian Hickie, inaugural CEO of *beyondblue*, and another prominent psychiatrist, Professor Gordon Parker, who argued against beyondblue's 'dumbed-down model' of depression (Robotham 2002a).

In the UK, Sarah Boseley, *Guardian* health editor, has published many articles critical of antidepressants and their manufacturers. In 2002, she received the Mind [UK National Association for Mental Health] Journalist of the Year Award for her 'excellent investigative journalism' into the psychiatric drug industry. Several articles by these authors are cited in this thesis.

Pharmaceuticals are often regarded by the media as little more than a financial issue, particularly in the UK (Boseley, personal communication, 22 May 2002). Many new drugs are featured in television and newspaper reports, generally in positive terms. These reports are often based uncritically on pharmaceutical company press releases (Shuchman & Wilkes 1997; Moynihan et al. 2000).

Media reports of industry criticism of government policy are also relatively common. As mentioned above, Medicines Australia has a relatively high media profile, and it is frequently quoted objecting to regulatory actions and defending drug company conduct. Less frequently, journalists publish informed critical analyses of drug use and drug promotion which go beyond adversarial scuffles (e.g. Boseley 2003; Sweet 2001).

3.12 HEALTH INSURANCE COMPANIES AND HEALTH MANAGEMENT ORGANIZATIONS

Health insurance companies, including health management organizations (HMOs), play a very significant role in the US healthcare system. Such companies fund

depression treatments, particularly antidepressants. Many health insurance companies strongly regulate which antidepressants and other drugs can be prescribed, and which other treatments can be provided.

Health insurance companies are affected by the cost and cost-effectiveness of antidepressants, so they theoretically would be motivated to minimise the cost and maximise the cost-effectiveness. However, they not uncommonly have alliances with pharmaceutical companies, which can create conflicts of interest.

A key issue in relation to US health insurance companies is 'mental health parity', the principle that health insurance benefits for psychiatric treatment should not be capped at much lower levels than benefits for other medical treatment, as they historically have been. Parity is discussed briefly in chapter 7, primarily in relation to alliances between pharmaceutical companies and consumer/community mental health organisations. It is not particularly relevant to Australia, because psychiatric treatment is not restricted in the same way. However, it is a significant driver of the orthodox story.

3.13 PLAYERS' POSITIONS REGARDING DEPRESSION AND ANTIDEPRESSANTS

Players' positions and attitudes in relation to depression and antidepressants vary enormously and can be very polarised. There are several dimensions on which players can usefully be viewed. Some are simple categorical distinctions such as psychiatrists versus general practitioners versus consumers. Some are polar axes, an obvious one being antidepressant advocate versus antidepressant critic. Three main groups of dimensions are relevant to this thesis.

The first group of dimensions is professional status: health professionals versus laypeople, medical practitioners versus other health professionals, psychiatrists versus general practitioners, health academics versus front-line clinicians, health academics versus other academics (e.g. economists), and so on. Often players will be only one

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(or neither) of each pair, although many academic health professionals have multiple roles, for example as researchers and educators who also do some clinical work, some health professionals are also qualified as non-health professionals (e.g. economists), and some health professionals are also consumers of mental health services.

The second group of dimensions relates to potential conflicts of interest. Many such conflicts are due to financial interests, which occur on a continuum. Pharmaceutical companies have strong financial interests; many doctors have minor financial interests, for example if they accept honoraria from pharmaceutical companies for conference presentations and so on; some doctors own shares in pharmaceutical companies. Health insurance companies have strong but complex financial interests, primarily in relation to the cost-effectiveness of treatments for depression. Other potential conflicts of interest include social status (which is often but not always linked to financial interests) and emotional investment in an issue, often a result of personal or family history.

The third group of dimensions consists of issues on which there is significant disagreement. As mentioned above, there is a polarity between depression/antidepressant advocates and depression/antidepressant critics. In this thesis, I frequently use such terms to refer to groups of people who are generally positive or generally negative about antidepressants (similarly, I also use terms such as depression advocates, depression critics, orthodoxy supporters, and critics of the orthodoxy). However, I recognise that few people are *totally* in favour of or opposed to antidepressants or the orthodox story about depression, and much of the debate focuses on some specific issues that interest both advocates and critics.

Such specific issues include: the validity of diagnosis and treatment of depression, the prevalence and burden of depression, the risk of suicide in depression, the appropriateness of antidepressants and other treatments for depression, the dependence potential of antidepressants, the potential for antidepressants to trigger suicide, and their harmfulness more generally. These and other key issues are discussed in detail in chapters 4 to 6.

However, there are significant incentives for players to be depression/antidepressant advocates overall. As mentioned in chapter 1, using Greenberg's (2009) conceptualisation and terminology, I argue that the orthodoxy about depression and

antidepressants constitutes a powerful network of interconnected belief systems supported by citation distortions. Many of these belief systems are *information cascades*, participating in which can be very beneficial to academic researchers in particular. Such participation is very widespread, and many of the publications I cite in this thesis to illustrate problems with the orthodoxy could readily be replaced by numerous other publications written by other players. However, I also identify some key participants and publications that I believe have been particularly influential.

3.14 CONCLUSION

The players in relation to depression and antidepressants (and many other prescribed drugs) are diverse. Several key distinctions can be made among them, for example in relation to professional status (in particular, being a patient who uses antidepressants is very different from being a doctor who prescribes them; however, some people occupy both roles).

Further distinctions relate to financial interests, which occur on a continuum. Pharmaceutical companies have very strong financial interests, and many other players, including doctors and consumer groups and community mental health organisations, have minor to moderate financial interests, which may result in conflicts of interest.

In Australia, the main medical players in relation to depression and antidepressants are general practitioners, psychiatrists, the Royal Australian College of General Practitioners, and the Royal Australian and New Zealand College of Psychiatrists. Some prominent Australian psychiatrists are discussed in subsequent chapters, particularly chapter 9, which focuses primarily on the Australian depression and antidepressant arena.

General practitioners are the most numerous medical players, providing the bulk of depression diagnosis and treatment. They are significantly influenced by psychiatrists, particularly by industry-funded key opinion leaders.

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Psychologists and other health professionals are much less significant players than doctors, largely because of (and reinforcing) the dominance of antidepressant treatment. Pharmacists play a practical role in dispensing antidepressants, but are sometimes also involved in medication reviews and compliance interventions.

Most pharmaceutical companies relevant to antidepressants are branches of multinational corporations based in the US or Europe. However, Medicines Australia, the peak body for the Australian pharmaceutical industry, plays a distinctively Australian role, including administration of an industry code of conduct for drug marketing. The Australian Government, which has enshrined collaboration with industry in national medicinal drug policy, plays multiple roles, primarily funding GP and psychiatric treatment, subsidising antidepressant prescriptions, and funding approaches to 'mental health' that are congruent with the current orthodoxy.

Most consumers are relatively uninvolved in the depression/antidepressant arena, apart from their own lived experience. However, consumer/community organisations have become more prominent players in recent decades, and often engage with other players.

Many players have multiple and/or ambiguous roles in relation to depression and antidepressants. For example, consumers and potential consumers may also be health professionals, professional bodies may simultaneously represent both advocates and critics, consumer/community mental health organisations may be funded by pharmaceutical companies, and so on. Some of these roles, and potential conflicts of interest, are discussed in more detail in other chapters in relation to specific issues and debates.

Chapters 4 to 6 analyse claims made about depression, suicide, and antidepressants respectively. Many of these claims are made most powerfully by doctors, often in concert with other players, particularly pharmaceutical companies and consumer/community organisations.

Chapter 7 focuses specifically on the pharmaceutical industry and its strategies, including its relationships with other players, particularly the medical profession, consumers, consumer/community organisations, governments. There is also a focus on claims made about these relationships, as well as claims about the role of the industry.

Chapter 8 focuses on depression awareness campaigns, a key strategy for marketing depression as well as antidepressants. Key opinion leaders, consumer/community organisations, and the media play major roles in these campaigns. Health professional organisations are also often involved. Less commonly governments

Chapter 9 shifts the focus more specifically to the Australian depression/antidepressant arena, analysing the activities and alliances of some high-profile players and claims-makers, particularly in the National Depression Awareness Campaign.

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Chapter 4
Current debates about depression

4.1 INTRODUCTION

It is commonly claimed that depression is common, serious, and treatable (Regier et al. 1988; Ellis et al. 2003; Royal Australian and New Zealand College of Psychiatrists [RANZCP] 2004b). Implicit in the third claim, that depression is treatable, is a fourth claim, that it is an illness or disease.[1] These four claims, and associated variants, are the most dominant and influential claims about depression, constituting the core of the current orthodoxy about depression.

As stated in the introduction to this thesis, I argue that there has been a systematic inflation of the extent and significance of depression in Australia (and most other developed countries). These four claims about depression, separately and in tandem, are powerful drivers of this inflation. This chapter discusses and critically analyses these claims as they are promoted primarily by people who advocate the use of antidepressants. Claims are analysed both in terms of who is arguing what and why, and to what extent the claims are supported by evidence.

Each of the claims has multiple variants that are considered. Many of the claims are explicit, and are forcefully argued. However, some claims tend to be expressed implicitly, making them harder to subject to critical scrutiny.

Many of the claims have first been articulated in the psychiatric literature, and have subsequently been disseminated in pharmaceutical company promotional materials, in the broader medical literature (particularly general practice literature), by consumer organisations, and in the media. However, it is important to recognise that the majority of psychiatric research is funded and influenced by the pharmaceutical industry (this is discussed in chapter 7). Consequently, the origins of many claims are strongly linked to pharmaceutical industry agendas.

[1] The terms disease and illness are used interchangeably in this thesis, as they are in many of the publications and other sources discussed. Although there are valid arguments for distinguishing between the two terms in some contexts, with 'disease' denoting pathology and 'illness' denoting the experience of unhealth (Boyd 2000, pp. 9-10), that distinction is not important for the analysis in this thesis.

The majority of this chapter is organised under main four headings, each of which subsumes multiple variants of the main claim:

- Depression is a disease
- Depression is common
- Depression is serious
- Depression is treatable

These claims are key components of 'depression literacy', according to the advocates of which people need to be educated that depression is a disease, and so on (beyondblue 2007; Parslow & Jorm 2002). Depression literacy is the major focus of 'mental health literacy', which is promoted as an important strategy for encouraging early recognition of, and help-seeking for, mental health problems (Wright et al. 2006).

The penultimate section of this chapter discusses claims about critics of depression, for example that they are ignorant or callous.

There are many other claims about depression that are also worthy of critical analysis, including:

- Depression has strong genetic underpinnings
- Depression is a chronic disease
- Depression is common among old people
- The incidence/prevalence of depression among young people is increasing
- Subthreshold depression is likely to progress to clinical depression
- Depression screening is necessary, particularly for young people
- Depression treatment guidelines are evidence-based
- Depression usually requires long-term treatment
- There are much better treatments for depression today than previously

However, space precludes consideration of these claims here.

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A number of problematic claiming techniques or strategies used by depression advocates emerge as patterns in this chapter. Most notable are:

- inappropriate generalisation
- blurring of categories
- emotive language and arguments
- lack of referencing
- selective citation of references, omitting those that challenge the orthodox story
- attacking convenient scapegoats

A number of logical fallacies crop up repeatedly in this chapter and the next two chapters, which focus on debates about suicide and antidepressants respectively. These include:

- false dichotomies
- ad hominem arguments
- straw man arguments

These are used to defend the orthodox story and/or attack critics.

4.2 DEPRESSION IS A (BRAIN) (CHEMICAL) DISEASE

It is commonly asserted that depression is a disease or illness. This medicalisation of distress is fundamental to the orthodox story about depression.

Medicalisation is the process of constructing an issue (often a problem) as something to be viewed with a medical lens and addressed with medical skills and technologies. The term tends to have negative connotations – people who use the term are usually critical of the construction. Natural processes such as childbirth and death are well established targets of medicalisation (Conrad 1992), generally accepted by the community; more contentious targets include personal and social problems such as shyness (Moynihan et al. 2002, p. 888) and sexual orientation (Tiefer 2006). Medicalisation of depression occupies a middle ground of acceptance.

There is such concern about inappropriate medicalisation of personal and social problems that the *BMJ* (previously the *British Medical Journal*) devoted a special issue to the topic (13 April 2002). The issues identified included old age, sexual behaviour, baldness, and anxiety (Double 2002). Critics of the medicalisation of distress specifically include Heath (1999), Gardner (2003), and Fullagar and Gattuso (2002).

Among those most vociferously claiming that depression is a disease or illness are two of the most prominent US consumer/community advocacy groups, National Alliance for the Mentally Ill (NAMI) and Mental Health America (previously the National Mental Health Association). 'Depression is a real, biological disease', David Shern, President of the National Mental Health Association was quoted by NAMI (2006). More recently, NAMI (2009, inside cover) asserted that 'Major depression is a medical illness that affects thoughts, feelings, behavior, mood and physical health'.

Depression is also commonly referred to as a disease or illness in Australia. A key proponent of this claim is Professor Ian Hickie: 'Depression is a devastating illness' (Hickie et al. 2003, p. 7); 'Depression is a serious illness that causes both physical and psychological symptoms' and 'Depression is a common illness' (Hickie & Scott 2007, p. 2).

Several decades ago, one US psychiatrist expressed particular enthusiasm for the status of depression as a disease:

> From the psychiatrist's viewpoint only, depression is an exceedingly satisfactory disease. It is comforting, in this day of existential doubt and psychosocial malaise, to have an illness that is quite treatable and that is recognized by almost everyone as a real illness demanding real treatment. (Cole 1974, p. 204)

However, advocates of the depression orthodoxy argue that the attitudes of the public are far from satisfactory, because many people do not accept that depression is an illness (Gattuso et al. 2005, p. 1641). Consequently the Australian government (among other players) seeks to remedy this by promoting 'depression literacy' (p. 1640).

A major problem for such advocates is that depression does not fit mainstream medical criteria for disease status. There is no objective biological diagnosis – there

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are no pathological signs, nor are there any biochemical tests that can accurately confirm that someone is suffering from depression.[2] According to the DSM-IV (*Diagnostic and statistical manual of mental disorders*, 4th edition) (American Psychiatric Association [APA] 1994, p. 323): 'No laboratory findings that are diagnostic of a Major Depressive Episode have been identified'.

This is the case for most psychiatric disorders: there are few definitive biochemical tests or genetic markers comparable to those for many physical illnesses:

> The diagnosis of mental disorders is often believed to be more difficult than diagnosis of somatic or general medical disorders since there is no definitive lesion, laboratory test or abnormality in brain tissue that can identify the illness. (US Department of Health and Human Services 1999, p. 2-18)
>
> With a few exceptions, the unit of analysis in psychiatric epidemiology – the case – is not flagged by a 'pathognomonic lesion' or by a disease marker, such as high blood pressure or tumour cytology, that could reliably identify 'caseness'. (Jablensky 2002, p. 298).

The lack of objective biological diagnostic methods is actually useful to the pharmaceutical industry, because it facilitates disease (condition) branding:

> No therapeutic category is more accepting of condition branding than the field of anxiety and depression, where illness is rarely based on measurable physical symptoms and, therefore, open to conceptual definition. (Parry 2003)

Disease/condition branding is a key marketing strategy related to disease awareness campaigns (discussed in chapter 7).

Advocates of depression as a disease almost always regard it as a brain disease. According to the NAMI (2006):

> Indisputable scientific evidence shows depression to be a biologically-based disease that destroys the connections between brain cells and can affect every aspect of a person's health.

Depression is very often referred to as a 'chemical imbalance', a type of brain disease caused by a deficiency or imbalance of the brain neurotransmitter serotonin, and/or other neurotransmitter abnormalities (Leo & Lacasse 2008). According to Australian

[2] In the 1980s, some researchers claimed that the dexamethasone suppression test (DST), which measures suppression of plasma cortisol after dexamethasone administration (non-suppression is considered abnormal) was a suitable diagnostic test for at least some subtypes of depression. However, both its sensitivity and its specificity are weak, giving it limited clinical utility (APA 1987), and it is infrequently mentioned in the current literature.

psychiatrist Phillipa Hay (2008), 'Depression is a serious medical illness caused by imbalances in the brain chemicals that regulate mood'.

The theory that depression is a chemical imbalance leads logically to claims that it requires antidepressants to correct it (National Alliance for Research on Schizophrenia and Depression 1995, reproduced in Valenstein 1998, p. 178; Weinstein 2004, p. 2). This theory has been very influential in Australia, permeating government documents such as the Commonwealth Department of Health and Aged Care's (2000) brochure, 'What is depression?', which declared: 'depressive episodes are thought to be due in part to a chemical imbalance in the brain. This can be corrected with anti-depressant medication' (p. 4). A National Prescribing Service newsletter informed consumers and consumer organisations that:

> People with moderate and severe depression often have lower levels of some of the chemicals found in the brain. These chemicals include serotonin, noradrenaline and dopamine. Prescription antidepressant medicines reduce the symptoms of depression by restoring the imbalance of these chemicals. (2008, p. 1)

According to *beyondblue* Deputy Chief Executive Officer Nicole Highet, antidepressants 'work over time to restore a normal chemical balance in the brain' (Barr 2006), and a *beyondblue* (2008) fact sheet asserted:

> Research shows that more severe forms of depression are associated with specific changes in the brain's chemical message systems. When someone is depressed, they have lower levels of brain chemicals such as serotonin, noradrenaline and dopamine. This makes it more difficult for messages to be conveyed within the brain. Antidepressant medication is designed to correct this imbalance, which helps the brain function in a normal way. (p. 1)

However, the chemical imbalance theory is being increasingly questioned (Lacasse & Leo 2005; Leo & Lacasse 2008, Valenstein 1999, Healy 1999; Jureidini & Raven 2009). Remarkably, prominent US Professor Ronald Pies argued last year that the theory had in fact never been accepted by psychiatrists but was a straw man argument used by critics of psychiatry:

> I am not one who easily loses his temper, but I confess to experiencing markedly increased limbic activity whenever I hear someone proclaim, "Psychiatrists think all mental disorders are due to a chemical imbalance!" In the past 30 years, I don't believe I have ever heard a knowledgeable, well-trained psychiatrist make such a preposterous claim, except perhaps to mock it.

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> On the other hand, the "chemical imbalance" trope has been tossed around a great deal by opponents of psychiatry, who mendaciously attribute the phrase to psychiatrists themselves. And, yes – the "chemical imbalance" image has been vigorously promoted by some pharmaceutical companies, often to the detriment of our patients' understanding. In truth, the "chemical imbalance" notion was always a kind of urban legend – never a theory seriously propounded by well-informed psychiatrists.

Despite the decline of the chemical imbalance theory, the term 'neuropsychiatric' is increasingly used to refer to depression and other mental disorders (e.g. World Health Organization 2001, p. 23), and research methods are shifting accordingly. Among advocates, there is optimism that neuroimaging ('brain scans') and other neurological technologies will rectify the lack of objective diagnostic methods (First & Regier 2003; Pincus 2003). Meanwhile, however, psychiatric diagnosis and nosology (classification of diseases) and epidemiology remain inherently complex and contentious, necessarily involving subjective assessments:

> because the classic psychiatric disorders have no pathognomonic laboratory tests, interviewing and precise observation (the mental status examination) are the core of psychiatric diagnosis. (Sierles et al. 2004, p. 1477)
>
> the need to rely almost exclusively on symptoms, behavioral observation, response to treatment, course, and outcome – manifestations that are more difficult to measure with reliability and precision – has put psychiatric nosology at a great disadvantage compared with physical illness. (Schoenbach & Rosamond 2000, p. 69)
>
> the psychiatric epidemiologist has to make sense of subjectively reported symptoms or observed behaviour to infer a diagnostic classification of cases (Jablensky 2002, p. 298).

Despite the lack of objective diagnostic methods, many psychiatrists argue that depression diagnosis is valid:

> "There isn't a blood test for depression but it can be diagnosed quite accurately," says Professor Beverley Raphael, Director of Mental Health Services in NSW. "If you've been feeling miserable for more than two weeks in the profound sense, are unable to function in the usual way, have lost interest in the outside world or have any thoughts of suicide then it's time to go to your doctor." (Hospitals Contribution Fund 1999)

Claims such as Raphael's that diagnosis can be accurate despite the lack of objective assessment methods are challenged by evidence that reliability, including inter-rater reliability (agreement among independent assessors), can be relatively low (Beck 1962; Shear et al. 2000; Spiegel 2005; Aboraya et al. 2006; Kendell et al. 1971). In addition, for many disorders there are multiple sets of diagnostic criteria, agreement

among which can be relatively low (Bertelsen 2004). Furthermore, diagnostic criteria have changed significantly over time and are sometimes very contentious. Depression was not included in the American Psychiatric Association's *Diagnostic and statistical manual of mental disorders* (DSM) until the third edition (1980) (Hirshbein 2006).

Depression is officially diagnosed on the basis of standard diagnostic criteria, the most dominant globally being the American Psychiatric Association's *Diagnostic and statistical manual of mental disorders* (DSM), followed by the World Health Organization's (1992) *ICD-10 Classification of mental and behavioural disorders*. The DSM and ICD criteria for depression, like those for other psychiatric disorders, are based on the *opinions* of expert psychiatrists, most of whom have financial links to pharmaceutical industry. So claims that depression is a disease are based on subjective opinions of people with vested interests. Many lay people would be surprised to know this, assuming that there are objective scientific criteria for diagnosis of depression.

Claiming that an entity is a disease is often a highly political act, involving strong vested interests. Money is at stake, but often there are non-monetary payoffs as well, including professional status, public attitudes towards sufferers, and legal ramifications (e.g. the use of depression as a legal defence in criminal cases).

As briefly mentioned in chapter 1, there are significant parallels between the claim that depression is a disease and the claim that alcohol dependence is a disease called 'alcoholism' (and derivative claims that dependence on other drugs, and problem gambling, and an increasing list of other problems characterised by harmful behaviour are similarly diseases). The claim that such dependence is a disease underpins and is fiercely defended by a very profitable treatment ('rehab') industry in the United States in particular. It is also fiercely defended by members of Alcoholics Anonymous (AA), who are taught that 'alcoholism' is a progressive disease over which they are powerless. People who find this a useful explanation are likely to remain in AA, at least until they relapse, at which point they may be likely to drink heavily because of their belief that they are powerless, as stated in the first step. Other people (the majority of people with alcohol problems) reject this proposition and explore other solutions.

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There has been debate for decades about the validity of the disease model of 'alcoholism'. The evidence for it, and for the effectiveness of AA's twelve-step program, is slight (Ferri et al. 2006; Miller 2008). However, the ideology for both is very powerful. Generally, alcoholism has been viewed as *either* a disease or a moral failing; this false dichotomy is accepted by most participants in the debate. Other possible explanations, such as social influences, are generally ignored. This is a major reason for hostility towards people who dispute the disease model – they are considered to be blaming alcoholics.

Much of the debate about the validity of the disease model of 'alcoholism' and other so-called addictions has occurred in the sociological literature, often focusing on claims-making processes in historical context. An excellent example is Reinarman's (2005) paper, 'Addiction as accomplishment: The discursive construction of disease'. According to Reinarman (p. 307), 'The ubiquity of the disease concept of addiction obscures the fact that it did not emerge from the accretion of scientific discoveries'. A similar case can be made for depression.

There has been less debate about the validity of the disease model of depression, for a number of reasons. Firstly, depression-as-disease is more plausible to many people than alcoholism-as-disease, because the traditional symptoms of depression (e.g. sleep problems, lack of energy, and weight loss) are expressed more internally than many of the symptoms of alcoholism (e.g. drunkenness, violent/abusive behaviour, drink-driving, vomiting and other bodily incontinence, sexual impropriety, and absenteeism). Secondly, although widely regarded as weakness, depression is not as likely as alcoholism to be seen as a *sin*. Depression symptoms are more socially acceptable than alcoholism symptoms. There is a significant gender dimension to this: it is more acceptable (and more likely) for a woman than a man to be depressed, and it is more acceptable (and more likely) for a man than a woman to be alcohol dependent. Thirdly, psychiatrists have historically been more interested in treating depression than alcoholism, and their willingness to treat it has given it credibility as a medical problem. Fourthly, depression was not recognised as a profitable problem until the 1960s, so there was no commercial promotion of the concept of depression-as-disease until recent decades, and therefore less need for critics to challenge the concept.

Nevertheless, there currently is a debate about whether depression is a disease. Most health professionals would probably agree that it is a disease (although they might be

more comfortable with the word 'illness'), but a minority, including some psychiatrists, strongly disagree. Lay people are less likely than health professionals to endorse the disease concept.

The desire of psychiatrists to persuade people that depression is a disease is also related to negative public attitudes towards psychiatry. Commenting on poll results finding that many Americans mistrust psychiatrists, the chair of the APA's Committee on Public Affairs emphasised that 'It is important that the public understand that psychiatrists are medical doctors who are charged with the treatment of medical illnesses' (Bender 2007). Currently depression is the most likely reason for people to receive psychiatric treatment, so it is particularly important for psychiatrists to persuade people that depression is a disease.

4.3 DEPRESSION IS COMMON

> Depression is common, serious, and treatable. (Ellis et al. 2003, p. 34)

It is often claimed that depression is common (Kessler et al. 2003, p. 3095; Andrews et al. 1999, p. 7; Hickie, Davenport, Naismith, & Scott 2001, p. S4), and that its prevalence is increasing (Bland 1997; Lewinsohn et al. 1993). It is also claimed that depression is *increasingly* common.

In this section, it is argued that these claims overstate the magnitude of the problem. There are several reasons, most significant of which is increasingly broad diagnostic criteria.

The above quote from the summary of RANZCPs' (2004b) 'Australian and New Zealand clinical practice guidelines for the treatment of depression' echoes the key message of the industry-funded US National Institute of Mental Health's (NIMH's) Depression Awareness, Recognition, and Treatment (D/ART) Program, that depressive disorders are 'common, serious, and treatable' (Regier et al. 1988, p. 1351). The RANZCP guidelines themselves go a step further, stating that '*Clinical* depression is common, serious and treatable [italics added]' (p. 389), asserting that it is *real* depression that is common, not everyday blues.

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Depression is now accepted in many countries as a major social and public health issue. In the World Health Organization's landmark Global Burden of Disease study, unipolar major depression was calculated to be the fourth leading cause of disease burden in the world in 1990 (Murray & Lopez 1996, p. 4). In Australia, Mathers et al. (2000) found that depression was the fourth leading cause of disease burden in Australia in 1996, and the top-ranking cause of non-fatal disease burden, causing 8% of the total years lost due to disability.

In the US, the National Comorbidity Survey – Replication (NCS-R) reported a lifetime prevalence of 16.2% and a 12-month prevalence of 6.6% (Kessler et al. 2003, p. 3095). In Australia, the 2007 National Survey of Mental Health and Wellbeing found a lifetime prevalence of affective disorders of 15% among adults. The 12-month prevalence was 6.2% (Slade et al. 2009, p. 5). Women had higher rates than men (7.1% versus 5.3%) (p. 6). The Child and Adolescent Component of the survey found that the 12-month prevalence of depressive disorder among children and adolescents was 3.7% (Sawyer et al. 2000, p. 20).

Often there is an emphasis on the prevalence of depression among GP patients, in addition to prevalence in population surveys. According to Lader (2007, p. 1657), 'Depression is the most frequent and costly problem in primary care, where most of these patients are seen and treated'.

Furthermore, it is commonly claimed that the prevalence of depression is increasing. According to the Cross-National Collaborative Group (1992, p. 3098), 'Cross-nationally, the more recent birth cohorts are at increased risk for major depression'. Certainly diagnosis of depression has increased significantly in recent decades, as has the number of people receiving treatment (Olfson et al. 2002). Edward Shorter, a prominent historian of psychiatry, has noted:

> Depression has passed from being a rather obscure illness called melancholia, mainly seen in asylums to the number one cause of clinical disability in the world. (Shorter 2001, p. 1)

In the World Health Organization's Global Burden of Disease study, unipolar major depression has been projected to be the second leading cause of disability worldwide by 2020 by 2020 (Murray & Lopez 1996, p. 375) and the leading cause both for females and in developing countries (p. 377). Partly because of that projection, depression has been referred to as a 'Social and economic timebomb' (Dawson &

Tyrer 2001). There have been similar projections about depression in Australia (Mathers et al. 2000). However, the methodology used by Murray and Lopez to estimate the burden of depression is problematic for a number of reasons, including the fact that it attributed all cases of suicide entirely to depression, ignoring many other factors. This is discussed in chapter 5. In addition, according to Andrews (2000, p. 26), 'The burden due to unipolar depression used a case history for the disability weighting procedure that was severe, not average', and 'no allowance was made for comorbidity between mental disorders' (so there would have been double-counting).

The Australian projection was referred to in an address to National Press Club by the Chief Executive Officer of Medicines Australia:

> the rapidly growing incidence of depression is cause for major concern …. By 2020 depression will be the most common serious illness in Australia (Delaat 2005)

In Australia, depression was the fourth most common problem managed in general practice in 1998-99, compared with the tenth most common problem in 1990-91 (McManus et al. 2000).

Many commentators emphasise the economic dimension of depression. For example, according to Mendlewicz (2001, p. s1):

> Depression is a growing burden, in terms of both economics and quality of life, for patients, families, employers and payers worldwide

Obviously one reason for claiming that depression is common is to persuade governments to increase funding for depression treatment (and mental health services more generally). This is an example of 'demonstrating the problem' (Wiener 1981, p. 22). Another reason is the belief that public knowledge that depression is common will help to destigmatise it (beyondblue 2004; Pethick 2005).

However, there are several important challenges to claims that depression is common and that its prevalence is increasing:

1. Problematic diagnosis, and problematic changes in diagnostic criteria
2. Inaccurate interpretation of epidemiological evidence
3. Inappropriate medicalisation of distress

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Problematic diagnosis, and problematic changes in diagnostic criteria

Although statistics on the incidence/prevalence have increased dramatically in recent decades, the trends cannot be taken at face value. Probably the most important issue is that criteria used in successive versions of the American Psychiatric Association's *Diagnostic and statistical manual of mental disorders* have become increasingly broad. Earlier versions specified much narrower boundaries than recent versions, which have allowed a much greater proportion of the population, with milder forms of depression, to receive a diagnosis of depression (Ebmeier et al. 2006). According to Blair-West et al. (1997):

> In essence, current classifications of major depression now contain specified inclusion and exclusion criteria which can be attained with less severe levels of depression. (p. 262)

Bostwick & Pankratz (2000, p. 1925) noted:

> "depression" is no longer defined as it was in 1970. Subsequent editions of DSM have made the diagnosis of a major depressive episode more inclusive. Today up to 20% of the population meet criteria for a watered-down, broad, and, ultimately, a less lethal depressive diagnosis.… in 1972, the lifetime prevalence of depression in the American population in DSM-II terms was 2%–3%, when the definition of depression included only involutional melancholia, the unipolar form of manic depression, psychotic depression, and "severe depressive neuroses." By 1994, under the rubric of DSM-IV, the lifetime prevalence of depression had increased to 10%–20%. The major difference between 1972 and 1999 is not that we are caught in an affective epidemic…. Today, many more people carry a depressive label, but the incidence of the severe forms remains relatively low.

Notably, when the first antidepressants were developed, it was not considered that there was a viable market. Since then, broadened diagnostic criteria have helped to dramatically expand the market into an extremely profitable one.

There is *some* equivocal epidemiological evidence that the actual prevalence of depression is increasing (Bland 1997; Lewinsohn et al. 1993), but not to the same extent as its diagnosis and treatment. However, other evidence suggests relative stability in prevalence (Murphy et al. 2000; Hawthorne et al. 2008).

Inaccurate interpretation of epidemiological evidence

One factor in the inflated estimates relates to epidemiological interpretation. In particular, it is common for point prevalence to be confused with lifetime prevalence or twelve-month period prevalence. For example, according to a much-cited paper by

Kessler et al. (1994) reporting the results of the landmark US National Comorbidity Survey:

> More than 17% of respondents had a history of major depressive episode (MDE) in their lifetime, and more than 10% had an episode in the past 12 months. (p. 10)

The *twelve-month* prevalence of more than 10% is often misquoted as *point* prevalence. For example, according to Rascati et al. (2001, p. 402:

> Depressive disorders are among the most common illnesses seen in the general medical setting. More than 10% of the population suffers from depression *at any given time*. [italics added]

Rascati et al. cited Kessler (1994) in support of this claim. More often, no reference is cited. This makes it difficult to evaluate the validity of the claim.

Inappropriate medicalisation of distress

Many people are unhappy for significant periods of time. However, this does not necessarily mean that they have a disease called depression. Many people are unhappy because of their life circumstances; their unhappiness is often a rational response to losses, disadvantage, ill health, and so on.

Contradicting most of his peers, one Australian psychiatrist commented:

> Working in mental health, I am familiar with the regular references to a growing crisis in the sector, with statistics suggesting that up to one in three people suffer from an undiagnosed mental health problem. But my feeling is that as a society, especially in the dominant, secular, rational world view, the language of mental health provides the words we now use to describe any form of emotional distress, especially when used in combination with the word "stress". As a result, when we feel overwhelmed or even just contemplative, we are more likely to call the feelings depression or an anxiety disorder. (Ahmed 2006)

4.4 DEPRESSION IS SERIOUS

Claims that depression is common are more often than not accompanied by claims that it is serious (e.g. Ellis et al. 2003, p. 34; Ebmeier et al. 2006, p. 162). According to Kessler et al. (2003), depression is 'a very common and very serious illness' (p. 3096), and 'a seriously impairing condition' (p. 3104).

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Overall, the claim that depression is serious is most likely to be based on its association with suicide, followed by its association with reduced productivity and other economic costs. In recent years, however, its association with physical illnesses has received increasing attention.

Several of these claims are included in this emotive quote from the US *Depression is Real* campaign, launched in 2006 with funding from Wyeth, the manufacturer of antidepressants including Effexor®/Efexor®:

- Depression is a serious and debilitating disease that affects every aspect of a person's health. Depression affects 15 million Americans a year, as well as their family members, friends, and co-workers.
- Depression has serious and potentially fatal consequences. In fact, untreated depression kills thousands of Americans each year through suicide and by intensifying the symptoms of life-threatening illnesses like cancer and heart disease. (Depression Is Real Coalition 2006)

Obviously, pharmaceutical companies that market antidepressants have a vested interest in promoting the orthodoxy that depression is a serious problem. Similarly, it is beneficial for mental health community/consumer organisations to persuade people that depression is serious.

In this section, it is argued that the severity of depression is exaggerated, often greatly, in the academic literature and the media. There are several aspects to this, most significant of which is inappropriate generalisation, firstly from clinical samples to the population, and secondly from tertiary and secondary clinical samples to primary care (general practice) samples.

Furthermore, it is often claimed that it is *untreated* depression that is so serious. Several such claims are also critically analysed here. Often no evidence is cited about treatment status. When evidence is cited, it is frequently derived from studies of *treated* people, which are much more numerous than studies of untreated people. This blurring of treated and untreated depression represents citation misrepresentation.

4.4.1 Depression is serious

It is increasingly accepted by the Australian public that depression is a serious disorder. Two factors contributing to perceptions that it is debilitating are media coverage and exposure to *beyondblue* (Highet et al. 2006, p. 58).

In addition, authoritative medical sources routinely state that depression is serious. For example, according to the RANZCP (2004b, p. 390):

> Moderate to severe depression is as disabling as congestive heart failure, and its relapsing nature accounts for one of the highest levels of disease burden of any condition.

However, the RANZCP assertion, like many such claims, is problematic. Two references are cited for the first part of the sentence (Wells et al. 1989; Hays et al. 1995). Both are reports from the Rand Medical Outcomes Study, a key US study that investigated the outcomes of *treatment* of a range of conditions including depression. The RANZCP guidelines did not acknowledge that the reported disability occurred *despite* treatment. Many readers would assume that this disability was found in the absence of treatment.

Some commentators emphasise the personal impact of depression as well as its medical consequences. According to Ebmeier et al. (2006, p. 162), depression is 'a very common, incapacitating, and occasionally lethal illness…. which is by its very nature associated with the most profound suffering'.

The seriousness of depression is often distorted by inappropriate generalisation from extreme cases. Commonly, studies of depressed patients in tertiary treatment settings, who usually have very severe depression, are generalised to depressed patients in primary care and even depressed people in the general population. Very problematically, it is often assumed that people who meet diagnostic criteria for depression (and other common mental disorders) in community surveys such as the National Survey of Mental Health and Wellbeing (Australian Bureau of Statistics 2008) necessarily require treatment. This view is explicitly rejected by leading psychiatric epidemiologists (as discussed by Raven 2010c), but is part of the orthodox story about depression, and it is supported by inappropriate generalisation from clinical samples grossly unrepresentative of untreated people in the community.

The generalisation of severe cases of depression to the broader population of people with depression is a good example of the *clinician's illusion* or *clinician's fallacy* (Cohen & Cohen, 1984), the bias resulting from the fact that clinicians are more likely to see the more severe and chronic cases of any illness or problem (and to see them

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more often). Because the less afflicted cope better and need less help, clinicians are often oblivious to mild cases and cases that resolve with little or no treatment. Too often, they assume that all cases are like the ones they see, or will inevitably become as severe. Because clinicians are more likely to *repeatedly* encounter progressively severe cases, the clinician's illusion also encourages assumptions of progressiveness – the idea that a mild disorder is *likely* to become more severe over time, a common theme in psychiatry. However, assuming that all cases of depression are serious and progressive is akin to assuming that all cases of cancer are terminal.

Significantly, major depression is increasingly included under the rubric of 'serious mental illnesses' (e.g. Gallop 2009; FDA 2009), which are distinguished from less serious mental illnesses. The clinician's illusion is a major contributor to this.

Inappropriate generalisation also happens in the media. For example, according to a journalist (Mascarenhas 2005):

> In his haunting memoir Darkness Visible, US writer William Styron described depression as a "howling [storm] inside the brain ... a torment alien to everyday experience". This is what sufferers have to stifle each time they attend a job interview, address a meeting, hobnob after work or make small talk with the boss in the lift.

However, Styron's experience of depression – which he described in harrowing detail – was unusually severe. He was hospitalised for seven weeks (Styron 1990, p. 72); most people with depression are never hospitalised.

Clearly, for some people, depression is a very negative state indeed. However, it is often relatively mild (Hegarty 2005, p. 8) and relatively brief (Patten 2001; Spijker et al. 2002). Many cases are self-limiting (Kendler et al. 1997), resolving without treatment (Posternak et al. 2006; Parker 2000b). This is particularly the case for GP patients (Van Weel-Baumgarten et al. 1998), and even more so for people who do not seek treatment, because of the 'powerful effect of self-selection' based on severity (Coryell et al. 1995, p. 1129).

4.4.2 Depression is potentially lethal

Claims that depression is potentially lethal (e.g. Ebmeier et al. 2006) usually focus on suicide. The relationship between depression and suicide is discussed in chapter 6. However, it is also claimed that depression is responsible for increased mortality from other causes. According to Hickie et al. (2003, p. 7):

> People with depression … not only die as a consequence of suicide and accidental death but also from increased abuse of alcohol and tobacco as well as increased rates of heart disease.

It is generally implied, and often explicitly claimed, that it is *untreated* depression that is potentially lethal. The Depression Is Real Coalition (2006) quote above claimed that 'untreated depression kills thousands of Americans each year'. Similarly, according to the US National Alliance for the Mentally Ill (2006): 'depression is a serious, debilitating disease that can be fatal if left untreated". Such claims have also been made in Australia. According to Hickie et al. (2003, p. 7):

> people with untreated depression are at risk of a whole range of adverse medical and social consequences. A person's capacity to work and function in personal settings is greatly reduced…. The lifetime risk of suicide, attempted suicide and accidental injury is greatly increased.

However, as mentioned earlier in this section, there is frequent blurring of treated and untreated depression, and relatively little evidence about the latter.

4.4.3 Depression is a risk factor for physical illnesses

Depression is increasingly claimed to be a significant cause of physical illnesses. According to Hickie et al. (2003, p. 7):

> Depression causes a wide variety of bodily changes, including disturbances of the immune system, hormones, heart and gut. People with depression become physically ill as well as emotionally disturbed.

This claim is largely based on evidence that depression is associated with physical illnesses. However, such associations do not prove causation, and they result partly from 'Berkson's bias': 'an increased tendency for persons with multiple diagnoses to seek and receive treatment and thus fall into study populations drawn from treatment sources' (Helzer & Pryzbeck, 1988, p. 219), which is related to the clinician's illusion.

4.4.4 Depression imposes major societal and economic costs

The famous claim by the World Health Organization and the World Bank that unipolar depression will be the second leading cause of disability world-wide by the year 2020 (Murray & Lopez 1996, p. 375) has been generally accepted at face value with very little scrutiny of the assumptions on which it is based.

Economic costs were also emphasised in the NIMH D/ART Program:

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> Unrecognized, untreated, and undertreated depressive disorders extract an inordinate human and economic cost, despite the availability of an extensive array of effective clinical interventions (Regier et al. 1988, p. 1351)

As mentioned earlier in this section, it is common for treated and untreated depression to be blurred. Inappropriate blurring, related to economic costs, is exemplified in this quote from WorkplaceBlues.com (2007):

> Untreated depression is costly. A RAND Corporation study found that patients with depressive symptoms spend more days in bed than those with diabetes, arthritis, back problems, lung problems or gastrointestinal disorders. Estimates of the total cost of depression to the Nation in 1990 range from $30-$44 billion. Of the $44 billion figure, depression accounts for close to $12 billion in lost work days each year. Additionally, more than $11 billion in other costs accrue from decreased productivity due to symptoms that sap energy, affect work habits, cause problems with concentration, memory, and decision-making. And costs escalate still further if a worker's untreated depression contributes to alcoholism or drug abuse.

The RAND study referred to is Wells et al. (1992), which focused on depressed patients *receiving treatment* from mental health specialists and general practitioners. The $44 billion figure discussed is derived from Greenberg et al.'s (1993) analysis of the economic costs of depression in the US in 1990. $12.4 billion of this was accounted for by direct *treatment* costs. In other words, the study was not about untreated depression per se. Yet the above paragraph mentions untreated depression in both the opening and closing sentences, strongly implying that the figures relate to *untreated* depression.

A variant of this claim occurs in a Mental Health America (2006) information sheet:

> Left untreated, depression is as costly as heart disease or AIDS to the US economy, costing over $43.7 billion in absenteeism from work (over 200 million days lost from work each year), lost productivity and direct treatment costs

The author's obliviousness to the contradiction between the words 'untreated' and 'treatment' is symptomatic of the fact that the blurring of treated and untreated depression is pervasive and very rarely challenged.

All of these examples occur in publications extolling the need for more treatment of depression, ignoring the fact that the adverse outcomes outlined occurred *despite* treatment.

There is often an emphasis on workplace productivity. In Australia in recent years, *beyondblue* has had a major focus on depression in the workplace. According to *beyondblue* (2004):

> For example, depression accounts for three to four days off work per month for each person experiencing depression – that's over six million working days lost each year in Australia. Untreated depression can result in a significant reduction in work performance. Depression accounts for more than 12 million days of reduced productivity each year, with serious implications for work safety

Andrews et al. (1999) was cited as a reference for the 12 million days claim. However, according to Andrews et al. (p. 26):

> In the four weeks before the interview, persons who had none of the mental or physical disorders specified in the survey reported that in the past month there had been, on average, one day in which they had not been able to carry out their usual activities fully. We presume that this was mainly because of fleeting and minor conditions, such as, headaches, colds and flu. Persons with depression had, on average 2.7 days out of role

This makes it clear that depressed people average only 1.7 days *more* out of role per month than other people. This suggests that it might be reasonable to attribute at most approximately 60% of depressed people's days out of role to depression.

Another example, related to economic costs, is Sumner's (1998) article, 'Untreated depression results in lost workplace productivity'. The title implies that the focus is on *untreated* depression. However, untreated depression is mentioned only once in the body of the article:

> Lynn DeWitt, director of community education for the Mental Health Association of Atlanta, says …. "Untreated, the depressed employee shows a dramatic drop in productivity.

Ms DeWitt was not quoted as giving any data to support this claim.

Sumner's article highlighted a national study that found that depression causes an average of 40 days lost from work (presumably days absent per year). This study was Greenberg et al.'s (1993) analysis of the economic costs of depression in the US in 1990, which also estimated the costs of depression to be approximately $43.7 billion, $12.4 billion of which were direct *treatment* costs.

Common acronyms in this chapter: AHCPR Agency for Health Care Policy and Research; APA American Psychiatric Association; D/ART Depression Awareness, Recognition, and Treatment (Program); DDD defined daily dose; DSM Diagnostic and statistical manual of mental disorders; FDA Food and Drug Administration; ICD International Classification of Diseases; NAMI National Alliance for the Mentally Ill; NIMH National Institute of Mental Health; RANZCP Royal Australian and New Zealand College of Psychiatrists

Another major problem in estimates of the societal costs of depression is that it is generally assumed that depression causes low productivity, absenteeism, and so on, in a unidirectional causal relationship. This ignores evidence that work stress can cause depression. In the Dunedin Multidisciplinary Health and Development Study, a rigorous New Zealand study of young people, it was found that 'Work stress appears to precipitate diagnosable depression and anxiety in previously healthy young workers' (Melchior et al. 2007, p. 1119). Similarly, in a Finnish study, Laaksonen et al. (2012, p. 663) concluded that:

> Adjustment of work environments by reducing mental strenuousness and improving job satisfaction might help in prevention of mental health problems that account for a major part of the disease burden among employees.

However, such findings tend to be ignored in economic analyses (and in the academic and grey literature more broadly), which take for granted a simplistic unidirectional relationship. For example, a very recent Australian analysis of the impact of mental disorders in young men (Degney et al. 2012) estimated the extent of absenteeism and unemployment and so on among 12-25 year old males and attributed all the economic costs to mental illness rather than assuming a two-way causal relationship.

4.5 DEPRESSION IS TREATABLE

Claims that depression is treatable provide a putative solution to the problem raised in claims that it is common and serious. This is very important in the depression orthodoxy, which emphasises that there is hope despite the magnitude of the problem. There are many subsidiary claims about the treatability of depression. Among the most important are claims that depression treatment is effective. Also important are the closely linked claims that depression *requires* treatment and that *untreated* depression has a poor prognosis.

4.5.1 Depression is treatable

Claims that depression is treatable are very common. Treatable, of course, means amenable to *medical* treatment.[3] The possibility of non-medical interventions – for

[3] However, as discussed in chapter 7, sometimes a distinction is made between 'medical' treatment, meaning pharmacological treatment, and psychological treatment, which implies that psychological treatment is non-medical.

example, addressing problems such as job loss that have triggered depression – is generally ignored. Claims of treatability also reinforce the medicalisation of distress.

Antidepressants strongly dominate depression treatment (Wilson et al. 2003, p. 685; van Weel-Baumgarten et al. 2000; Eccles et al. 1999, p. 103; Norman 2006, p. 394). Furthermore, claims that depression is treatable are strongly biased towards antidepressants. In many claims, treatment is explicitly equated with antidepressants. In other claims, lip service is paid to psychological therapies (and occasionally other therapies), but it is clear that the real agenda is promotion of antidepressants. So most claims about the effectiveness of depression treatment are actually about the effectiveness of *antidepressants*, even if antidepressants are not explicitly mentioned. Similarly, most claims that current treatments for depression are more effective than earlier treatments are more about promoting antidepressants than about persuading people that depression is treatable. Explicit claims about the effectiveness of antidepressants are discussed in chapter 7.

There is no question that depression *can* be treated medically. Whether or not such treatment is effective and appropriate, as is implied in treatability claims even when not explicitly stated, is discussed below in relation to subsidiary claims.

4.5.2 Depression treatment is effective

A key claim of the NIMH D/ART Program was that 'Today, 80% to 90% of persons with a major depressive disorder can be treated successfully' (Regier et al. 1988, p. 1351). More recently, the *beyondblue* (2010) promotional materials sent to Australian households state that 'effective treatments are available' and 'With the right treatment, most people recover'. As in many claims about effectiveness, treatment is not defined in the *beyondblue* assertions. However, it is defined in this quote in the influential US Agency for Health Care Policy and Research (AHCPR) clinical practice guideline for depression in primary care:

> Once identified, depression can almost always be treated successfully, either with medication, psychotherapy, or a combination of both. (AHCPR 1993)

When treatment is explicitly defined, it is most often as 'medication(s)' (which most people would understand to mean antidepressants) or psychological therapy or both, as in the AHCPR quote above, and this quote from the D/ART program:

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> There are effective pharmacological and psychological treatments that are often used in combination. (Regier et al. 1988, p. 1352)

Leaving aside the issue of what depression treatment consists of, what is the evidence about the outcomes of treatment? A number of key studies of general practice treatment are very relevant, and have findings that challenge the depression orthodoxy, because they provide evidence that treatment does little to influence the outcome of depression. Reviewing Canadian population data, Patten (2004) reported that:

> Episodes occurring in antidepressant users lasted longer than those in non-users. The apparent incidence of major depressive episodes among those taking antidepressants was higher than that among respondents not taking antidepressants.

In a population-based study of first-onset depression, Eaton et al. (2008) found 'no obvious long-term effect of treatment for depressive disorder' (p. 518). In a longitudinal Canadian population study, Wang (2004) found that people treated for depression were *more* likely than untreated people to report major depressive episodes during the six-year follow-up period.

A crucial issue in relation to such evidence is *confounding by severity*. Overall, in Australia and other western countries, although many factors influence access to treatment, the more depressed a person is, the more likely they are to be treated for depression. And the more depressed they are, the worse the prognosis is likely to be. Consequently, comparisons of treated and untreated people are likely to be biased against finding better outcomes for treated people, unless treatment status is randomly allocated.

Undoubtedly, confounding by severity is a significant factor in studies that find little or no evidence that treatment improves outcomes, and studies that find that treated people have worse outcomes. It would be ludicrous to claim that such evidence proves that treatment is useless or even harmful. Discussing his findings that higher incidence and duration of depression occurred among antidepressant users that among non-users, Patten (2004) concluded: 'The most probable explanation for these results is confounding by indication and/or severity: members of the general population who are taking antidepressants probably have more highly recurrent and more severe mood disorders'.

Confounding by indication/severity is sometimes claimed to be an explanation for findings of adverse outcomes with treatment, generally in relation to suicide risk. This is discussed in chapter 7. However, the issue of confounding by severity is routinely ignored in claims that treatment is necessary for depression.

Claims that long-term treatment is necessary also undermine claims that depression treatment is effective. However, it is increasingly claimed that depression is a chronic disease like diabetes, for which long-term treatment is often necessary. Claims about the necessity of long-term antidepressant use are discussed in chapter 6.

It is also claimed that it is important to treat depression as early as possible. For example, in an analysis of an Australian community awareness campaign designed to improve young people's mental health literacy and encourage early help-seeking, Wright et al. (2006) claimed that early detection and treatment of depression in young people has been found to improve long-term outcomes, citing a study by Kupfer et al. (1989) in support of the claim. However, that study was undertaken in a university department of psychiatry, and Kupfer et al. commented that it might not be valid to generalise the findings to unipolar depression more broadly. Furthermore, the study was of 45 people with a mean age of 42.7 years and at least three episodes of unipolar depression. This is serious citation misrepresentation (Raven 2010a).

A few commentators have noted that dramatic increases in recent decades in antidepressant use – the dominant form of treatment – have not reduced the prevalence and impact of depression at the population level (Helgason et al. 2004; Patten 2004). This is briefly discussed in chapter 6.

In summary, the evidence about depression treatment does not support claims of high levels of effectiveness at either the individual level or the population level. Such claims are a form of 'wishful thinking' informed by commercial and ideological biases.

4.6 CRITICS OF DEPRESSION ORTHODOXY ARE WRONG

Critics of the orthodox story about depression attract sharp criticism. They are often emotively dismissed as ignorant and callous, and they are accused of blaming people

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with depression for their suffering. These purported attributes and attitudes are considered to be major sources of stigma about depression (Thornicroft et al. 2007).

Two more accusations, more powerful and discrediting, are that depression critics are dangerous, and that they are Scientologists, or at least influenced by Scientology. These latter two accusations are discussed in chapter 7 because they are most often made in response to criticisms of antidepressants (and other psychiatric drugs).

4.6.1 Critics of depression orthodoxy are ignorant

Probably the most common criticism of depression critics is that they are ignorant. This is a stronger rendering of the 'depression literacy' message – that people need to be educated that depression is common, serious, and treatable, and a disease (beyondblue 2007).

Depression critics are sometimes referred to as ignorant in the sense of simply not knowing the so-called scientific facts about depression, of having a deficit of knowledge that could be corrected with appropriate information. It is commonly claimed that people who do not seek treatment for depression are also ignorant in this sense, as are health professionals who do not recognise depression in patients.

However, in other cases the claim of ignorance is of a more ad hominem nature, accusing depression critics of wilful wrong-thinking and/or unwillingness to listen to reason. According to Gattuso et al. (2005, p. 1641): 'People who refuse to take up the expert view of depression as illness can only be seen as non-compliant, ignorant or, in the dominant discourse, illiterate'. I incurred relatively strong public criticism in *The Australian* newspaper in response to an abstract of a conference paper:

> Melissa Raven, a lecturer in public health at Flinders University, will tell a conference today there is "too much scaremongering" about depression and drug companies are encouraging such messages because the market for anti-depressant drugs is "extremely lucrative".
>
> Her comments have infuriated experts at the national depression initiative Beyondblue, who branded the attacks as "ignorant". (Cresswell 2006)

Journalists seem happy to report such disagreements between health professionals: I was contacted by several other journalists following up this news story.

Some depression sufferers also take offence at criticism of the orthodox story. An Australian journalist (Pryor 2008) published an article about depression, in which she

discussed her own experience and included her 'List Of Ignorant Things People Say About Depression Which Shit Me'. The second item on her list of 'ignorant things' focused on the concept of inappropriate medicalisation: 'Depression is another case of doctors trying to turn ordinary life events into illnesses'.

Even prominent experts who accept much of the orthodoxy sometimes attract claims of ignorance. When Arthur Kleinman, a professor of psychiatry and medical anthropology, expressed concern about the medicalisation of unhappiness, his criticism was dismissed by a leading psychiatric epidemiologist as ignorance due to lack of relevant experience:

> [Ronald] Kessler dismisses Kleinman's criticism as the "false enthusiasm of the noncombatant"—by which he means that if you haven't worked directly with people who suffer from so-called mild disorders, it's easy to write them off as ordinary. (Pettus 2006, p. 40)

Sometimes depression critics are simply labelled ignorant without explanation. In other cases, reference is made to the large body of superficially strong epidemiological and clinical evidence – funded primarily by the pharmaceutical industry – that depression is common, serious, treatable, and so on. Increasingly depression critics are accused of being ignorant of the 'advances' in neuroscience or 'brain science' that are purported to provide evidence of biological causation.

4.6.2 Critics of depression orthodoxy are callous, trivialising people's suffering

It is often asserted that depression critics are callous towards people with depression, trivialising their suffering and their needs. For example, leading Australian psychiatrist Ian Hickie has publically criticised health journalist Ray Moynihan in this way, citing Moynihan (1998) as a source of trivialising attitudes:

> Clear differentiation of the illness of depression from other normal forms of human distress is essential. Otherwise the suffering of patients and the needs of consumers of services are trivialised. (p. 129)

Sometimes accusations of callousness and trivialisation are linked with a claim that critics have obviously never suffered from depression themselves,[4] the implication

[4] I personally have had this said to me on multiple occasions.

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being that the experience of depression is far worse than critics realise. For example, a Google search (7 June 2009) yielded 17 hits for the phrase 'obviously never suffered from depression' and 84 hits for 'obviously never been depressed'; almost all were criticisms of critics of depression and/or antidepressants.

However, criticism of depression orthodoxy does not inherently involve trivialisation. In a debate with significant parallels (as briefly discussed in chapter 2), a prominent critic of the dominant US disease discourse about drug problems, Craig Reinarman (2005), has pointed out that challenging that discourse does not necessarily mean trivialising the experience of people with drug problems: 'The notion that addiction-as-disease is a historically and culturally specific social construction and political accomplishment should not be taken to mean that the lived experience of what is called addiction is therefore somehow less "real", less powerful, or less deserving of attention' (p. 316). Similarly, challenging the depression-as-disease orthodoxy does not inherently imply that the lived experience of what is labelled depression cannot be extremely painful and worthy of compassionate assistance.

The claim that depression critics advocate that depressed people should be left to suffer is usually a straw man argument, stating or implying that critics believe that *nothing* should be done to alleviate emotional distress. This is supported by the very common belief and deliberate implication that treatment means *antidepressants*. However, it ignores the fact that there non-pharmacological treatments such as cognitive-behavioural therapy, as well as many non-medical interventions that can be implemented at the individual level, in addition to interventions at the community and population level.

Most depression critics do not callously advocate that people who are depressed should simply tough it out; instead they advocate non-pharmacological treatment and assistance to address underlying problems. Many also advocate community-level prevention strategies such as employment and education programs for disadvantaged young people, school programs that encourage resilience in children, and social support for pregnant women and new mothers.

4.6.3 Critics of depression orthodoxy blame people for their illness

A stronger version of the callousness accusation is that depression critics blame people with depression for their illness and suffering, just as people who dispute the

disease model of addiction are likely to be accused of blaming people who have alcohol problems. This is a corollary of the false dichotomy that if depression is not a disease, it must be a weakness, a character flaw:

> workplaces, like the rest of society, have long stigmatised depression, treating it as a sign of weakness or a poor attitude rather than an illness to be managed like asthma or diabetes. "It's just a phase, they'll snap out of it," the ignorant, non-afflicted tend to say. (Mascarenhas 2005)

The illness/weakness dichotomy has been very successfully 'sold' by the pharmaceutical industry, and unfortunately it fits very well with compassionate neoliberal ideology that locates the problem in the brains of unfortunate individuals.

However, many depression critics would argue for one or more alternative explanations. One such explanation is that depression is a product of accumulated stresses due to aversive life events. This explanation does not blame the victim, but it does tend to locate the problem within the individual. A more sociological and political explanation is that depression is a reaction to dysfunctional and inequitable social structures. However, such explanations, which challenge dominant social ideologies, are much harder to understand and to 'sell', and much less politically expedient than the simplistic illness or weakness dichotomy.

In summary, depression critics are often criticised quite contemptuously. Sometimes this is based on deliberate misrepresentation, but more often it is based on lack of understanding of their non-simplistic beliefs.

4.7 CONCLUSION

Depression is highly medicalised in the orthodox depression/antidepressant story that dominates the depression arena in Australia and many developed countries. The claim that depression is a disease medicalises it, as does the claim that it is treatable. Medicalisation of problems profoundly influences how those problems are dealt with. It opens some avenues of intervention and closes many others.

The orthodoxy about depression is powerful and persuasive. Many of its claims have filtered into everyday constructions of depression specifically and psychological distress more generally:

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> dominant depression discourses of scientific and consumer literatures circulate through culture in tandem, constructing a popularized "common sense" script of depression that is difficult for consumers to think outside of (Gardner 2003, p. 106)

Depression has become 'popularised' in recent decades, particularly since – and to no small extent because of – the introduction of Prozac (fluoxetine) to the US market in 1988.[5] Although depression is still associated with stigma, it has become much more common, and much more socially acceptable, to disclose a depression diagnosis.

Overall, depression advocates have had considerable success in persuading Australians that depression is a common, serious, and treatable disease. This is reflected in community surveys (e.g. Jorm et al. 2005), in government policy, particularly the *Second National Mental Health Plan* (Australian Health Ministers 1998), which emphasised the disease burden related to depression (p. 11), and in the establishment and continuation of *beyondblue: the national depression initiative*. Chapter 9 discusses in detail a major historical contributor to this, the National Depression Awareness Campaign.

However, there is substantial evidence that the depression orthodoxy is misleading. Most of the claims about depression made by antidepressant advocates are questionable. Some are clearly untrue. Some are based on flimsy evidence and/or selective use of evidence. Others are true at face value but are used inappropriately.

In this chapter, a number of claiming strategies or techniques used by antidepressant advocates have emerged as patterns. Most notable are:

- blurring of categories (e.g. referring to twelve-month prevalence as point prevalence)
- inappropriate generalisation (e.g. extrapolating prognosis from patients in tertiary treatment to patients in general practice)
- lack of referencing, which makes it difficult for the reader to locate the source evidence and evaluate the validity of the claim
- citation misrepresentation (e.g. referring to adverse outcomes associated with *treated* depression as adverse outcomes associated with *untreated* depression)

[5] Fluoxetine was approved by the FDA on 29 December 1987 (FDA 2008).

- emotive language and arguments (e.g. referring to depression as 'potentially fatal')
- convenient scapegoats (e.g. dismissing valid criticisms as the result of stigma or ignorance)

A number of logical fallacies cropped up repeatedly:

- false dichotomies (e.g. the assumption that if depression is not a disease it must be a moral failing)
- ad hominem arguments (e.g. accusing critics of the claim that depression is a disease of being ignorant)

Many of these strategies and fallacies also feature in the next two chapters, which similarly analyse claims about suicide and antidepressants respectively.

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Chapter 5
Current debates about suicide

5.1 INTRODUCTION

Suicide is a key issue in relation to depression and antidepressants. It is a tragic occurrence and a very emotive social problem, particularly in relation to young people. Individual suicides profoundly impact on relatives and acquaintances; collectively, suicides impose huge social and economic costs on society.

In Australia in 2010, 2361 deaths (1.6% of all deaths) were officially attributed to suicide (Australian Bureau of Statistics (ABS) 2012, p. 21). Males (77%) greatly outnumbered females. The highest suicide rates occurred among men aged 30-49 and 75-85 years; among women, the rate peaked between 45 and 49 (p. 22). However, there is particular concern about teenagers, partly because suicides are a much more common cause of death relative to other causes. For example, the age-specific rate for males in 2010 was lowest between 15 and 19 years, but it represented 23% of all deaths in that age-group (p. 22). Also Australian youth suicide rates in recent decades have been relatively high compared with those of other western countries (Cantor et al. 1999, p. 137).

In recent years, suicide has had an increasingly prominent focus in the public arena as well as the medical literature. Suicide also has a huge cultural imprint. It has featured prominently in literature (e.g. Flaubert's *Madame Bovary*), drama, movies (e.g. Sofia Coppola's *The Virgin Suicides*), and music (particularly opera and punk rock).

Depression is a well known risk factor for suicide. Indeed, it is often regarded as a necessary and sufficient[1] explanation: if someone kills themselves, they *must* have been depressed, and the depression must have caused the suicide. Furthermore, recurrent suicidal thoughts/actions are included in the diagnostic criteria for a major depressive episode in the DSM-IV (*Diagnostic and statistical manual of mental disorders*, 4th edition) (American Psychiatric Association (APA) 1994, p. 327).

[1] Sufficient as an *explanation*, but not as a *cause*: no-one would suggest that *all* depressed people kill themselves.

However, the belief that suicide is overwhelmingly caused by depression is challenged in this chapter. Many other factors, both distal (e.g. poverty and discrimination) and proximal (e.g. alcohol intoxication and interpersonal conflict), contribute to suicide, but dominant discourses privilege depression over all other factors.

Inflated estimates of the suicide risk associated with depression are common in the academic literature and the mass media. It is commonly claimed that up to 90% of suicides are associated with, or actually caused by, depression. It is also claimed that 15% of depressed people kill themselves, an alarming statistic. These claims are further examples of Wiener's (1981, p. 22) 'selecting supportive data', an element of 'demonstrating the problem'.

The central point of this chapter is to discuss evidence that the actual rates are much lower, thereby challenging two key planks of the orthodox story about depression.

There are a number of related issues also worthy of detailed analysis, but which can only be mentioned briefly here. Suicide, particularly youth suicide, is often emotively referred to as an 'epidemic', invoking fears of both contagion and escalation. Suicide prevention is widely advocated, particularly in relation to young people. However, the evidence base for suicide prevention strategies is very weak. Each of these issues could be analysed with the same approach as used in this chapter.

Suicide, including suicide prevention, is a key issue in relation to antidepressants. According to the current orthodoxy, the risk of suicide is significantly reduced by antidepressants, and it is often taken for granted that prevention necessarily involves antidepressants. Because of the assumption that depression is *the* cause of suicide, and because antidepressants are often regarded as *the* remedy for depression, suicide prevention is often equated with antidepressant prescription. Paradoxically, however, there is some evidence that use of antidepressants can also increase the risk of suicide. Currently the most significant debate about antidepressants is whether they increase or decrease the risk of suicide, particularly among young people. This very contentious issue is discussed in chapter 6 rather than this chapter, because it is closely intertwined with the promotion and regulation of antidepressants.

Other debates about suicide are relatively muted, because the orthodox story about depression is so powerful: there is strong consensus that suicide is caused by

Common acronyms in this chapter: ABS Australian Bureau of Statistics; APA American Psychiatric Association; DSM Diagnostic and statistical manual

depression and that suicide prevention demands early detection and treatment and prevention of depression. However, there is considerable evidence to challenge these claims, but this evidence is frequently ignored.

In this chapter, as in chapter 4, explicit and implicit claims made primarily by people who promote the orthodox story about depression and advocate the use of antidepressants are analysed both in terms of who is arguing what and why, and to what extent claims are supported by evidence.

The focus of this chapter is on claims that suicide is caused by depression. As mentioned, the same sort of analysis could readily be applied to other claims about suicide, including:

- There is an epidemic of suicide
- There is an increasing epidemic of youth suicide
- Suicide is an equal opportunity affliction
- Suicide prevention interventions are essential
- Suicide screening is crucial

As in chapter 4, a number of problematic claiming techniques or strategies emerge as patterns in this chapter. Most notable are:

- blurring of categories (e.g. referring to treated cases of depression as untreated)
- inappropriate generalisation (e.g. extrapolating suicide risk from patients in tertiary treatment to patients in general practice)
- lack of referencing
- citation bias: selective citation of references, systematically excluding sources and evidence that challenge the orthodox story
- citation misrepresentation: misrepresenting content and relevance of sources cited in *support* of claims
- emotive arguments

This chapter also illustrates the difficulties in clarifying and challenging questionable claims. Here I draw on my experience of contacting players who have made such claims, and responding to misleading statements in the academic literature.

5.2 SUICIDE IS CAUSED BY DEPRESSION

Depression is considered to be the major cause of suicide. According to Silverman (1967, pp. 889-890):

> Depressives are regarded in clinical psychiatric practice as a high-risk group with respect to suicide. In epidemiologic terms, there also appears to be a strong association between depressive illness and suicide. Examination of both the contribution of depressive disorder to the suicide problem and the termination of depressive disorder in suicide leads to a reasonable hypothesis that suicide is the mortality of depressive mental illness.

Indeed it is often taken for granted that people who kill themselves *must* be depressed. Sometimes this is expressed implicitly:

> Sometimes teens feel so depressed that they consider ending their lives. Each year, almost 5,000 young people, ages 15 to 24, kill themselves. (Mental Health America 2007b)

At other times the claim is more explicit. A key proponent is Swedish psychiatrist Göran Isacsson, whose career has focused on the value of antidepressants for prevention of suicide:

> Suicide rarely occurs in the absence of depression. (Isacsson et al. 2010, p. 429)
>
> depression appears as a common factor for most suicides (Isacsson & Rich 2008, p. 26)

Claims that depression is *the* cause of suicide are common in Australia. Two of the key proponents are psychiatrist Robert Goldney, a prominent key opinion leader (as discussed in chapter 9), and child psychologist Michael Carr-Gregg. Goldney (2003) used a 'real estate analogy':

> The most important contributing factors to suicidal behaviors are depression, depression, depression. (Goldney 2003, p. 88)

Carr-Gregg has had a high media profile in recent years in the aftermath of several widely publicised teenage suicides:

Common acronyms in this chapter: ABS Australian Bureau of Statistics; APA American Psychiatric Association; DSM Diagnostic and statistical manual

> WHEN renowned child psychologist Michael Carr-Gregg visits the Geelong high school where 14-year-old Chanelle Rae last week became the fourth student this year to kill herself, he will carry a blunt message to parents.
>
> The internet did not kill her. Neither did cyber bullying. She was suffering from an illness and had it been diagnosed, she could have been treated.
>
> "This is not about suicide. It is about depression. I will keep saying that until someone listens," Dr Carr-Gregg said. (Le Grand 2009)
>
> Dr Carr-Greg [sic] said a joint suicide pact between girls was rare.
>
> "It's very, very unusual to have girls kill themselves and particularly kill themselves in this way," he said.
>
> "So my only conclusion is that they must have been depressed." (Hill-Douglas 2007)

In an analysis of the perceptions of depression and suicidal behaviours of young people who had attempted suicide, Bennett, Coggan, & Adams (2003, p. 289) noted that regardless of whether depression was seen as a disease or as a moral failing, it was assumed that suicidal behaviour was caused by depression:

> Two dominant discourses of depression emerged: a medicalised discourse, and a moral discourse. The medicalised discourse was accessible to the majority of participants, and constructed depression as a disease. This discourse prioritised the voices of health professionals and suggested that depression was difficult to resist. The moral discourse was an alternative to the medicalised discourse, and constructed young people who experienced depression and suicidal behaviours as failures. Both discourses were informed by a mechanistic cause-and-effect relationship between depression and suicidal behaviours: *attempting suicide was seen as an inevitable outcome of experiencing depression, and suicidal behaviours were inevitably undertaken by young people who were depressed.* [italics added]

Surprisingly, given his pro-antidepressant stance and his strong financial ties to Forest Laboratories, the manufacturer of Celexa® and Lexapro® (discussed in chapter 6), Andrew Solomon, in his best-selling book *The Noonday Demon* (2001), challenged the assumption that depression and suicide are inextricably linked:

> Many depressives never become suicidal. Many suicides are committed by people who are not depressed. The two subjects are not parts of a single lucid equation, one occasioning the other. They are separate entities that frequently coexist, each influencing the other. "Suicidality" is one of the nine symptoms of a depressive episode listed in DSM-IV, but many depressed people are no more inclined to end their lives than are people with appalling arthritis: the human capacity to bear pain is shockingly strong. Only if one decides that suicidality is a sufficient cause for a diagnosis of depression can one say that the suicidal are always depressed. (p. 243)

Suicides are under-reported by relatives, doctors, and police. A major factor in this is the stigma attached to suicide. However, this under-reporting is biased in relation to depression. Because most people associate suicide with depression, sudden deaths by people known or suspected to be depressed are more likely to be reported as suicides. In the absence of any evidence of depression, deaths are more likely to be considered accidental or (less often) suspicious. These biases strengthen beliefs that suicide is caused by depression.

5.2.1 70%-90% of suicide is associated with or caused by depression

It is often argued that 80% or 90% of people who kill themselves have depression or mental illnesses more generally. Such claims tend to be based on psychological autopsy studies, in which clinicians and/or relatives/friends are asked their opinions about reasons for suicide. Psychological autopsies are methodologically problematic for multiple reasons. Pouliot & De Leo (2006) concluded:

> Pervasiveness of methodological shortcomings, lack of equivalence in study design, and inconsistencies in findings suggest that a standardization of PA procedures be pursued. More valid and reliable data, and improvement in the general value of the approach are likely to follow. Before getting to this point, however, there is a critical need to perform methodological research on the various aspects entailed by the psychological autopsy technique. (pp. 503-504)

Social acceptability biases are a significant limitation: 'Relatives often seek relatively socially acceptable explanations, and may be unaware of or unwilling to disclose certain problems, particularly those that generate shame' ([Jureidini & Raven in] Isacsson et al. 2010, p. 430)[2].

Nevertheless, psychological autopsy studies are often cited authoritatively and uncritically to support the orthodox story about depression. For example, according to Goldney (2005, pp. 129-130):

> Psychological autopsy studies have consistently demonstrated, across countries with different cultures, that 80% to 90% of suicides had mental disorders, particularly depression and substance abuse (Cheng, 1995).

In a submission to the Senate Select Committee on Mental Health, Orygen Research Centre (2005, p. 12) asserted that 'depression is present in 88% of suicides'. However, the cited source, Lönnqvist (1990), reported 88% as the *upper limit of a very wide*

[2] In this debate article, Isacsson and Rich argued that psychological autopsy studies provided good evidence of a causal relationship between depression and suicide; Jureidini and I argued against this.

Common acronyms in this chapter: ABS Australian Bureau of Statistics; APA American Psychiatric Association; DSM Diagnostic and statistical manual

range: 'Findings from psychological autopsy studies conducted over the past 40 years suggest that depression is found in 29-88% of all suicides' (p. 107). The source of the 88% figure was the study cited by Cheng (1995) of suicide in east Taiwan – the same study that was cited by Goldney (2005). Chen's finding was extreme: the next two highest percentages in the studies reviewed by Lönnqvist were 70% and 59%. Lönnqvist summarised his findings as: 'about half (29-88%) of the suicide victims suffered from depressive disorder' (p. 111). So Orygen's flat claim that depression is present in 88% of cases misrepresented Lönnqvist's review.

More strongly, 80-90% of suicides have at times been *attributed* to depression. For example, according to Australian psychiatric epidemiologist Colin Mathers, 'around 80% of suicides are probably *attributable* to depression' [italics added] (Australian Broadcasting Corporation 1999). Mathers was involved in the enormously influential Global Burden of Disease study (Murray & Lopez 1996), in which *all* cases of suicide were attributed to depression:

> To get a better understanding of the *true* magnitude of the total burden attributable to unipolar major depression, we have combined DALYs [disability adjusted life years] from suicide with DALYs from unipolar major depression. [italics added] (p. 250)
>
> These calculations are based on the assumption that everyone that commits suicide is clinically depressed, which may result in a slight overestimate of the impact of depression. (p. 269)

An even stronger variant of the claim is that such high percentages of suicides are attributable to *untreated* suicide. For example, according to the President and Chief Executive Officer of Mental Health America, appealing to common belief rather than evidence, 'As is well known, 90 percent of suicides are attributed to *untreated* or *undertreated* depression' (Shern 2006). Similarly, Australian psychologist Michael Carr-Gregg has advocated focusing on 'the undiagnosed and untreated depression that underlies 90 per cent of suicides' (Toy 2009).

However, some estimates are much lower. A review by Angst et al. (1999) attributed a third or less of cases of suicides to depression: 'Psychological autopsy studies of suicide victims identified high rates of major depressive disorders within the range of about 20% to 35%' (p. 61). Angst's estimate was quoted by the US Surgeon General's landmark 1999 mental health report (United States Department of Health and Human

Services 1999, p. 244), but unfortunately this is cited less often than more alarmist estimates.

There is substantial evidence that depression associated with suicide is usually comorbid (occurring simultaneously) with other psychiatric disorders. Angst (1999, p. 61) noted that 'Comorbidity increases suicide risks substantially'. According to Lönnqvist (2000, p. 117), 'Research findings among suicide victims show that depression has generally been co-morbid and complicated, and has caused difficulties in health care'. Henriksson et al. (1993, p. 935) emphasised the significance of comorbidity and its implications for both research and clinical practice:

> The majority of suicide victims suffered from comorbid mental disorders. Comorbidity needs to be taken into account when analyzing the relationship between suicide and mental disorders and in planning treatment strategies for suicide prevention in clinical practice.

Furthermore, depression is often a *secondary* diagnosis, comorbid to a different principal diagnosis. According to Blair-West et al. (1997, pp. 260-261):

> There is a body of evidence which suggests that our figure of 70% for all suicides attributed to MDD is too high. This figure is over-inclusive because all but a handful of studies failed to distinguish primary MDD from depression secondary to other psychiatric diagnoses such as alcoholism. Morrison found that primary unipolar depression only represented 15% of completed suicides. Henriksson, from the very precise Finnish suicide studies, recently found that only 31% of 229 suicides had a 'principal diagnosis' of MDD (while 59% had a non-specific 'depressive disorder'). This replicates Dorpat & Ripley's 1960 American figure of 30%

Overall the evidence does not support nearly as strong a causal association between depression per se and suicide as is generally taken for granted. Furthermore, the focus on depression as *the* explanation for suicide deflects attention away from socioenvironmental factors (Pouliot & De Leo 2006, p. 504; Jureidini & Raven 2009).

5.3 DEPRESSED PEOPLE ARE AT HIGH RISK OF SUICIDE

The belief that suicide is common in suicide is pervasive and troubling, and it is used to argue for increased funding for clinical and preventive interventions. Inflated estimates of the suicide risk associated with depression – 'the termination of depressive disorder in suicide', in Silverman's (1968, p. 890) parlance – are well entrenched in the academic literature and the mass media.

Common acronyms in this chapter: ABS Australian Bureau of Statistics; APA American Psychiatric Association; DSM Diagnostic and statistical manual

In fact there is a small but significant risk of suicide in depression (Goldsmith et al. 2002). Most depressed people do not kill themselves (Davies et al. 2001, p. 1500; Gunnell et al. 2004, p. 35), although many attempt suicide and even more consider it (Moller 2003, p. 73). The risk is generally expressed as the percentage of depressed people who kill themselves (sometimes but not always compared with the percentage of non-depressed people who do so).

5.3.1 Suicide risk in depression: The 15% myth

One of the most emotive and powerful claims about the relationship between depression and suicide is that suicide claims the lives of 15% of depressed people. A variant of this claim is that 15% of people with *untreated* depression kill themselves. Another variant, probably unique to Australia, is that 10% of people with a mental illness kill themselves within 10 years. These three claims are discussed next, the first in detail because of its popularity.

5.3.2 15% of all depressed people die by suicide

Claims that 15% of all depressed people kill themselves are entrenched in the literature, and are usually used to underscore the severity of depression, as in this quote by Schotte et al. (2006, p. 313), which cited two commonly cited sources:

> The tendency toward underdiagnosis and undertreatment, the strong association with somatic problems, the high rate of relapse ... and the high prevalence of suicide, which is estimated at 15% [American Psychiatric Association, 1994; Lönnqvist, 2000], further stress the fact that the depressive disorders are some of the most severe mental health problems. [square brackets in original]

As discussed below, both sources are secondary and influential, as is often the case. They are also misrepresented by Schotte et al., as is often the case. The implications of this are discussed below.

The 15% claim is also used to counter claims that antidepressants can be dangerous. In Australia in 2001, Professor Ian Hickie, then Chief Executive Officer of *beyondblue*, was quoted in the media arguing:

> "People with depression have a one in six chance of being dead by suicide,' Hickie says. It's just wrong to say that the risk of drugs mean patients should not take them. (Harvey & Videnieks 2001, p. 14)

However, this 15% statistic is a gross overestimate based on very biased samples. The primary source is Guze & Robins' (1970) much-cited review, which concluded that

'the ultimate risk of suicide in [primary affective disorders] disorders is about 15 per cent' (p. 437). Guze & Robins reviewed studies of depressed people, many of whom had been hospitalised for severe depression, and were therefore highly unrepresentative of the broader spectrum of depression. Furthermore, suicidality is a key indication for hospitalisation (Blair-West et al. 1997, p. 261). Consequently it is very inappropriate to generalise Guze & Robins' findings to the broader population of people with depression.

The generalisation of severe cases of depression to the broader population of people with depression is an important example of the *clinician's illusion* (Cohen & Cohen, 1984). As discussed in chapter 4, this illusion occurs because clinicians are more likely to see the more severe and chronic cases of any illness or problem (and to see them more often), because the less afflicted cope better and need less help.

The other study most frequently cited is Goodwin & Jamison's (1990) very influential book on bipolar disorder, *Manic-depressive illness*, which included a review of the evidence about suicide among people with unipolar or bipolar depression and reported a mean of 19% suicide risk (p. 228). Goodwin & Jamison endorsed Guze & Robins' (1970) 15% estimate, saying that their own findings did not differ significantly (p. 228).

Their findings were published in an earlier paper by Jamison (1986).[3] Among the 27 studies included were the 17 studies reviewed by Guze & Robins (1970), so there is considerable overlap between the two reviews, and they are similarly biased in relation to severity. However, the Guze & Robins review is more often cited in relation to unipolar depression, and the Goodwin & Jamison book is more often cited in relation to bipolar depression.

Guze & Robins based their estimate on a graph showing 'a tendency for the ratio of suicides to all deaths to approach an asymptote [a line that closely approaches a curve as they both approach infinity] at about 15 per cent as the deaths approached 100 per cent' (p. 437). However, in only two studies had more than 43% of the people died, so it is very speculative to extrapolate from the data. A number of commentators have criticised the methodology and interpretation of both reviews, arguing that *case-fatality rates* rather than *proportionate mortality* were calculated (Bostwick &

[3] This suggests that Jamison alone conducted the review. However, it is the book that is usually cited.

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Pankratz 2000, p. 1925; Sriescoldu 2006). A suicide case-fatality rate is the proportion or percentage of a total sample who die by suicide. Proportionate suicide mortality is the proportion of suicides among those who have died. Proportionate mortality is an appropriate proxy measure of case-fatality rate only when the relative risk (compared with other causes of death) is constant over time. This is very much not the case with depression, in which the risk of suicide is significantly greater early in its course, a point made by Guze & Robins (p. 437) but ignored in most citations of their review.

Goodwin & Jamison acknowledged the hospitalisation bias in their review, commenting that 'Most studies are done with hospitalized patients as subjects, a practice that skews the data toward the more severely ill' (1990, p. 228). However, this crucial acknowledgement is rarely mentioned when the book is cited. Instead, the 15% estimate is generally presented baldly, without explaining the biased sampling, as in Schotte et al.'s (2006) quote. This is a form of citation misrepresentation.

Several rigorous reviews have been subsequently published refuting the 15% claim, and providing significantly lower estimates. Five of the most significant (Bostwick & Pankratz 2000; Blair-West & Mellsop 2001; Boardman & Healy 2001; Inskip et al. 1998; Simon & VonKorff 1998) are discussed below. However, they are cited much less often than Guze & Robins and Goodwin & Jamison. The non-citation of these reviews and their contrary findings constitutes citation bias – systematic ignoring of published evidence that conflicts with a claim (Greenberg 2009).

In addition, the studies reviewed by Guze & Robins are decades old. The oldest studies were published in 1937 and 1938, and six each in the 1950s and 1960s. The studies reviewed by Goodwin & Jamison were published between 1937 and 1979. The data in Bond & Braceland (1937), included in both reviews, were collected in 1927 and 1928. However, when these two reviews are cited, there is rarely if ever any consideration of secular changes, cohort effects, and changes in prevention and treatment interventions that might severely limit the generalisability of suicide rates from three to eight decades ago.

Treatment methods have changed very significantly since the 1930s. In particular, mainstream antidepressants were first introduced in the late 1950s (Healy 2004, p. 7), but did not become widely used until years later. Given the strong claims of the effectiveness of antidepressants in the prevention of suicide, it might seem ironic that

suicide statistics from the pre-antidepressant era are widely cited. However, it is generally implied, and sometimes explicitly stated, that the vast majority of suicides among depressed people occur either in the absence of treatment or when treatment is inadequate (in both scenarios treatment is often equated with antidepressants).

More importantly, diagnostic criteria for depression have broadened dramatically in recent decades, resulting in much higher apparent prevalence rates. According to Bostwick & Pankratz (2000):

> "depression" is no longer defined as it was in 1970. Subsequent editions of DSM have made the diagnosis of a major depressive episode more inclusive. Today up to 20% of the population meet criteria for a watered-down, broad, and, ultimately, a less lethal depressive diagnosis.… 1972, the lifetime prevalence of depression in the American population in DSM-II terms was 2%–3%, when the definition of depression included only involutional melancholia, the unipolar form of manic depression, psychotic depression, and "severe depressive neuroses." By 1994, under the rubric of DSM-IV, the lifetime prevalence of depression had increased to 10%–20%.… Today, many more people carry a depressive label, but the incidence of the severe forms remains relatively low.

Bostwick & Pankratz (2000) noted five 'major American textbooks [that] report the 15% figure as correct for all depressed patients' (p. 1925). Their meta-analysis by produced a gradient of lifetime suicide prevalences:

- 8.6% in people ever hospitalised for suicidality
- 4% in affective disorder patients hospitalised but not specifically for suicidality
- 2.2% for mixed inpatient/outpatient populations
- <0.5% for the population without affective disorders (p. 1925)

Blair-West & Mellsop (2001, p. 322) also found a much lower risk than 15%:

> The suicide risk in major depression as it is currently defined diagnostically is of the order of 3.4% rather than the previously accepted figure of 15%. [italics in original]

Like Bostwick & Pankratz (2000), Blair-West & Mellsop argued that the studies included in Guze & Robins' (1970) meta-analysis were flawed by hospitalisation bias (p. 324), and they emphasised that changes in diagnostic criteria had lowered the diagnostic threshold for major depression and greatly increased the number of people

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diagnosed with it (p. 325) – many of them with significantly lower severity and suicide risk.

Blair-West & Mellsop also criticised the generalisation of Guze & Robins' findings to the broader population of people with depression, commenting:

> Because every major textbook quotes a suicide risk in major depression of 15%, every good psychiatry trainee and, quite reasonably therefore, any speaker who needs to emphasize the seriousness of major depression as a public health concern, uses this figure too. What is probably the most surprising is that a single paper, that by Guze and Robins, could be so uncritically accepted and so widely promulgated. (p. 324)

Boardman & Healy (2001) analysed data from a database of suicide cases in North Staffordshire, and used psychiatric prevalence rates from the US National Comorbidity Survey to calculate lifetime suicide risk in people with depression. Like Bostwick & Pankratz (2000), they found a gradient of risk:

> The model suggests a lifetime prevalence rate of suicide for any affective disorder at 2.4%, with a rate for those uncomplicated by substance abuse, personality disorder or non-affective psychosis at 2.4%, and a rate for uncomplicated cases who had no mental health service contact at 1.1%. (p. 400)

Inskip et al. (1998) similarly disputed the 15% claim. They estimated the lifetime risk of suicide by people with affective disorders to be 6%, commenting that 'The lifetime suicide risk figures often quoted in the literature appear to be too high' (p. 35).

Simon & VonKorff (1998) did not explicitly criticise Guze and Robins (1970) but attributed the 15% statistic to them, then argued that 'Data from inpatients are likely to yield biased estimates of suicide risk among all patients', adding that 'suicidal ideation and suicide attempt are frequent indications for hospitalization' (p. 155). Like Bostwick & Pankratz (2000) and Boardman & Healy (2001), they reported a gradient of risk, this time specifically for people *treated* for depression: 20% for psychiatric inpatients, 5.6% for patients with any mental health specialty visit, 2.4% for patients prescribed antidepressants, and a striking 0% for patients with none of those characteristics.

Jamison herself subsequently acknowledged that the 15% estimate derived from the Guze & Robins (1970) and Goodwin & Jamison (1990) reviews might be too high:

> 'For many years, the lifetime suicide risk in bipolar disorder was accepted as 15%, but recent researchers have suggested that the lifetime suicide risk may be lower.' (Simpson & Jamison 1999, p. 53).

The 'recent researchers' Simpson & Jamison referred to were Blair-West et al. (1997) and Inskip et al. (1998).

Despite the publication of these and other critical studies, claims of a 15% suicide rate for depressed people in general continue to be made in peer-reviewed literature as well as in other forums. Guze & Robins' (1970) and Goodwin & Jamison's (1990) reviews continue to be widely cited (or alluded to) without any mention of limitations stated by the authors, let alone criticisms made by subsequent authors.

It is particularly problematic when the 15% claim is made in leading medical journals. One instance is a *BMJ* editorial by Cipriani et al. (2005, p. 373), which cited a different *BMJ* editorial, Davies et al. (2001), in support of their claim that 'Up to 15% of patients with unipolar depression eventually commit suicide'. However, Davies et al. explained at some length what was wrong with the 15% statistic:

> It is widely assumed that early and accurate identification of depressive episodes will reduce suicides. This follows from a belief that suicide is a common adverse outcome in depressive disorders: a 15% lifetime risk is often cited. However, clinical experience and population based studies challenge this view.... The estimate of 15% lifetime risk of suicide emerged from a review [Guze & Robins] of 17 studies of depressed patients, mainly in secondary care, all before 1970. A recent meta-analysis [Inskip et al. 1998] revises the figure to 6%, but this may still be biased towards recurrent inpatients at tertiary centres. A study from the United States [Simon &VonKorff 1998] sharpens the focus, describing 62 159 person years' follow up for 35 546 insured patients treated for depression. Risk of suicide declined from 224 per 100 000 patient years for inpatients to 64 for outpatients, 43 for those receiving antidepressants in primary care, and 0 for those without drug or secondary treatment. These estimates are much lower and relate to treatment history. (p. 1500)

Although Cipriani et al.'s phrase 'Up to 15%' is not the same as '15%', the statement misleadingly suggests that 15% is a reasonable estimate. To make it worse, the online link to Davies et al. was incorrect (it leads to a different *BMJ* editorial), making it harder for readers to check that source. I pointed this out in a rapid response (Raven 2005), but it remains incorrect.

In another *BMJ* editorial, Scott (2006) claimed (without citing a reference) that: '15% of all patients with depression will eventually commit suicide' (p. 985). I responded to this claim, citing Bostwick & Pankratz (2000), Boardman & Healy (2001), and Blair-West et al. (2001), commenting: 'It is very disappointing that, once again, a BMJ

editorial is perpetuating the myth that 15% of people suffering from depression will eventually commit suicide' (Raven 2006).

Another critic of Scott's editorial (Sriescoldu 2006) cited Bostwick & Pankratz (2000) and concluded more strongly:

> I suggest it is time for BMJ editorials to undergo the same degree of scrutiny as major papers otherwise potentially important messages such as those carried here will be lost under a cloud of erranous [sic] scientific "facts"

As mentioned above, the two sources cited by Schotte et al. (2006) are secondary sources. The DSM-IV (APA 1994) does not cite any source for its claim that 'Up to 15% of individuals with severe Major Depressive Disorder die by suicide' (p. 340), but it is highly likely that this figure was derived from Guze & Robins (1970), whom Lönnqvist (2000) cited as the source of 'the often quoted rate of 15% of completed suicide among psychiatric patients with severe depressive disorders' (p. 109). These two statements are significantly more accurate representations of Guze & Robins' findings than Schotte et al.'s bald claim that the prevalence of suicide in depression 'is estimated at 15%' (2006, p. 313). As is often the case, the further removed from the source, the more inaccurate the claim.

Furthermore, Schotte et al.'s claim is given credibility by their citation of the DSM 'Bible of psychiatry', which is often cited in support of the 15% claim. Lönnqvist (2000) is also often cited. It is a chapter in the highly regarded textbook, arguably the 'Bible' of suicidology, *The international handbook of suicide and attempted suicide*, edited by leading suicidologists Keith Hawton and Kees van Heeringen (2000). A review of this book in the *British Journal of Psychiatry* began:

> No self-respecting worker in deliberate self-harm and suicide prevention, either clinical or research, can afford to be without access to this comprehensive handbook – possession (or at least, a copy in one's local library) and regular use, may well become a marker of serious involvement in the subject! Every university department of psychiatry, and every major hospital with a medical accident and emergency department striving to carry out their work to a high standard will need to have this accessible and well-thumbed. (Sims 2001, p. 376)

Few readers would question such sources. Citation bias and citation misrepresentation in authoritative sources are powerful methods of propagation of seriously misleading claims.

In a rare admission, the APA's *Practice guidelines for the treatment of psychiatric disorders* (APA 2006, p. 1392) acknowledged the limitations of the 15% statistic:

> Guze and Robins… reviewed 17 studies that assessed the risk of suicide in individuals with primary affective disorders….. High suicide rates were found, with the ultimate risk of suicide estimated to be about 15%…. *However, these studies generally assessed severely ill patient populations and individuals early in the course of their illness, when suicide rates are known to be highest*. [italics added]

As mentioned above, influential *beyondblue* Chief Executive Officer Ian Hickie was quoted in the media as saying: 'People with depression have a one in six chance of being dead by suicide' (Harvey & Videnieks 2001). It is possible that this was a misrepresentation of what Hickie said – journalists and subeditors often paraphrase experts' statements, sometimes distorting them. However, his subsequent co-authoring of a paper in which that statement from that source was quoted verbatim (Blood et al. 2003, p. 11), with no indication that it was problematic, suggests that he was not misrepresented.[4]

More recently the 15% statistic was invoked to justify the controversial use of antidepressants by adolescents, for example in a continuing medical education module by Nishawala et al. (2006):

> In the wake of the recent controversy over treating children and adolescents with selective serotonin reuptake inhibitors (SSRIs), it is critical to consider that depression is a serious, treatable illness which is highly impairing, causes tremendous suffering, and can derail normal development, as well as lead to suicide in up to 15% of cases. (p. 51)

Not surprisingly, the 15% suicide claim has been used by the pharmaceutical industry to argue the need for antidepressants. According to an Eli Lilly spokesperson, 'In people with depression there is probably a 15% suicide rate' (Boseley 1999).

5.3.3 15% of *untreated* depressed people die by suicide

An important variant of the 15% suicide claim is that it is 15% of *untreated* depressed people who die by suicide. The severity and hospitalisation bias of Guze & Robins' (1970) review is compounded by the total misrepresentation that the sample had not received treatment. In fact, most people in the studies had received treatment, and the majority had received more intensive treatment (including hospitalisation) than most

[4] Notably, Blood et al. did correct a different point related to Hickie made in a different newspaper article.

Common acronyms in this chapter: ABS Australian Bureau of Statistics; APA American Psychiatric Association; DSM Diagnostic and statistical manual

people with depression ever receive. The misrepresentation of the 15% suicide rate as being derived from people with untreated depression constitutes serious citation misrepresentation.

This even more inaccurate claim has been made by some very influential players, including the US National Institute of Mental Health:

> Left untreated, or inappropriately treated, mood disorders are potentially fatal; nearly one in six persons with severe, untreated depression will die by suicide. NIMH (2003, pp. 1, 15)
>
> Dr. Matthew V. Rudorfer, a panel member from the National Institute of Mental Health, said that 15 percent of teenagers with untreated depression commit suicide – a much greater risk than that presented by the drugs themselves, he said. (Harris 2004)

This variant claim is often used to argue that more antidepressant treatment is necessary. It was used by Eli Lilly to justify the use of antidepressants by adolescents: 'when people with depression are left untreated, 15 percent will actually commit suicide' (BBC 2004).

The Chief Executive Officer of Mental Health America more recently used this claim (Shern 2006) to argue against the US Food and Drug Administration's 'black box labeling' warning about the suicide risks associated with antidepressants (discussed in chapter 6):

> Without treatment, this disorder can be fatal – 15 percent of people who live with untreated depression take their own lives. Any knee-jerk or pressure-based actions by the FDA may put an untold number of Americans at risk of the tragedy the agency aims to avoid – suicide. The risk associated with not treating depression is far greater than any potential risk of adverse effects of medication. [italics in original]

I emailed Shern, enquiring about the source of this statistic. I was informed that it was based on Guze & Robins' (1970) review (personal communication, Heather Cobb, Senior Director of Media Relations, Mental Health America, 7 February 2007), as I expected, given the common misrepresentation of this source.

5.3.4 10% of people with a mental illness kill themselves within 10 years

Another variant of the 15% statistic is that 10% of people with a mental illness kill themselves within ten years of diagnosis. Although the estimated percentage is less than 15%, the ten-year specification makes this claim particularly alarming.

A key source (and possibly the original source) of this statistic is a factsheet, 'Suicidal behaviour and self-harm: The facts', published for a number of years by the prominent pharmaceutical industry funded mental health consumer organisation SANE Australia. According to both the 2004 version and the 2008 version:

> Suicide is the main cause of premature death among people with mental illness; over 10% of those affected kill themselves within the first 10 years of diagnosis. (SANE 2004, p. 1; SANE 2008, p. 1)

The claim has been repeated in a number of other publications, including the ABS's (2008) authoritative summary of the results of the National Survey of Mental Health and Wellbeing, which cited SANE (2008):

> Suicide is the main cause of premature death among people with a mental illness. More than 10% of people with a mental illness die by suicide within the first 10 years of diagnosis (SANE, 2008).

I contacted SANE, asking the source of the 10% claim. I was eventually given three references (personal communication, Paul Morgan, Deputy Director, 9 March 2010) that are relevant to the topic, but do not support it. Although all three papers reported that the suicide risk is higher in the early stages of mental disorders, none of them provides an estimate of ten-year suicide mortality. Furthermore, they do not support claims of a 10% *lifetime* risk; instead one gives no estimate, but criticises traditional estimates, and the other two give significantly lower estimates. Lifetime risk would always be greater than 10-year risk, unless there was 100% mortality within 10 years, or all suicides occurred within the first 10 years, in which case they would be equal. The first cited reference, Harris & Barraclough (1997), noted that 'Suicide risk seems highest at the beginning of treatment and diminishes thereafter' (p. 223). However, that paragraph continued:

> The rate of decline is probably determined by illness chronicity and recurrence of episodes. This suggests the lifetime risk assessed on small cohorts with relatively short follow-up should be re-determined (Guze & Robins, 1970; Miles, 1977). A paper on this subject is in preparation.

That 'paper in preparation' was published as Inskip et al. (1998), according to whom the methodology used by Guze & Robins and Miles was unsound, resulting in over-estimates. Inskip et al. estimated that the lifetime risk for affective disorder was 6%, and the lifetime risk for schizophrenia was 4%. Therefore it is clear that Harris & Barraclough would not have endorsed the 10%-in-10-years statistic.

The second cited reference, Palmer et al. (2005) reported that the highest risk of suicide in schizophrenia was in the early years after diagnosis, but many of the studies included in their review did not follow patients up for 10 years. Palmer et al. commented that 'The psychiatry literature routinely quotes a lifetime schizophrenia suicide prevalence of 10% based on 1 meta-analysis and 2 studies of chronic schizophrenics' (p. 247), but they argued that this was an over-estimate based on inappropriate use of proportionate mortality (the percentage of the dead who died by suicide) instead of case fatality rate (the percentage of the total sample who died by suicide) (p. 247). They estimated that '4.9% of schizophrenics will commit suicide during their lifetimes, usually near illness onset' (p. 247).

The third cited reference, Inskip et al. (1998) also reported that the risk of suicide is usually highest shortly after diagnosis. But they concluded that 'The lifetime suicide risk figures often quoted in the literature appear to be too high' (p. 35). They criticised the methodology and interpretation of Guze & Robins (1970) and Miles (1977), particularly the latter:

> Our methods have resulted in lower estimates than Miles calculated, indicating that the figures generally quoted may be in error. Higher percentages of suicide are seen when only a small proportion of the cohorts have died, usually soon after the onset of the disorder. (p. 36)

Inskip et al. estimated that the lifetime risk for affective disorder was 6%, and the lifetime risk for schizophrenia was 4%, both significantly less than 10%.

The fact that the unsupported 10% claim was repeated in the summary of the results of the National Survey of Mental Health and Wellbeing (ABS 2008) is a good example of a bad statistic being embedded in influential grey literature and given unwarranted legitimacy.

5.4 CONCLUSION

Suicide is a tragic occurrence and an extremely emotive issue. It features prominently in both academic and lay discourses about depression and antidepressants. However, many common claims about suicide, used strategically to 'demonstrate the problem' (Wiener 1981), are questionable, and some are outright wrong.

This chapter has challenged the belief that suicide is overwhelmingly caused by depression, including claims that 70%-90% of cases of suicide are associated with or caused by depression. Overall, the evidence does not support nearly as strong a causal association between depression per se and suicide as is generally taken for granted.

This chapter has explained in detail why the claim that 15% of depressed people kill themselves is wrong. It has been rebutted in the medical literature, yet it still re-emerges in peer-reviewed journals from time to time. Similarly, the variant claim that 10% of people with a mental illness kill themselves within 10 years is a good example of a spurious statistic that has been accepted as fact and become incorporated into the grey literature. It is likely to be repeated uncritically for years to come.

These claims are part of a clutch of closely-related statistics loosely based on research that is relevant but does not support them, These claims are enthusiastically used to support biased claims that place depression centre stage as *the* cause of suicide, ignoring many other contributing factors. Similarly, by extension, antidepressants are positioned as *the* solution, ignoring many other potential interventions at both the individual level and the population level. Key claims about antidepressants are discussed in detail in the next chapter.

Common acronyms in this chapter: ABS Australian Bureau of Statistics; APA American Psychiatric Association; DSM Diagnostic and statistical manual

Chapter 6
Current debates about antidepressants

6.1 INTRODUCTION

According to the current orthodoxy, antidepressants are 'safe and effective', and necessary for the treatment of depression and prevention of suicide. These claims feature prominently in the medical literature, in antidepressant advertisements and other promotional material, and in depression awareness campaigns (which are discussed in chapters 8 and 9). They have also saturated the media and they are influential in popular discourse.

Despite the strength of the orthodoxy, there are some heated debates about these claims. In particular, claims about the effectiveness and safety of antidepressants have been strongly challenged in recent years, both by the emergence of new evidence and by re-analysis of existing data.

A key debate about effectiveness focuses on how effective antidepressants are relative to placebo. There are also debates about the effectiveness of antidepressants relative to one another, relative to other forms of treatment (particularly psychotherapy and St John's wort). An extension of claims that antidepressants are effective, combined with claims about the seriousness of depression, is that they are necessary for the treatment of depression, and that they are under-prescribed. These claims are discussed in this chapter, along with claims that the antidepressant prescribing that does occur is appropriate.

Two very prominent debates have focused on safety issues: firstly the dependence potential of antidepressants, which was the key debate in the 1990s, and secondly the risk of suicide. Both of these debates are discussed in detail in this chapter. The importance of the first debate is signalled by repeated assertions by *beyondblue: the national depression initiative* that 'Antidepressants are safe, effective and not addictive' (beyondblue 2008, 2011). There are also debates about other risks associated with antidepressant use, such as birth defects and gastrointestinal bleeding. Some of these are briefly discussed.

Also discussed are criticisms of critics of antidepressants. Given the intensity of the debates about antidepressants, it is not surprising that some of the criticisms levelled against players who contest the orthodox story are very negative. This is discussed in some detail in section 6.9, the penultimate section of this chapter.

The purpose of this chapter is to challenge key orthodox claims about antidepressants, just as the purpose of chapters 4 and 5 respectively is to challenge key claims about depression and suicide. Together with chapter 7, which focuses on pharmaceutical industry practices, chapters 4 to 6 provide a background to chapters 8 and 9, which analyse depression awareness campaigns.

As in chapters 4 and 5, a number of problematic claiming techniques or strategies emerge as patterns in this chapter, including:

- inappropriate generalisation (e.g. extrapolating from patients in secondary and tertiary treatment to people with depression more broadly)
- lack of referencing
- citation bias: selective citation of references, systematically excluding sources and evidence that challenge the orthodox story
- citation misrepresentation: misrepresenting content and relevance of sources cited
- emotive arguments
- rhetorical strategies favouring antidepressants (e.g. subtle disparagement of psychotherapy

As is the case with depression and suicide, biased selection of evidence and misleading claims about antidepressants are used powerfully to promote the orthodox story, in this case that antidepressants are the solution to depression and suicide. In addition, they are used to discount increasing evidence that antidepressants themselves can be a problem.

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6.2 ANTIDEPRESSANTS ARE EVIDENCE-BASED

A key component of the orthodox story about depression and antidepressants is that antidepressants are an evidence-based treatment for depression (Regier et al. 1988; Kramer 1993). This underpins most of the key claims that are discussed in this chapter.

Being evidence-based is first and foremost about effectiveness and/or efficacy, but it is also about safety. Evidence-based medicine primarily rests on randomised controlled clinical trials that are generally designed to investigate efficacy (and monitor safety). Unfortunately there is considerable evidence that such trials – and evidence-based medicine itself – are frequently subverted by drug companies that fund the trials. This is discussed in chapter 7.

Claims that antidepressants are evidence-based are so influential that they are often unstated. However, they quickly emerge in the face of criticism of antidepressants. A key defender of antidepressants' evidence-based status is UK psychopharmacologist Professor David Nutt (e.g. Nutt 2003; Nutt & Malizia 2008), but there are many other key opinion leaders who have also leapt to the defence of antidepressants.

However, claims that antidepressants are evidence-based have been strongly challenged in recent years. Some specific claims about effectiveness have been challenged on the basis of contrary evidence. This is discussed in section 6.3.

Other challenges, most notably by UK psychiatrist Professor David Healy (1999, 2004, 2009), have been at a higher level, namely the co-optation and distortion of evidence-based medicine. Healy (2006) has provided a detailed analysis of this in relation to the marketing of SSRIs (selective serotonin reuptake inhibitors) for adolescent depression, concluding:

> Evidence-based medicine (EBM) is portrayed by its advocates as a value-free approach to the problems of clinical practice. In its early days, the appeal of EBM lay in the promise that the assessment of all available clinical trial data rather than judgments based on selected data sets would deliver clinical facts that should trump the values of individual clinicians, academic or nonacademic, which were all too often at risk of subversion by the free meals on offer from pharmaceutical companies. But … there are grounds to think that pharmaceutical companies have effectively subverted the process. (p. 151)

Similarly, according to Spielmans & Parry (2010, p. 13), 'we are actually now entrenched in *marketing-based medicine* (MBM), in which science has largely been

taken captive in the name of increasing profits for pharmaceutical firms' [italics in original]. And according to Ioannidis (2009, p. 1759):

> antidepressant research is under total industry control: it supplies randomised pseudo-evidence for multibillion markets, and is stuck with small studies affected by clearly documented selective reporting and subjective outcomes – a uniquely lethal combination

Rather more charitably, according to Fava (2010, p. 204):

> Prescribers may claim to be following the evidence, but are primarily influenced by the eminence of the authorities they listen to in meetings and read in journals or by the framing of the risk of medication side effects by the pharmaceutical industry. This occurs also because of the control of special interest groups over diagnostic classification and clinical guidelines committees

It is also claimed that antidepressant prescribing is evidence-based – that they are only prescribed on the basis of good clinical evidence. This is discussed in section 6.6.

6.3 ANTIDEPRESSANTS ARE EFFECTIVE

According to the dominant orthodoxy, antidepressants are effective treatments for depression, as indeed the term 'antidepressant' powerfully implies. Evidence of effectiveness[1] from both scientific trials and clinical practice is often cited to support such claims (e.g. Ellis, Hickie, & Smith 2003; Rothschild 2012). However, close scrutiny reveals that the evidence of effectiveness is relatively weak. This section proceeds by discussing claims and evidence of effectiveness in general, then in relation to clinical trials. Then a number of subsidiary claims are analysed, including effectiveness relative to psychotherapy and St John's wort.

6.3.1 Antidepressants are an effective treatment for depression

> SSRIs are very effective – they do work in relieving depression in most people who take them. (Pfizer 1997, p. 4)

> "Unlike 20 years ago, when antidepressants had side effects, modern medications have proven highly effective," says Dr Highet [beyondblue Deputy CEO]. (Barr 2006).

[1] The terms effectiveness and efficacy are sometimes used interchangeably, but efficacy means effects demonstrated in tightly controlled trials, whereas effectiveness means real-world effects (Gallo 1999; United States Department of Health and Human Services 1999, p. 72).

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Explicit claims that antidepressants are an effective treatment for depression are very common. Such claims occur in the vast majority of medical journal articles reporting clinical trials of one or more antidepressants. They also occur in broader reviews of antidepressants and/or depression, in the medical literature, pharmaceutical industry promotional materials, consumer organisation publications, and the media.

Many such claims either cite no evidence (e.g. the *beyondblue* quote above), making them harder to refute. When evidence is cited, it is usually from industry-funded clinical trials that are heavily biased in favour of antidepressants, or from reviews of such trials, which often compound the bias by selective citation and slanted interpretation (discussed in chapter 7).

It is also commonly *implied* that antidepressants are effective. Such statements reinforce the explicit claims of effectiveness, but are even more difficult to refute. Perhaps the most extreme examples of implicit claims of effectiveness are the *brand names* of some antidepressants. Effexor® (Efexor® in Australia) is in a class of its own in this respect, but many other names imply strength and success: Surmontil®, Zoloft®, Prozac®. Such names have attracted criticism in relation to their connotations:

> Allegron, Aurorix, Concordin, Lustral, Optimax, and Surmontil. Are we really to believe that these chemical substances can help the depressed patient, respectively, to get back up to full speed, see the light, achieve inner harmony, brighten up, reach the summit, or surmount his or her problems? None of the implied actions would ever be allowed to enter a serious list of indications for use, and it is accordingly strange that they should be allowed in the names. (Holm & Evans 1996, p. 1628)

Brand names of drugs are not a trivial issue, as marketers are very well aware (McNeil 2003). There is evidence that they do influence prescribing patterns. An Australian study by Ward et al. (2008) found that 'the brand name as much as chemical differences influenced the prescription of choice of antidepressants by both general practitioners and psychiatrists' (p. 258).

More importantly and much more authoritatively, the medical literature abounds with claims of the effectiveness of antidepressants based on evidence from clinical drug trials. However, there is increasing concern about the methodology and reporting of such trials. According to Schott et al. (2010), trial protocols are often advantageous to the drugs of the sponsors, for example by comparing them to placebo rather than to an

active control (p. 284). This avoids the risk of sponsors' drugs being demonstrated to be less effective than competitors' drugs. It also means that if sponsors' drugs are a bit more effective than placebo, relatively minor effects may be statistically significant despite not being clinically significant. Also the results of industry-funded trials were more likely to be *interpreted* favourably (p. 279). Another important factor is publication bias, particularly suppression and selective reporting of results (McGauran et al. 2010; Jureidini et al. 2008).

In fact, there is considerable evidence that antidepressants are not very effective. Evidence from antidepressant trials, methodological issues, and reporting issues are discussed in chapter 7, primarily in relation to placebo-controlled trials.

Lack of effectiveness of antidepressants has been demonstrated in a number of naturalistic studies. According to Coryell (2011):

> Despite a proliferation of pharmaceutical options for the treatment of major depression over the past 20 years, reported remission rates among patients given antidepressants have remained stubbornly low. (p. 664)

One notable paper, which telegraphs its conclusion in its title, is Brugha et al.'s (1992) study, 'Antidepressants may not assist recovery in practice: a naturalistic prospective survey', in which people attending psychiatric hospitals within six months of onset or relapse of depression were assessed twice, approximately four months apart. Brugha et al. reported that:

> Patients on treatment with antidepressants at the start of the study showed a nonsignificant trend for a lesser degree of clinical improvement, even when clinical severity and compliance were taken into account. Those who were not commenced on treatment until later in the study also fared no better than those who were never prescribed antidepressants (p. 5)

Citing Brugha et al. (1992) and Ronalds et al. (1997), Moncrieff & Kirsch (2005, p. 157) asserted:

> Two studies that prospectively assessed outcome in depressed patients treated naturalistically by general practitioners and psychiatrists found that people prescribed antidepressants had a slightly worse outcome than those not prescribed them, even after baseline severity had been taken into account. No comparable studies could be found that showed a better outcome in people prescribed antidepressants.

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There is even evidence to suggest that antidepressants may *delay* recovery from depression and/or *increase* the risk of relapse. A provocative recent article (Andrews et al. 2011) has argued that antidepressants 'may delay the resolution of depressive episodes (p. 14). A likely explanation is 'oppositional tolerance' (p. 1). According to Andrews et al., the monoamine neurotransmitters that antidepressants target are normally under homeostatic control, which is disrupted by antidepressants. This can result in 'oppositional tolerance' (p. 1) and deviation from normal levels, increasing the risk of relapse. Furthermore, according to Fava & Offidani (2011, p. 1593), oppositional tolerance can also cause withdrawal symptoms, treatment resistance, and other problems.

In addition, there is little evidence of long-term benefits of antidepressant treatment. Eaton et al.'s (2008) rigorous 23-year longitudinal cohort study of depression in the community is extremely important. It is much more rigorous than most such studies. Drawing on data from the US National Comorbidity Survey – Replication, Eaton et al. concluded that 'there was no obvious long-term effect of treatment for depressive disorder' (p. 518). Hughes & Cohen's (2009) review of long-term outcomes of antidepressant treatment similarly reported that 'No clear relationship emerged between drug treatment and positive outcomes' (p. 9), and that 'Studies of non-drug treated samples do not show worse outcomes, and some show superior outcomes' (p. 17). Unfavourable long-term outcomes have also been reported in a number of studies (Fava 2003).

Significantly, it is commonly claimed that antidepressants are necessary for a minimum of six months, and sometimes for much longer (Reynolds et al. 2006, p. 1136). Although not usually interpreted in this way, this is an acknowledgement that whatever beneficial effects antidepressants may have are short-lasting.

Of course, many antidepressant users and prescribers are convinced that they are effective. A major reason, relevant to both clinical trials and clinical practice, is regression to the mean. Depression often takes a fluctuating course, and there is likely to be significant reduction of symptoms in the early stages of treatment, because people are more likely to seek treatment when the symptoms are worse (as is the case with many disorders). In many cases the symptoms would subside without treatment. Regression to the mean is responsible for much of the improvement in cases of depression (Smith 2006, p. 72; Flett et al. 1995). In addition, some improvement may

occur simply because a person makes the effort to seek treatment, and/or because of non-specific treatment effects such as sympathetic listening.

It is sometimes claimed that newer antidepressants are more effective than older ones. Newer drugs are generally considered to be more effective than older ones, a message forcefully promoted by the pharmaceutical industry, and often endorsed by the medical profession. However, there is considerable evidence to the contrary (Lexchin 2004; Moulds 2004; Rolan et al. 2006). Claims that newer drugs are more effective (like claims that they are safer) are assisted by the fact that the limitations (both adverse effects and lack of effectiveness) of older drugs are more likely to be known, simply because they have been used more and for longer (Owens 1994: Lexchin 2004). Also, advertising and other promotion that emphasises the effectiveness of newer drugs, combined with the lack of promotion of older, less profitable drugs, tends to create the impression that the newer drugs are more effective. However, the evidence about the effectiveness of newer antidepressants relative to their predecessors is weak (Cipriani et al. 2005, p. 6; Williams et al. 2000; Owens 1994). In particular, according to MacGillivray et al. (2003, p. 1), 'The evidence on the relative efficacy of selective serotonin reuptake inhibitors and tricyclic antidepressants in primary care is sparse and of variable quality'.

6.3.2 Specific antidepressants are significantly more effective than placebos and/or other antidepressants

As mentioned above, the main source of evidence of effectiveness of antidepressants is industry-funded clinical trials. Most such trials compare an antidepressant with a placebo over a period of weeks. Others compare one antidepressant with another, often one which has already been approved for a particular indication and/or for a subsidisation/reimbursement mechanism.

However, the evidence from such trials is problematic. There is increasing concern about the methodology and reporting of drug trials in general (Bhandari et al. 2004; Herxheimer & Mintzes 2004; Garland 2004), even randomised controlled trials, the 'gold standard' of clinical trials. Industry-funded drug trials generally have significant biases that favour funders' drugs (Jørgensen et al. 2006). Furthermore, pharmaceutical

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companies have until recent years been under no obligation to report trials that demonstrate ineffectiveness, and they have suppressed many unfavourable findings (Bekelman et al. 2003, p. 463; McGauran et al. 2010; Kerridge et al. 2005).

There is significant evidence of suppression of unfavourable antidepressant trials (Whittington et al. 2004; McGauran et al. 2010). According to Fava (2010, p. 204), overprescribing of antidepressants based on suppression of negative studies and findings is one example of 'the spectacular achievements of propaganda that took place in psychiatry' in the last two decades or so.

Not surprisingly, given concerns about drug trials in general, there are significant concerns about the methodology of antidepressant drug trials. The main evidence about the effectiveness of antidepressants comes from industry-funded trials that are biased in favour of antidepressants (Angst, Kupfer, & Rosenbaum 1996; Bland 1997; Medawar 1997). A key source of bias is the use of selective exclusion criteria. According to Keitner et al. (2003), *most* people with depression who apply to participate in antidepressant trials do not meet eligibility criteria. People with comorbid psychiatric or physical disorders are routinely excluded (Posternak et al. 2002), despite the fact that comorbidity is arguably the norm in depression (Ellen et al. 1998, p. 19). Also routinely excluded are people considered to be suicidal (Goldsmith et al. 2002, p. 8), despite the fact that antidepressants are promoted as the solution to suicide.

Perhaps most problematic, from a methodological perspective, is the exclusion of 'placebo responders' – people who respond positively to placebo during the placebo run-in period (also referred to as 'placebo lead-in', and sometimes referred to as 'placebo washout'), in which all participants are given placebo for days or weeks, before the trial proper begins. Some placebo responders are indeed responding to the placebo; others probably have short self-limiting depressive episodes which would have resolved without any treatment. Exclusion of placebo responders eliminates people who would be more likely than others to respond to placebo during the trial. Their exclusion makes it easier for significant differences to be found between the active drug and placebo.

People with mild cases of depression are also sometimes excluded from trials. Because depression tends to fluctuate in severity, and because of the contribution of

regression to the mean to observed improvement (Smith 2006, p. 72; Flett et al. 1995), people with more severe depression may be more likely to improve significantly, regardless of treatment.

In short, 'Premarket trials are often carried out in restricted patient populations that inadequately represent the users of a drug once it is on the market' (Herxheimer & Mintzes 2004, p. 487). In addition, trials often provide more intensive treatment than normal clinical practice. These limitations are related to the distinction between effectiveness and efficacy. Although the terms are often used interchangeably, efficacy refers to effects demonstrated in tightly controlled trials, effectiveness to real-world effects (Gallo 1999; Department of Health and Human Services (United States) 1999, p. 72; Nathan & Gorman 2002, p. 644). The fact that trials of antidepressants (and medicinal drugs generally) are unrepresentative is one of many reasons why their efficacy results should not be uncritically generalised to everyday clinical practice (Horder et al. 2010), where effectiveness is what is required. However, this limitation, among others, is widely ignored.

As discussed in chapter 7, there is considerable evidence that evidence-based medicine, including psychiatry, has been co-opted by the pharmaceutical industry. The most prominent exponent of this view in relation to psychiatry is David Healy, according to whom 'The majority of recent psychotropic drug trials are business rather than scientific exercises, constructed for the purposes of achieving regulatory approval and thereafter market penetration' (2001, p. 290).

According to Ioannidis (2008), the so-called evidence about the effectiveness of antidepressants is profoundly flawed:

> the use of many small randomized trials with clinically non-relevant outcomes, improper interpretation of statistical significance, manipulated study design, biased selection of study populations, short follow-up, and selective and distorted reporting of results has built and nourished a seemingly evidence-based myth on antidepressant effectiveness. (p. 1)

Another bias, which may be inadvertent, is that many trial participants can distinguish antidepressants from placebos on the basis of their side-effects (e.g. dry mouth); this

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'unblinding' can favour antidepressants (Moncrieff et al. 1998) because patients and doctors often have positive expectations of antidepressants.

Furthermore, several of the commonly used depression scales are biased in favour of antidepressants. In particular, the Hamilton Depression Rating Scale (HDRS [HRSD is also used as an acronym, much less often]) has been widely criticised. Particularly strong criticism has come from Levine (2007):

> When legitimate scientists examine the HRSD, they immediately notice its biases in how depression is defined, the arbitrariness of a point total for qualifying a person as depressed, the arbitrariness of what qualifies as remission of depression, and the subjective nature of how responses are interpreted and evaluated….
>
> The HRSD is heavily loaded with items that are most affected by psychotropic drugs, and thus it is not surprising that pharmaceutical-company-sponsored researchers use the HRSD in their antidepressant studies.

Levine quoted Bagby et al.'s (2004) conclusion that 'Evidence suggests that the Hamilton depression scale is psychometrically and conceptually flawed' (p. 2163) and Zimmerman et al.'s (2005) assessment that 'When looking closely at the construction and content of the HRSD, it is clear that this is a flawed measure' (p. 109).

However, even with these biases in favour of antidepressants, there is significant evidence that they are not much more effective than placebos in clinical trials. As Levine (2007) observed, 'it is therefore especially damning for antidepressants that even with such measurement dice loading, these drugs routinely fail to outperform placebos'.

Two studies published in 2008 have focused attention on the issue of the limited magnitude of differences between antidepressants and placebos, partly because of their conflicting conclusions. Turner et al. (2008) compared US Food and Drug Administration (FDA) reviews of randomised double-blind placebo-controlled trials of twelve antidepressants for the short-term treatment of depression with published reports of trials for those same antidepressants. They found that 31% of the studies reviewed by the FDA had not been published, and that there was a strong bias for studies with positive results, but not those with negative results, to be published. In addition, studies with negative findings were often published with a positive slant and interpretation. As a result, 94% of published trial reports were positive, but only 51% of the trials reviewed by the FDA. Turner et al. were very critical of selective

publication of trials, but concluded that 'Each drug, when subjected to meta-analysis, was shown to be superior to placebo' (p. 259).

Kirsch et al. (2008) conducted a meta-analysis of all trials submitted to the FDA for four antidepressants (fluoxetine, paroxetine, venlafaxine, and nefazodone). They found that there was virtually no difference between antidepressant and placebo for moderate levels of depression, and only a relatively small difference for very severe depression. Furthermore, they concluded that the relationship between depression severity and antidepressant efficacy was attributable to decreased responsiveness to placebo, rather than increased responsiveness to antidepressant, in very severe depression.

Turner & Rosenthal (2008) responded to Kirsch et al.'s analysis, criticising, among other things, their use of the UK National Institute for Health and Clinical Excellence (NICE) criteria for clinical significance. Among numerous responses, Kirsch & Johnson (2008) countered the criticism, arguing that Turner & Rosenthal had overstated the difference in their respective conclusions, but reasserting the ineffectiveness of antidepressants for 'the average depressed patient'.

In Australia, Professor Ian Hickie (2008) more obliquely attacked Kirsch et al.'s paper in an emotive opinion piece in *The Australian* newspaper published a month after that paper was published:

> if one heard the reports carried by most media outlets in the last three months, one may have come to the erroneous conclusion that treatments for depression don't work

Fournier et al. (2010) analysed six placebo-controlled antidepressant trials and concluded that antidepressants have 'minimal or non-existent' benefit over placebo for people with mild or moderate depression, but that the benefit of antidepressants for severe depression is substantial (p. 47). They commented (p. 52) on the 'striking' consistency of their findings and those of Kirsch et al. (2008) and those of an earlier study by Khan et al. (2002). Therefore, not only is there strong evidence of biases in the methodology and reporting of industry-funded drug trials, but also there is strong evidence that antidepressants have little effectiveness for the majority of users, who do not have severe depression.

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Horder et al. (2011) also criticised Kirsch et al.'s (2008) analysis on methodological grounds. However, they acknowledged that there were serious problems with antidepressant trials, concluding: 'The true lesson of the present controversies may be not that antidepressants do not work very well, but that antidepressant research does not work very well' (p. 1283). Their pro-antidepressant bias was apparent in this comment, which suggests that they were more concerned about bad publicity for antidepressants than the lack of evidence of effectiveness:

> So long as the evidence base on antidepressants remains so limited in scope, it seems likely that challenges such as those of Kirsch et al. will continue, with negative effects on public attitudes towards these drugs (p. 1283).

More recently, Isacsson & Adler (2011) challenged Fournier et al.'s (2010) meta-analysis and conclusions. Isacsson & Adler reanalysed some of the data used by Fournier et al. (most of the endpoint data; a request for data from one study was declined), using Rasch analysis (a statistical method used to investigate psychometric properties of rating scales). They found that the HDRS performed much less well at lower levels of depression, and argued that this invalidated Fournier et al.'s analysis. The title of their paper asserted that 'Randomized clinical trials *underestimate* the efficacy of antidepressants in less severe depression' [italics added], but the body of the paper provided no justification for this. Firstly, the Rasch analysis demonstrated that the HDRS *lacked precision* at low levels of depression, not that it *underestimated* depression. Secondly, the imprecision applied equally to placebo. Most importantly, efficacy, which would have required analysis of both baseline and endpoint data, was not analysed; instead Isacsson & Adler focused on the psychometric properties of the endpoint data.

The body of the paper more accurately stated that the imprecision applied to all study participants, and that the difference occurred between higher and lower levels of depression, not between antidepressants and placebo, as implied by the title:

> Comparisons of score reductions on HDRS between study persons on different levels of depression severity at baseline will therefore not be valid as improvement starting at lower levels of depression will be systematically underestimated compared with improvement starting at higher levels. (p. 5)

However, Isacsson et al. did not justify their claim that the imprecision resulted specifically in *under*estimation of improvement.

6.3.3 Relapse on discontinuation of antidepressants demonstrates effectiveness

One of the main arguments used to support claims of antidepressant effectiveness is the common re-emergence of depression symptoms when people stop taking them. This is interpreted as evidence that the depression was being held at bay by the antidepressants, which need to be resumed. The Director of the US NIHM, Thomas Insel, recently articulated this assertively:

> Perhaps the best evidence for efficacy comes from patients who have been treated successfully with antidepressants and are switched in a blinded fashion to placebo. In a meta-analysis of 31 withdrawal studies among more than 4,000 patients, Geddes and colleagues found that 41 percent of patients who were switched to placebo relapsed, compared to 18 percent who remained on an antidepressant. These studies provide compelling evidence that antidepressants are effective for some people. (Insel 2011)

The re-emergence of symptoms is also used to argue that antidepressant adherence is necessary to prevent relapse (e.g. Mann 2005, p. 1830). This is discussed in section 6.5.3.

Insel cited Geddes et al.'s (2003) systematic review of the use of antidepressants for relapse prevention, ignoring Geddes et al.'s acknowledgement that some supposed relapses might actually be withdrawal:

> Unavoidably, the design of the trials included in this review necessitated that some patients were withdrawn from active treatment. Therefore, the possiblity [sic] is raised that the risk of relapse or recurrence might be increased by a direct quasi-pharmacological response to the withdrawal of medication per se rather than the relapse or recurrence being solely due to the underlying disorder…. If there is an effect, the effectiveness of continuation therapy could have been overestimated. (Geddes et al. 2003, p. 660)

According to an increasing number of critics, relapse symptoms that occur on discontinuation would more accurately be interpreted as withdrawal symptoms, as suggested by Geddes et al.. However, as noted by Lejoyeux & Adès (1997, p. 11): 'Because the symptoms of antidepressant discontinuation include changes in mood, affect, appetite, and sleep, they are sometimes mistaken for signs of a relapse into depression'.

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UK psychiatrist Joanna Moncrieff (2007, p. 97) expressed this particularly emphatically, emphasising the significance of withdrawal symptoms in antidepressant trials:

> The fact that many people appear to relapse after discontinuing long-term maintenance treatment with antidepressants for recurrent depression is often perceived as strong evidence for the efficacy of antidepressants. However, the evidence does not warrant this conclusion. Studies of maintenance or long-term treatment are effectively discontinuation studies. They take a group of individuals who have improved on antidepressants and randomize some of them to have the antidepressant withdrawn and replaced by placebo, usually quite rapidly. Thus the placebo group is really an antidepressant discontinuation group. It is now well recognized that antidepressants are associated with a discontinuation syndrome, but this was not widely acknowledged when most maintenance studies were done. Discontinuation symptoms potentially invalidate maintenance trials, first, because they may be mistaken for early signs of relapse in their own right and, second, because they may unblind participants, making them more vulnerable to relapse through a "nocebo effect" – the inverse of the placebo effect – wherein negative expectations cause physical illness or psychological distress. Negative expectations are likely in participants in maintenance trials, given that by definition they initially "responded" to antidepressants and are therefore likely to believe in their efficacy.

Furthermore, there is evidence linking antidepressant withdrawal to suicidality (Tint et al. 2008). This is discussed in section 6.8.

6.3.4 Antidepressants are effective for treating depression in children and adolescents

Antidepressant prescribing for children and adolescents increased significantly in the 1990s and has remained high (Delate et al. 2004; Zito et al. 2002). Only fluoxetine has been approved by the FDA for use for depression in children and adolescents (ADRAC 2004), and on the basis of only two trials. In Australia, no SSRIs have been approved by the TGA for treatment of depression. However, there is considerable off-label prescribing of antidepressants, to children (Davies 2008).

There has been enthusiastic promotion of antidepressants, particularly SSRIs, for children (Jureidini & McHenry 2009). For example, according to Andrade et al. (2006, p. 251), 'the clinical, epidemiological, and forensic data do suggest overall safety and efficacy of the SSRIs' for paediatric depression. However, Jureidini and Tonkin (2005) have referred to such claims as 'wishful thinking'. Herxheimer and Mintzes (2004) have similarly argued that SSRIs are largely ineffective in treating depression in children and adolescents.

As is the case with most classes of drugs, there have been very few paediatric trials of antidepressants, so there is little evidence about their effectiveness for children and adolescents. What evidence there is available is weak. Jureidini et al. (2004) reviewed all six published randomised controlled trials of newer antidepressants published in refereed journals (identified by a rigorous literature search), and concluded:

> Investigators' conclusions on the efficacy of newer antidepressants in childhood depression have exaggerated their benefits
>
> Improvement in control groups is strong; additional benefit from drugs is of doubtful clinical significance (p. 879)

However, in a meta-analysis published two weeks later, Whittington et al. (2004) concluded that there was evidence of efficacy for fluoxetine (p. 1343). Mansfield et al. (2006) compared the two reviews, concluding that the difference in conclusions about fluoxetine was due to differences in the method of review. In particular, unlike Jureidini et al. (2004), Whittington et al. did not examine the quality of the trials, Also, Whittington et al. analysed a binary endpoint, remission rate, and found a relative risk of non-remission with fluoxetine versus placebo of 0.78 (95% CI 0.67–0·90), suggesting moderate effectiveness. Mansfield et al. concluded that the use of the binary endpoint favoured fluoxetine, and noted that the two trials, which they criticised, had also been criticised in a US FDA statistical review (Mosholder 2001).

Furthermore, efficacy has been exaggerated in published reports of studies (Jureidini et al. 2004, p. 880). One particularly egregious example is Keller et al.'s (2001) report, in the *Journal of the American Academy of Child and Adolescent Psychiatry*, of a randomised controlled trial comparing paroxetine and imipramine with placebo for the treatment of adolescent depression, which concluded that 'Paroxetine is generally well tolerated and effective for major depression in adolescents' (p, 762). The trial was funded by GlaxoSmithKline, the manufacturer of paroxetine (p. 762). Jureidini and Tonkin (2003) pointed out that Keller et al.'s article showed 'evidence of distorted and unbalanced reporting', because the definition of response was changed to obscure the fact that the primary outcome measure was not significantly different for paroxetine compared with placebo. Keller et al. (2003) responded angrily, defending their analysis, but the article has been widely condemned.

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At the time of the trial, Keller was Professor and Chairman in the Department of Psychiatry and Human Behavior at Brown University School of Medicine, where he remains Professor. As part of a long campaign against the article by Jureidini and colleagues, a letter was sent to the University in October 2011, explaining the history and provocatively requesting that it support a request to the *Journal of the American Academy of Child & Adolescent Psychiatry* for retraction of the journal article.[2]

6.3.5 Antidepressants are an effective treatment for symptoms of menopause

Middle-aged women are a traditional key market for psychotropics (Kaufert & Gilbert 1986). Menopause causes many symptoms for which psychotropics are often prescribed. The use of antidepressants to alleviate menopausal symptoms has been increasingly promoted in recent years, since the large US Women's Health Initiative study was prematurely terminated because preliminary results indicated that hormone replacement therapy (HRT) significantly increased the risk of both breast cancer and heart disease (Rossouw et al. 2002). For example, McIntyre et al. (2005) encouraged practitioners to:

> be vigilant for breakthrough psychiatric and climacteric symptoms in patients discontinuing HRT and to familiarize themselves with the beneficial effects of serotonergic antidepressants on climacteric symptoms. (p. 57)

It is striking that, in a paper acknowledging the 'potential harmful effects of HRT' (p. 57), McIntyre et al. encouraged practitioners to familiarise themselves with only the *benefits* of antidepressants, not also the *harms*, which evidence-based practice would require, even in the absence of knowledge that HRT and antidepressants may have 'overlapping molecular targets' (p. 57).

Furthermore, antidepressants have not been clearly shown to be effective for menopausal symptoms. A rigorous review by Nelson et al. (2006) concluded that they are not optimal for most women. Although there was some evidence of efficacy, the effects were relatively weak, and adverse effects were greater than for placebo. In addition, there were few published trials and most had methodological problems. Overall, claims that antidepressants are effective for menopausal symptoms are another example of wishful thinking.

[2] I am a signatory to that letter.

6.3.6 Antidepressants improve the health of people with physical illnesses such as cardiovascular disease and diabetes

As mentioned in chapter 4, depression is increasingly claimed to be a significant cause of potentially serious physical illnesses, particularly cardiovascular disorders. This claim is largely based on evidence that depression is *associated* with physical illnesses. However, such associations do not prove causation.

Leaving aside the issue of whether or not depression can *cause* major physical illnesses, it is commonly claimed that depression worsens the prognosis of people with such illnesses, and that consequently it is crucial that depression be screened for in such patients and treated assertively – usually with antidepressants. A small number of trials have found evidence that antidepressants *might* improve health outcomes, but these trials are methodologically weak. Furthermore, the reporting of these trials has been biased, exaggerating the evidence.

Many of the claims focus on patients with cardiovascular disease. In Australia in 2007, a medical column ('Ask the Doctor') in *The Australian* by a GP who is also a journalist and editor claimed, without citing any references, that 'Studies have shown that depressed cardiac patients treated with SSRIs generally have very good outcomes' (Calabresi 2007).

However, there is little good evidence to support such claims. The MIND-IT study in the Netherlands compared the effects of antidepressant treatment versus usual care after a myocardial infarction (van Melle et al. (2007). It found that antidepressants did not alter 18-month outcomes in terms of either depression or cardiac status.

In a key US study, the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) of patients hospitalized for acute myocardial infarction or unstable angina, a non-significant difference in mortality was found between patients on sertraline and those on placebo (Glassman et al. 2002). Furthermore, there was no evidence of a difference in depression outcome between sertraline and placebo for patients with no prior history of depression.

Furthermore there is increasing evidence that SSRIs can be detrimental to people with heart failure. Sherwood et al. (2007) concluded that patients who used antidepressants

had an increased likelihood of death or hospitalisation because of cardiovascular disease over a median three-year follow-up period, after controlling for severity of depressive symptoms and established risk factors including age and severity and aetiology of heart failure. Similarly, a US study of people aged over 50 with heart failure and/or chronic pulmonary disease found that use of antidepressants was associated with worse outcomes for people with either major depression (Koenig et al. 2005) or minor depression (Koenig et al. 2006).

There is a strong association between depression and diabetes, and there is some evidence of a bidirectional causal relationship (Golden et al. 2008). There is also evidence that the combination of depression and diabetes is particularly harmful. Consequently, it is often assumed that antidepressant treatment of depressed people with diabetes, or at risk of developing it, is necessary. However, there is some evidence that outcomes are no better, or even are worse (Katon et al. 2008, p. 1574), for those prescribed antidepressants. Furthermore, there is some evidence that antidepressants themselves can *cause* diabetes (Rubin et al. 2008).

6.3.7 Increases in antidepressant use have improved population health

Although antidepressant advocates generally focus on their value for individual patients in clinical practice, they sometimes claim that antidepressants have improved the health of the population. In Australia, commenting on the significant increases in antidepressant prescribing in the 1990s, McManus et al. (2000, p. 461) predicted a positive effect at the population level in Australia and elsewhere: 'Public health benefits of this major change in drug use (eg, reductions in suicide rates) are anticipated in the long term'. Notably McManus et al. did not refer to any public health *costs*, such as the burden of adverse reactions or the opportunity costs of greatly increased expenditure on antidepressants.

However, a number of commentators have noted that there is little or no evidence that the massive increases in antidepressant use in recent decades have reduced the incidence, prevalence, or burden of depression. Moncrieff (2001, p. 288) concluded that 'There are no signs that the rapidly escalating use of antidepressants is reducing the burden of depressive disorders', and Moncrieff & Kirsch (2005, p. 157) similarly noted that 'the overall prevalence of depression is rising despite increased use of antidepressants'. According to Patten (2004, p. 1):

> Whereas antidepressant use increased considerably [between 1994 and 2000], differences in episode incidence and duration over time were not observed. This suggests that the impact of antidepressant medications on population health may have been less than expected.

Similarly, Helgason et al. (2004, p. 157) concluded that 'The dramatic increase in the sales of antidepressants has not had any marked impact on the selected public health measures'. Significantly, US National Institute of Mental Health (NIMH) Director Thomas Insel admitted the lack of evidence of improved population health:

> In 2007, the third and fourth most heavily purchased medications in the United States were antipsychotics and antidepressants, respectively, with a combined market of $25 billion (48). Remarkably, despite the heavy use of these medications, we have no evidence that the morbidity or mortality of mental disorders has dropped substantially in the past decades. (Insel 2009, p. 703).

Ostler et al. (2001, p. 16) went further, arguing that it was unrealistic to expect that antidepressants and other depression treatments *could* have much impact at a population level:

> While individuals may benefit from specific treatments for depression there is little evidence that even their most effective use, without other measures, could significantly reduce the public health burden of the condition.

In fact, it would be nigh on impossible to definitively determine the impact of antidepressants at a population level. McManus et al. (2000, p. 461) commented that 'measuring population-level outcomes from changes will not be easy'. Antidepressants are prescribed for many indications besides depression. This makes investigation of effectiveness (and safety) at a population level difficult, because indications are often not recorded in prescription databases (Gardarsdottir et al. 2009, p. 7), the main source of data. This is particularly problematic in relation to the contentious debate about how antidepressants influence the risk of suicide, which has prompted numerous ecological studies, mostly of very poor methodological quality. This is discussed in section 6.8).

6.3.8 Antidepressants are more effective than psychotherapy

It is often claimed, and very often implied, that antidepressants are more effective than psychotherapy as treatment for depression. Claims tend to be that *serious* depression requires antidepressants:

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> Psychotherapy can be a first-line therapy for mild depression but not for severe depression, particularly psychotic and bipolar forms, unless used in combination with pharmacology. (Mann 2005, p. 1830)

> While some patients only need psychological treatments, others (e.g. those with severe or psychotic depression) respond best to drug treatments. (Hickie & Scott 2007, p. 9)

More often, psychotherapy is subtly dismissed, or damned with faint praise. A pamphlet called 'Conquering Depression', funded by Wyeth-Ayerst, and distributed by US advocacy organisation NARSAD, reported that 'Some evidence indicates that cognitive-behavioral therapy can relieve the symptoms of less severe forms of depression' (Valenstein 1998, p. 179). In contrast, the answer to the question 'Are Antidepressant Medications Effective?' was emphatic:

> They most certainly are. Estimates are that eight or nine of every ten patients with depression can be helped by currently available antidepressant medications. (p. 177)

Some comments by journalists are also noteworthy. For example, an ABC journalist trivialised psychotherapy in an interview with an antidepressant critic:

> IRVING KIRSCH: I do think that they are currently over-prescribed and that there is an under-utilisation of alternative treatments right now.
>
> RAFAEL EPSTEIN: By alternative do you mean just people *simply talking through their problems* with a professional? (Epstein 2008) [italics added]

There is a relative dearth of rigorous research on the effectiveness of psychotherapy. Nathan & Gorman's (2002a) comprehensive and authoritative tome 'A guide to treatments that work' (second edition) reported 'Many, many Type 1 and Type 2 studies of the SSRIs' for major depressive disorder, but only 'At least two Type 1 or Type 2 RCTs' (p. xvii) for behaviour therapy, cognitive behaviour therapy and interpersonal therapy for major depressive disorder. Type 1 studies are the most rigorous, involving a randomised prospective clinical trial (p. v); type 2 studies are somewhat less rigorous (p. vi).

A major reason for this is the fact that, not surprisingly, pharmaceutical companies selectively fund research that is ultimately likely to demonstrate the efficacy and/or cost-effectiveness of their drugs (Fried et al. 2008, p. 60), so many potential avenues of research (particularly non-pharmacological interventions) are ignored.

One exception is a recent study by Barber et al. (2012), which found no significant differences in the effectiveness of supportive-expressive psychotherapy, sertraline (replaced by venlafaxine in the absence of response to sertraline) plus clinical management, and placebo plus clinical management. As well as having surprising results – suggesting that neither psychotherapy nor antidepressants were particularly beneficial – this study is unusual for having compared psychotherapy and antidepressants with placebo.

According to the chapter in Nathan & Gorman (2002) on psychosocial treatments for depression (Craighead et al. 2002), there was good evidence for the effectiveness of behaviour therapy, cognitive behaviour therapy and interpersonal therapy, and suggestive evidence that psychosocial interventions are as effective as antidepressants, but insufficient evidence about whether antidepressants are superior for severe depression:

> Behavior therapy (BT), cognitive behavior therapy (CBT), and interpersonal psychotherapy (IPT) have each been shown by at least two Type 1 randomized clinical trials, as well as by four meta-analytic reports of the literature, to be effective psychosocial interventions for patients meeting criteria for major depressive disorder (MDD). All three psychosocial treatments have yielded substantial reductions in scores on the two major depression rating scales (the Beck Depression Inventory and the Hamilton Rating Scale for Depression), significant decreases in percentage of patients meeting the criteria for MDD posttreatment, and substantial maintenance of effects well after treatment has ended.
>
> The data on outcomes of psychosocial and pharmacological interventions for major depressive episodes suggest that the two treatment modes are comparable. At least one major study lends strong support for the superior effectiveness of combined psychosocial and pharmacological treatments. There are not yet adequate published data to answer the question of whether antidepressant medications, either alone or in combination with a psychosocial intervention, are superior to psychosocial interventions in the treatment of *severely* depressed patients. [italics in original] (Craighead et al. 2002, p. 245)

In Nathan & Gorman's third edition, Craighead et al. (2007, p. 289) reported much the same, except that 'Additional recently published data suggest that psychosocial interventions may be as effective as antidepressant medications in the treatment of severely depressed patients'. Hagen et al. (2010) similarly reported that counselling is

as effective as antidepressants for non-severe depression, and that it might be as effective for severe depression, but the evidence is equivocal.

However, according to Pilgrim (2011), a higher evidence hurdle is imposed on psychotherapies than on antidepressants:

> why is it that if psychological therapies have an evidence base, they are simply not implemented immediately?
>
> After all antidepressants are not trialled in services in 'demonstration sites' before being licensed for general medical use. This shows that drug company pressure shapes political decisions and that a psychological approach (of any sort) has less political leverage with policy makers.
>
> The bid from beyondblue [to introduce a model of mental health treatment dominated by cognitive behavioural therapy] is confirming the same point as the English experience – even though evidence is there already, policy makers want 'demonstration' sites. This might be an opportunity as well though to apply this logic equally – in future maybe new drugs (and given their toxic history and poor efficacy, old ones) should also be demonstrated in actual services to work.

Pilgrim presumably does not realistically expect that new drugs will be required to demonstrate effectiveness rather than just efficacy in very unrepresentative trials. The reality is that drugs have a much more comfortable fit with the medically dominated health system than psychotherapy does.

6.3.9 Antidepressants are more effective than St John's wort

St John's wort (the plant *Hypericum perforatum*) is used as an antidepressant by many people, particularly in Germany (Mitchell 1999). In Australia, therapeutic preparations of it are available over the counter.

Its 'natural' status makes it more acceptable than mainstream antidepressants to many people who are wary of drugs (Cowap 2006). In fact, it can cause a variety of adverse reactions, and it can interact adversely with other drugs (Smith 2002, p. 50), as can mainstream antidepressants. However, it generally has better tolerability than mainstream antidepressants (Mitchell 1999; Linde et al. 2008)).

St John's wort has limited patentability, because it is a naturally occurring biological entity. Consequently, according to Cowap (2006), pharmaceutical companies are not interested in it. A more cynical interpretation is that pharmaceutical companies have a vested interest in *actively discrediting* it because it is a threat to the mainstream antidepressant market.

A number of trials have demonstrated that St John's wort is more effective than placebo in the treatment of mild to moderate major depression, and as effective as several prescribed antidepressants (e.g. Szegedi et al. 2005). However, the methodology of such trials has been criticised (Mitchell 1999; Shelton et al. 2001); but so has that of many antidepressant trials (see chapter 7).

Other trials have found that St John's wort is less effective than antidepressants. However, some of these trials have been funded by pharmaceutical companies, and their methodology and interpretation have also been problematic and biased in favour of antidepressants. For example, Shelton et al. (2001), which was funded by Pfizer and found that St John's wort was not superior to placebo, had an unusually low placebo response, which the lack of an antidepressant arm made difficult to interpret. Furthermore, the participants were recruited at tertiary care clinics in academic medical centres and had an average duration of depression of more than two years, unrepresentative of most people with depression (Patten 2001).

Government-funded trials have also been problematic. One of the most significant trials (Hypericum Depression Trial Study Group 2002) – which did have an antidepressant arm – was funded by the US NIMH. It found that both sertraline and St John's wort were less effective than placebo. However, a report by (Schwenk 2002) was titled 'No benefit of St. John's wort in major depression'. Only at the end of the article did Schwenk state that 'sertraline was not effective either'. There was considerable controversy about the methodology as well as the interpretation of the study (Rosack 2002).

Overall, what is most clear from these trials is the influence of vested interests. The effectiveness of St John's wort, like that of mainstream antidepressants, remains contentious. More recently, however, a Cochrane review (Linde et al. 2008) concluded: 'The available evidence suggests that the hypericum extracts tested in the included trials a) are superior to placebo in patients with major depression; b) are similarly effective as standard antidepressants'. Ernst's (2009) review of the Cochrane review strongly endorsed St John's wort in its title: 'St John's wort superior to placebo and similar to antidepressants for major depression but with fewer side effects'. The

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2010 update of adult depression treatment guidelines of the UK National Institute for Health & Clinical Excellence (NICE) concluded:

> St John's wort is more effective than placebo on achieving response in both moderate and severe depression, and on reducing symptoms of depression in moderate depression.
>
> There appears to be no difference between St John's wort and other antidepressants, other than in moderate depression where it is better at achieving response and in severe depression where it is less effective than low-dose antidepressants in achieving response.
>
> However, St John's wort appears as acceptable as placebo and more acceptable than antidepressants, particularly TCAs, with fewer people leaving treatment early due to side effects and reporting adverse events. (National Collaborating Centre for Mental Health 2010, p. 390)

This suggests that St John's wort warrants at least the same legitimacy as prescribed antidepressants for the treatment of depression.

6.3.10 Antidepressants are not particularly effective

Despite the centrality of effectiveness claims to the orthodoxy about antidepressants, it is increasingly admitted by the pharmaceutical industry and key opinion leaders that antidepressants are ineffective for a significant proportion of patients. Significantly, despite his organisation's staunchly pro-psychotropic stance, US NIMH Director Thomas Insel admitted in 2009 that current antidepressants are not very effective:

> The unfortunate reality is that current medications help too few people to get better and very few people to get well. Most clinical trials have used acute statistical symptom improvement as an outcome, rather than assessment of the long-term functional improvements that would be desired for treatment of a chronic illness. (Insel 2009, p. 704)

Patients who are not helped by antidepressants are often referred to as having 'treatment-resistant' depression, or being 'non-responders' (Thase & Rush 1997; Thase et al. 1998). According to Ruelaz (2006) such patients are very common:

> Despite advances in our understanding of depression therapy, many patients with depression remain unresponsive to treatment. As many as 50% of patients who begin treatment with an antidepressant do not respond. In fact, even after 2 antidepressant trials, 30% to 40% of patients do not report significant improvement in their symptoms.

The readiness to admit the ineffectiveness of antidepressants seems generally to be motivated by loss of patent protection for existing antidepressants, and are used as a

rationale for developing and marketing and prescribing more expensive drugs. Currently there is strong promotion of atypical antipsychotics as alternative antidepressants and/or as augmentation (Parker & Malhi 2001; Dew et al. 2007). Another theme, criticised by Davey Smith (2011), is the pharmacological tailoring of antidepressant prescription on the basis of 'gene by environment interactions, or phenotypic sub-groups' (p. 555). However, detailed discussion of these issues is beyond the scope of this thesis.

6.3.11 Conclusion: Effectiveness of antidepressants

Antidepressants have long been assertively promoted as effective, and this promotion continues today. Claims that antidepressants are effective have been a key strand of clinical guidelines, depression awareness campaigns, and antidepressant marketing.

However, there is considerable evidence for a contrary view, that antidepressants are relatively ineffective (Moncrieff & Kirsch 2005). There is strong evidence that they are not much more effective than placebos in clinical trials, despite the fact that almost all such trials are funded by pharmaceutical companies, and are usually biased in favour of antidepressants, and, as is the case with prescribed drug trials generally, trials with negative findings are often suppressed.

There are also problems with interpretation of evidence. Significantly, the 'best evidence for efficacy', according to the Director of the US NIHM, is arguably evidence of withdrawal symptoms caused by discontinuation, rather than the return of depression symptoms that had been successfully suppressed by antidepressants.

There is little evidence of the effectiveness of antidepressants for children. As is the case with most classes of drugs, there have been very few paediatric antidepressant trials. Those that have been trialled have not performed much better than placebo, despite biased trials.

Despite massively increased prescribing, there is little evidence of a population-level benefit in terms of reduced depression rates. This is discussed in relation to suicide specifically in section 6.8.

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There is little good evidence that antidepressants are more effective than alternative treatments, including psychotherapy and St John's wort. Furthermore, it is increasingly admitted by antidepressant advocates that antidepressants are *not* particularly effective.

In summary, it is clear that claims of effectiveness, like claims of safety, are seriously overstated. For all these reasons, it is highly problematic that organisations such as *beyondblue* (2008, 2011) continue to assert without qualification (and without references) that antidepressants are 'effective'.

6.4 ANTIDEPRESSANTS ARE SAFE

> First-line agents would be any of the newer antidepressants, including SSRIs, SNRIs, or agents like mirtazapine or bupropion. These are all new agents that are safe, and there is no significant risk of toxicity. (Blier 2004)

Claims that antidepressants, particularly SSRIs, are safe are central to the antidepressant orthodoxy. In Australia, antidepressants have been vigorously promoted in Australia as safe (e.g. Berk & Dodd 2005; beyondblue 2008). Such claims often contrast antidepressants with other prescribed psychotropic drugs, particularly benzodiazepines. Antidepressant advocates also sometimes emotively contrast antidepressants favourably with historical treatments that are today considered barbaric and/or dangerous, including long-term confinement in grim asylums, psychosurgery, and insulin shock.

However, there are longstanding significant concerns about the safety of antidepressants (Parker 2000b; Medawar 1997), and there has been increasing debate about this in recent years, as evidence of harms has increased.

There are also more specific debates about whether antidepressants are safe for children, older people, and in pregnancy. For children, by far the most contentious issue is whether antidepressants increase or decrease the risk of suicide. This is arguably the most important antidepressant debate currently, and is discussed in detail in section 6.8. Apart from this, due to space constraints, there is only limited discussion here about safety issues for children, elderly people, and in pregnancy.

All antidepressants – like all other drugs – have potential 'side-effects'. In relation to prescribed drugs, the term 'side-effects' is often used in common parlance; in the

medical literature, the terms 'adverse drug reactions' (ADRs) and 'adverse drug events' (ADEs) are more often used. ADRs impose a significant burden on the health system (Roughead 2005).

A major factor is 'polypharmacy' – the use of multiple drugs. Many drugs interact pharmacologically, so the risk of ADRs – or more specifically adverse drug *interactions* – increases as the number of medications rises (Pillans & Roberts 1999; Veehof et al. 1999). Furthermore, prescribed drugs can also interact with alcohol, tobacco or other nonmedicinal drugs, and many foods (Corrigan 2002).

Many ADRs are minor and acute, resolving rapidly when medication is reduced or discontinued. However, many ADRs can result in hospital admissions, and. Roughead, Gilbert, Primrose, and Sansom (1998) estimated that 81,000 public hospital admissions in Australia in 1994-1995 would have been related to prescribed drugs. Some ADRs are fatal. There are also long-term risks such as the increased incidence of cancer associated with hormone replacement therapy (Rossouw et al. 2002).

An important problem is the inadequacy of post-marketing surveillance – the monitoring of ADRs once prescribed drugs have been launched on the market. According to Healy (2009), 'Posted parcels meanwhile are tracked far more accurately than adverse treatment effects on patients'. In the absence of systematic post-marketing surveillance, observational studies are the main source of evidence about ADRs.

Psychotropic drugs account for a significant proportion of ADRs. According to unpublished AIHW data, 12.67% of female drug-poisoning hospital admissions in Australia in 1994-1995 were related to the use of tranquillisers, antidepressants, analgesics, hypnotics, and sedatives (Williams 1997, p. 43). For males, the equivalent figure was 4.87%.

Reviews of antidepressant ADRs have produced long lists of symptoms and syndromes across a range of categories. Spigset (1999), analysing reports to the Swedish Adverse Drug Reactions Advisory Committee, found that the most commonly reported ADRs were neurological symptoms, psychiatric symptoms and

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gastrointestinal symptoms. Dermatological symptoms and 'general symptoms' were also common.

It is often claimed that SSRIs have a lower side-effect profile compared with older antidepressants such as TCAs and MAOIs. However, the evidence is questionable (Brambilla et al. 2005), and there is increasing concern about a range of risks, which range from relatively trivial side-effects through troublesome but non-life-threatening symptoms to potentially fatal ADRs (Trindade et al. 1998; Spigset 1999).

One of the most well documented ADRs to SSRIs is sexual dysfunction. Male erectile dysfunction is common (Damis et al. 1999) and has received by far the most attention, but women also frequently experience SSRI-induced sexual dysfunction (Michelson et al. 2000). Viagra and similar drugs are sometimes prescribed for male erectile dysfunction caused by antidepressants (Damis et al. 1999; Taylor et al. 2005). Ironically, antidepressants are increasingly being used as a treatment for premature ejaculation, harnessing their potential to blunt sexual arousal. In Australia, off-label use of antidepressants for this purpose is well established (albeit clinically and socially questionable) (Burke & McClymont 2009). In February 2010, Provigil® (dapoxetine hydrochloride; Janssen-Cilag) became the first antidepressant approved by the TGA for premature ejaculation (TGA 2010).

Two potentially serious ADRs are cardiac disturbances and serotonin syndrome (potentially fatal serotonin toxicity) (Burggraf 1997). There is also some evidence that antidepressants may increase the risk of breast and ovarian cancer (Steingart et al. 2003; Cosgrove et al. 2011). Other risks, including heart attacks (Thorogood et al. 1992), and pulmonary embolism (Parkin et al. 2003), have generally received little attention.

Antidepressants have been found to contribute significantly to prescribed drug-related deaths. In a Canadian study of drug-related mortality, Mittmann et al. (1997, p. 165) reported that nervous system drugs were the most commonly reported suspect drugs in ADRs, and they dominated non-suicidal cases as well as suicide reports. Several years later, Cheeta et al. (2004) noted that 'Deaths from antidepressants continue to account for a substantial proportion of drug-related deaths'. The relative toxicity (particularly cardiotoxicity) of TCAs in overdose has been emphasised as an argument in favour of SSRIs, but deaths also occur with SSRIs (Cheeta et al. 2004).

Controversially, there is some evidence that exposure to antidepressants can increase the risk of bipolar disorder ('manic depression') (Cicero et al. 2003; Cipriani & Geddes 2008; Fava & Offidani 2011). This is likely to be a prominent debate in the next few years, but as yet it is relatively low-key, and it is not discussed in this thesis.

Two other risks in particular that have received significant attention are discussed in detail in this chapter: the risk of dependence, and the potential to trigger suicide (and to a lesser extent homicide). These are discussed in sections 6.7 and 6.8 respectively.

6.4.1 Antidepressants have been proven to be safe

> It is proven scientifically that all new classes of antidepressants are safe, effective and are not habit-forming. (*beyondblue* 2008)

It is argued that antidepressants have been *proven* to be safe because they have been rigorously tested in clinical trials and subsequently approved by regulatory authorities such as the FDA. This ignores the fact that a number of potentially harmful drugs – including some antidepressants[3] – have been tested and approved and have subsequently been removed from the market because of their risks.

It also ignores the serious clouds hanging over the FDA regarding the integrity of its regulatory activities (Angell 2005, pp. 208-214). The FDA's reliance on pharmaceutical industry funding is a particular concern, along with conflicts of interest of staff who personally receive industry payments.

As noted in relation to effectiveness, there is significant evidence of biases in the methodology and reporting of industry-funded drug trials. This is discussed in some detail in chapter 7. It includes biases against detection and documentation of ADRs. In relation to treatment of a range of mental health problems including depression, Papanikolaou et al. (2004, p. 1692) reported serious deficiencies in safety reporting:

> Among drug trials, only 21.4% had adequate reporting of clinical adverse events, and only 16.5% had adequate reporting of laboratory-determined toxicity, while 32.0% reported both the numbers and the reasons for withdrawals due to toxicity in each arm.

[3] For example nefazodone, which is discussed in chapter 8.

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In addition, considerable 'spin' is often used in reports of ADRs, to minimise their apparent prevalence and significance. More importantly, the short duration of antidepressant trials greatly reduces the likelihood of many harms emerging and being detected.

According to Ioannidis (2008):

> Antidepressant trials are not geared towards demonstrating the possible harms of these medications. The imbalance of emphasis between effectiveness and harms in the design and reporting of randomized trials has been repeatedly demonstrated in various medical specialties, including mental health interventions. Small trials are unlikely to pick any major harms, even relatively common ones, let alone uncommon harms that are life-threatening and may lead to death. Antidepressants are thus licensed in almost perfect vacuum on harms information.

Despite these problems, some evidence of harms has emerged from clinical trials (Aursnes & Gjertsen 2008; Cipriani et al. 2007).

6.4.2 Newer antidepressants are safer

It is often claimed that newer antidepressants are safer than older ones. Often this is expressed in terms of having 'milder side-effects'. Occasionally it is claimed that newer antidepressants are *free* of side-effects. For example, the Deputy Chief Executive Officer of *beyondblue* has been quoted as saying: '"*Unlike 20 years ago, when antidepressants had side effects*, modern medications have proven highly effective," says Dr Highet' [italics added] (Barr 2006).

Australian psychiatrists Beerworth and Tiller (1998) took a particularly strong stance in relation to the superior safety of newer antidepressants, asserting that:

> There needs to be compelling reasons for prescribing medicines with a greater likelihood of adverse outcomes such as the older antidepressants (e.g. tricyclics) rather than the newer antidepressants such as RIMAs, SSRIs, SNRIs and 5HT2 receptor antagonists. The higher likelihood of an adverse outcome of treatment where an older antidepressant has been prescribed raises the potential for professional negligence claims to be brought against medical practitioners who prescribe such medicines for reasons other than established medical need. (p. 560)

However, the adverse effects of older drugs are more likely to be known, simply because they have been used more. Pharmaceutical companies exploit this situation to promote newer, more expensive drugs as safer.

6.4.3 Antidepressants are safe for children and adolescents

As mentioned earlier, antidepressants have been promoted as safe for children and adolescents (Jureidini & McHenry 2009). However, considerable concern has emerged about their safety in recent years (Tonkin & Jureidini 2005; Safer & Zito 2006). Much of the concern has focused on the risk of suicidal ideation and behaviour. This is discussed in detail in section 6.8.

As mentioned earlier, there have been very few paediatric antidepressant trials. Furthermore, adverse effects have been downplayed in published studies (Jureidini et al. 2004, p. 880). For example, a controversial paper by Wagner et al. (2003) concluded that 'sertraline is an effective, safe, and well-tolerated short-term treatment for children and adolescents with MDD [major depressive disorder]' (p. 1040), despite significantly higher rates of adverse effects in the sertraline group than in the placebo group (Jureidini et al. 2004, p. 880).

Jureidini and McHenry (2009) concluded that, contrary to the claims of key opinion leaders:

> Antidepressants have not been demonstrated to be safe and effective for the treatment of depression in children or adolescents. There is, however, good evidence that they do harm (p. 200)

6.4.4 Antidepressants are safe for older people

Older people tend to have the highest rates of antidepressant use (Hall et al. 2003; Page et al. 2009; Hollingworth et al. 2010). According to Kennedy (2001) newer antidepressants are 'safe and effective' for older people. However, older people are routinely excluded from drug trials and clinical trials more generally (Lee et al. 2001), so there is often little relevant evidence from trials. This is very problematic, because older people often metabolise drugs less well than younger people (National Health and Medical Research Council (NHMRC) 1994, p. 4), increasing the risk of adverse reactions.

Furthermore, polypharmacy is very common among older people (NHMRC 1994, p. 18; Bolton et al. 2004, p. 78), who are typically prescribed multiple drugs for multiple

conditions, and are therefore at great risk of ADRs. As mentioned earlier, polypharmacy is a major factor in ADRs.

Observational studies have revealed that elderly people experience significant risks associated with antidepressants. In an Australian study of community-dwelling elderly people (Roughead et al. 2004), nervous system drugs were second only to cardiac drugs in causing ADRs. Antidepressants and psycholeptics (anxiolytics and antipsychotics) were the most commonly implicated nervous system drugs. Antidepressants, like benzodiazepines, increase the risk of accidents. Dizziness seems to be a major factor in this (Thapa et al. 1998). Elderly antidepressant users have increased rates of falls (Kerse et al. 2008; Leipzig et al. 1999; Thapa et al. 1998) and fractures (Hubbard et al. 2003). This has important public health and economic ramifications, including loss of mobility and loss of independence, which often result in institutionalisation.

Furthermore, a recent review by Coupland et al. (2011) found increased all-cause mortality among people aged 65 and older who took antidepressants. Notably, they also found an increased risk of several adverse outcomes for SSRIs compared with tricyclic antidepressants, contrary to perceptions that SSRIs are safer for elderly people (Diniz et al. 2011).

6.4.5 Antidepressants are safe in pregnancy

Antidepressant use in pregnancy is also an important issue, with the wellbeing of both mother and baby potentially at risk. Antidepressant advocates (e.g. Blier 2006; Koren et al. 2005) often use emotive arguments, claiming that the risk of untreated prenatal/postnatal depression is greater than the risks associated with antidepressant use. In such claims, untreated almost invariably means unmedicated, invoking the false dichotomy of antidepressants or no treatment.

Pregnant women are usually excluded from randomised controlled drug trials (Goldkind et al. 2010). However, observational studies have revealed increased rates of adverse events including preterm birth (Suri et al. 2007; Lewis et al. 2010), congenital malformations (Pedersen et al. 2009) persistent pulmonary hypertension of the newborn (Chambers et al. 2006), and autism (Croen et al. 2011).

6.4.6 Antidepressants are not entirely safe but….

Increasingly it is somewhat grudgingly admitted that antidepressants are not entirely safe, but it is argued that they are safer than 'the alternative', which is usually framed as no treatment, other options being ignored. Again, this is an example of the false dichotomy – antidepressants or nothing – that is common in the depression arena and is discussed further in section 6.5.1. Furthermore, such claims frequently raise the spectre of suicide (the risk of which in untreated depression is inflated, as discussed in chapter 5).

A minor theme among antidepressant advocates is that psychotherapy, the most common alternative to antidepressants, is not safe either. This is discussed in section 6.9.5 in relation to the claim that antidepressant critics are biased advocates of psychotherapy.

6.4.7 Conclusion: Safety of antidepressants

As is the case with safety, antidepressants have long been promoted as safe, and this promotion continues today. Claims that antidepressants are safe have been a major strand of the orthodox story about depression, and they figure prominently in depression awareness campaigns such as the Defeat Depression Campaign, to counter negative public perceptions.

However, there is substantial evidence of significant risks. Much of this evidence has emerged from observational studies. Some evidence has also emerged from clinical trials, despite biased methodology and reporting.

Some of the risks have emerged relatively recently (e.g. the risk of autism in children of women who use antidepressants during pregnancy (Croen et al. 2011)). Therefore it is not surprising that these risks were not considered in the 1990s and early 2000s. However, other risks have been documented but largely ignored for as long as several decades. In any event, it is highly problematic that organisations such as *beyondblue* (2008, 2011) continue to assert without qualification that antidepressants are 'safe'.

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6.5 ANTIDEPRESSANTS ARE NECESSARY

> Michael Dudley, chairman of Suicide Prevention Australia and a senior lecturer in psychiatry at the University of NSW, says antidepressants are vital for people suffering moderate and severe depression, and steering clear of them is "a grave mistake". (Benson 2008)

Another important claim is that antidepressants are necessary when depression occurs. Historically this claim has often been implicit, but increasingly it is being expressed explicitly, partly because of increasing criticism of antidepressants. Claims that antidepressants are necessary are often rhetorically supported by claims about the risks associated with untreated depression, as in Dudley's comment above. Foremost among these risks is suicide, which is discussed in section 6.8.

It is also increasingly claimed that antidepressants are necessary for sub-threshold or sub-clinical depression. However, space precludes detailed discussion of those claims.

A number of methodologically sound studies challenge the orthodox story that treatment – which primarily consists of antidepressants – is necessary for people experiencing depression, because it is often mild, transient, and self-limiting. As part of the US NIMH Collaborative Depression Study (NIMH CDS), Posternak et al. (2006) investigated depression without 'somatic' (pharmacological) treatment. They followed the naturalistic course of people who recovered from one episode of major depression then experienced a recurrence, reporting that only 15% of the participants who had not received antidepressants were still depressed twelve months later (p. 327). They concluded that 'there is a high rate of recovery in individuals not receiving somatic treatment of their depressive illness, particularly in the first 3 months of an episode' (p. 324), From this, they concluded that 'as many as 85% of depressed individuals who go without somatic treatment spontaneously recover within 1 year' (p. 328). However, it is questionable whether the recovery was spontaneous; in some cases there are likely to have been non-treatment factors that assisted recovery. Furthermore, the sample was of treatment-seeking patients, and it is likely that the recovery rate in the community is ever higher.

A recent review of randomised controlled antidepressant trials (Hegerl et al. 2012) concluded that antidepressants are not necessary for minor depression, nor is psychotherapy. According to Hegerl et al., 'For minor depression, unspecific support

like active monitoring, unspecific group counselling or internet-based guided self-help activities are reasonable treatment options' (p. 1), and 'Combination of antidepressants and specific psychotherapy does not appear to be justified in most patients with minor or mild depression' (p. 4).

There is stronger evidence to support the value of antidepressants for some people with persistent and/or severe depression, but it falls far short of proving that they are necessary. Unfortunately these findings are generally ignored, most likely because they do not support the orthodox story about depression.

6.5.1 Depression treatment equals antidepressants

One important way in which the message that antidepressants are necessary for people with depression is sold is by equating depression treatment with antidepressants. In many cases, depression treatment is discussed in the medical literature without any mention of anything other than antidepressants. Combined with claims about the risks of untreated depression, this is effectively a claim that antidepressants are necessary for people with depression.

Claims that treatment *means* antidepressants are common and influential but are usually implicit, which makes them harder to notice and harder to effectively critique. For example, in a *New Scientist* article about airline pilots being allowed to fly when using antidepressants, Australian psychiatric epidemiologist (and self-disclosed depression sufferer and antidepressant user) Professor Kathy Griffiths is quoted as implying that there is no treatment option other than antidepressants:

> "Antidepressants can be prescribed for years, so that means you are asking people to give up their livelihoods, or leave their depression untreated," notes Griffiths. (Nowak 2007)

Another example of this false dichotomy occurred in a recent editorial in the *American Journal of Psychiatry* that completely ignored the possibility of non-drug treatment when it commented that:

> Clinicians confronted with an inadequate antidepressant response have four options open to them—a dose adjustment, a switch to an alternative antidepressant, the introduction of another drug not considered itself an antidepressant (augmentation), or the addition of another antidepressant. (Coryell 2011, p. 664)

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One particularly influential publication that has equated depression treatment with antidepressants is 'The National Depressive and Manic-Depressive Association Consensus Statement on the Undertreatment of Depression' (Hirschfeld et al. 1997). This was the outcome of a consensus conference sponsored by Bristol-Myers Squibb. Its abstract lists 'failure to consider psychotherapeutic approaches' as a factor in undertreatment, yet Hirschfeld et al. paid only lip service to psychotherapies in the body of the paper. Most notably, in a 1600-word section in response to the questions 'Is depression undertreated in the community and in the clinic? How extensive is the gap between current available knowledge and actual treatment?', psychotherapy was mentioned only twice. Once was in passing: 'In most instances the medical specialty or graduate degree of the person who treated the patient (perhaps in psychotherapy or in a general medical office setting) and the person who prescribed the treatment is not known' (p. 334). The second instance was in the final paragraph, which was appended like a postscript to the conclusion in the paragraph preceding it, and subtly disparaged psychotherapy by implying that it needs to be delivered for a long period of time:

> In conclusion, it is unfortunate that the vast majority of those treated with antidepressant medication are not prescribed an adequate dose for a long enough time. It is not yet clear if use of the newer antidepressants will lessen this problem because of their generally more favorable adverse effects profiles.
>
> Effective structured psychotherapies for depression also exist. Unfortunately, few patients with depression actually receive these psychotherapies. When they do, they may not receive them for a long enough period of time. (p. 335)

The treatment-equals-antidepressants message also lurks in other messages. For example, the message that antidepressants are safer than 'the alternative' implies that no other treatments are available.

Equating treatment with antidepressants serves another important purpose: it allows advocates to promote antidepressants but claim to be advocating treatments more generally.

In relation to more mild depression, counselling/psychotherapy is mentioned as an afterthought (or less frequently paid lip service to at the beginning of the discussion and then totally ignored). Frequently counselling is referred to as an *adjunct* to antidepressants rather than a treatment in its own right. More insidiously, counselling is sometimes promoted by pharmaceutical companies as a strategy for increasing compliance with antidepressant treatment. Such counselling includes playing down of

side-effects. An example of an Australian adherence counselling program for patients prescribed Aropax® (paroxetine) is discussed chapter 9.

Linguistic strategies are also used to devalue counselling by subtly implying that it is not real treatment. Commonly, antidepressants are referred to as 'medical treatment' whereas counselling is referred to as 'talking therapy'. People who believe that depression is a brain disease are unlikely to perceive *talking* as an effective remedy.

Influential Australian psychiatrist Professor Ian Hickie has repeatedly distinguished counselling from 'medical' treatment in phrases like 'medical and psychological treatments' (Hickie & Scott 2007; Hickie 2008).

More explicitly, prominent key opinion leader J. John Mann's (2005) influential review of the medical management of depression declared 'Antidepressants are the treatment of choice for moderate-to-severe episodes of depression' (p. 1826). It included a diagrammatic 'Algorithm for the Acute Treatment Phase of a Major Depressive Episode in Major Depressive Disorder' (p. 1827, figure 2) which began:

> Initiate treatment with selective agent:
>
> SSRI
>
> NRI
>
> Other drug

Only on the fourth step of the algorithm did it mention psychotherapy, saying only that it should be *considered*:

> Consider psychotherapy at any time during treatment

In addition, it emphatically declared that psychotherapy alone was not appropriate for severe depression:

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> Psychotherapy can be a first-line therapy for mild depression but not for severe depression, particularly psychotic and bipolar forms, unless used in combination with pharmacology. (Mann 2005)

In Canada in 2001, a working group of the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the Canadian Psychiatric Association jointly developed clinical guidelines for depression treatment. Kennedy et al. (2003, p. 490) summarised the guidelines, with this table featuring prominently:

Table 1. Recommendations for treating major depressive disorder

First-line treatments

- SSRIs and novel agents (level I evidence)
- Venlafaxine might have higher remission rates than SSRIs (level I evidence)

Second-line treatments

- Amitriptyline and clomipramine have greater efficacy than SSRIs among hospitalized patients (level II evidence)
- Safety and tolerability issues need to be addressed
- In the frail elderly, nortriptyline has fewer adverse effects than amitriptyline or clomipramine

Third-line treatments

- Other tricyclic agents and monoamine oxidase inhibitors, because of safety and tolerability issues (level II evidence)

Psychotherapy was mentioned rather half-heartedly in the text of the article, with stringent restrictions on its use, but the message in this table is that it is not even a third-line treatment.

Other problems with antidepressant guidelines, including non-adherence, are discussed in section 6.6.4.

6.5.2 Antidepressants are necessary for months or even years

> For some people, antidepressants are needed only for a short time (generally 12 months)…. For others, antidepressants are needed on an ongoing basis – in the same way that someone with diabetes would use insulin or someone with asthma would use respiratory medication. (beyondblue 2008, p. 3)

As mentioned above, Hirschfeld et al. (1997) argued that the vast majority of people treated with antidepressants were not prescribed an adequate dose for a sufficient time (p. 335). Antidepressant advocates routinely claim that antidepressants are necessary for at least six months; some claim that they are necessary for at least *two years*, for people with recurrent depression.

One of the main arguments used to justify relatively long-term antidepressant use is the likelihood of re-emergence of depression symptoms when people stop taking antidepressants. However, as discussed in section 6.3.3, such symptoms are more accurately interpreted as withdrawal symptoms, according to an increasing number of critics (e.g. Moncrieff 2007).

A key study is Geddes et al.'s (2003) systematic review of the effectiveness of antidepressants as relapse prevention. Although Geddes' work tends to be more rigorous than much of the depression/antidepressant literature, this influential analysis is problematic for several reasons.

Firstly, it focused on patients unrepresentative of general practice patients. Geddes et al. acknowledged the limited generalisability of their findings:

> The trials were mainly done in secondary care settings, with patients at a high risk of relapse. This is an important patient group contributing substantially to the prevalence and burden of disease posed by major depression. How our results would apply to patients who were under-represented in the trials is unclear, particularly those with milder illnesses who might have a low underlying risk of relapse. (p. 660)

However, this caveat has been largely ignored, and the findings have been inappropriately generalised to general practice patients. This is unsurprising, given that not only was the caveat not stated in the abstract (nor was it simply reported that the patients were not from primary care), but also Geddes et al. largely ignored it in their discussion. Furthermore, they did not comment on the significance of the fact that there are relatively few primary care relapse trials and the possibility that this dearth might be largely due to suppression of negative findings. These omissions were compounded by their comment that 'Few other interventions in psychiatry are supported by such robust findings' (p. 660).

According to Fava (2010, p. 204), prolonged prescribing of antidepressants based on studies such as Geddes et al.'s (2003) that fail to take publication bias into account is another example of 'the spectacular achievements of propaganda that took place in psychiatry'.

6.5.3 Antidepressant adherence is crucial

According to Keller et al. (2002, p. 265). 'Compliance with antidepressant medication is essential to consolidate treatment response and prevent relapse and recurrence'. Such claims are based on problematic interpretations of withdrawal symptoms (discussed in section 6.3.3), biased evidence about rates of relapse, and selective literature citation.

Prominent US key opinion leader J. John Mann (2005) emphatically declared: 'Early discontinuation is associated with a 77 percent higher risk of relapse as compared with continuation treatment' (p. 1830), citing a very influential study by Melfi et al. (1998). However, according to Gardarsdottir et al. (2009, p. 281), that study had 'obvious methodological flaws in the method used to define exposure and measure follow-up'. To illustrate, Gardarsdottir et al. analysed data from a Dutch general practice survey. Using Melfi et al.'s methodology, they found a significantly higher risk of relapse/recurrence for early discontinuers. In contrast, a more sound methodology produced no significant difference. Not only was Melfi et al.'s study funded by Eli Lilly (p. 1132), but the lead and third authors were Lilly employees (p. 1128). Gardarsdottir et al. did not comment on this, but emphasised the problematic influence of the study:

> With depression being the fourth leading cause of disease burden in the world, the clinical implications of studies that report on optimizing therapy and improving treatment outcomes are large. Since publication of the study by Melfi et al. on the beneficial effects of continuing antidepressant treatment, their results have been cited numerous times by other researchers and in treatment guidelines that aim to optimize antidepressant drug treatment outcomes. Given the impact that published data have on decision making by health care providers and policy makers, use of the right methodology is crucial when performing observational studies. (p. 284)

The Melfi et al. study is an important example of a strategic industry-funded publication that has been designed and successfully used to have a major influence on antidepressant prescribing. Other examples of such publications are discussed in chapter 8.

In addition, published evidence to the contrary of claims about the value of adherence is routinely ignored in the literature. For example, Aikens et al. (2005, p. 229) found that 'Patients who discontinued were significantly less likely to be depressed 9 months after starting medication than those who either continued or switched medication, and were less symptomatic and impaired than patients who switched'.

6.5.4 Antidepressants are under-prescribed

It is commonly claimed that antidepressants are seriously under-prescribed. One of the strongest statements of this has been 'The National Depressive and Manic-Depressive Association Consensus Statement on the Undertreatment of Depression' (Hirschfeld et al. 1997), which concluded that 'There is overwhelming evidence that individuals with depression are being seriously undertreated' (p. 333). As discussed above, it barely mentioned psychotherapy; clearly the under-treatment it railed against was underprescription of antidepressants, which is unsurprising given that it was sponsored by Bristol-Myers Squibb.

In Australia, Ian Hickie has been a prominent exponent of this claim. In an article in the *Depression Awareness Journal*, which is discussed in detail in chapter 9, he asserted:

> Treatments provided in general practice are largely non-pharmacological, and consist mostly of non-specific advice and support which are unlikely to have significant effects on the outcome of more severe depressive or anxiety disorders; and,
>
> Pharmacological treatments are not widely used for common mental disorders (only 12% of all patients, 39% of patients in whom a doctor makes a diagnosis, and 27% of patients with the most severe disorders. (Hickie et al. 2003, p. 6)

Hickie based these claims on data from his SPHERE clinical practice audit, which is discussed briefly in chapter 9.

However, antidepressants are 'the mainstay of treatment' (MacGillivray et al. 2003, p. 1), and there is considerable evidence in Australia, as in many other countries, that people who are diagnosed as suffering from depression have a high chance of being prescribed antidepressants (AIHW 2004, p. 211), generally by GPs (McManus 2000, p. 458; AIHW 2011, p. 22). A five-year follow-up study of Australian GP patients

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found that 93.6% of patients diagnosed with depression received an antidepressant at some time during the study period (Wilson et al. 2003, p. 685). The authors commented that 'diagnosis of depression is almost routinely followed by the prescription of an antidepressant at some stage' (p. 688). Similarly, in a German study, Wittchen et al. (2001) reported that 'Among correctly identified depression cases doctors decided to prescribe drug treatments in 72.7% (DSM) and 60.8% (ICD)' (p. 121). In a 10-year follow-up study in the Netherlands, van Weel-Baumgarten, van den Bosch, Hekster, van den Hoogen, & Zitman (2000) found that 94% of patients who had recurrences of depression were prescribed antidepressants at some point.

Often antidepressants are prescribed very quickly. Ornstein et al. (2000) reported that 49% of newly diagnosed patients were prescribed antidepressants, mostly (81%) SSRIs, within five days.

Furthermore, there is considerable evidence of excessive and inappropriate prescribing. In particular, antidepressants are commonly prescribed for subclinical depression and other types of distress. This is discussed in section 6.6.1.

6.5.5 Conclusion: Necessity of antidepressants

Claims that antidepressant prescription and adherence are necessary for people with depression, sometimes for years, are a key part of the depression/antidepressant orthodoxy. Such claims are supported by equating treatment with antidepressants. Sometimes this is explicit, but often it is implicit, for example when psychotherapy is mentioned but subtly disparaged.

Claims that antidepressants are necessary are often rhetorically supported by claims about the risks associated with untreated depression. However, as discussed in chapter 4 and again briefly in this chapter, many people with depression recover without treatment, antidepressant or otherwise.

6.6 ANTIDEPRESSANT PRESCRIBING IS APPROPRIATE

Antidepressant prescribing is often promoted and defended on a number of persuasive and authoritative grounds that form part of the orthodox story about depression and antidepressants. Firstly, it is argued that antidepressants are only prescribed for approved diagnoses, primarily depressive disorders. Most significantly, it is argued

that depression treatment – including decisions about whether or not to prescribe an antidepressant and choices among antidepressants – is evidence-based and, therefore, antidepressant prescribing is appropriate. It is also argued that prescribing is governed by evidence-based guidelines.

6.6.1 Antidepressants are only prescribed for approved diagnoses

In Australia, among other countries, antidepressants are approved for prescription to people who meet established diagnostic criteria for disorders such as DSM-IV (*Diagnostic and statistical manual of mental disorders* (4th ed.)) (American Psychiatric Association [APA] 1994) major depression. However, antidepressants are frequently prescribed for people who do not meet such criteria, sometimes for other indications (conditions), and sometimes for subthreshold diagnoses.

In a US study, Streator & Moss (1997) found that 56% of SSRI claims for members of a health management organisation were for non-FDA-approved diagnoses. In a study focusing on a national network of primary care physicians, Ornstein, Stuart, & Jenkins (2000, p. 68) reported that more than 40% of patients who were prescribed antidepressants had never been diagnosed with depression. Such 'off-label' prescribing of antidepressants and other psychotropic drugs is common in many countries.

In a nationally representative US study, Pagura et al. (2011) found that 52% of antidepressant users did not meet criteria for any past-year DSM-IV diagnosis assessed (depressive disorders, anxiety disorders, alcohol and other drug use disorders, and eating disorders), and 26% did not meet criteria for any lifetime diagnosis (p. 497). However, most of the latter (89%) reported at least one 'indicator of need' (hospitalisation, suicidal behaviour, perceived need for mental health treatment, subthreshold disorders, past-month disability, lifetime traumatic events) (p. 497, table 2). This provides clear evidence of antidepressants being used inappropriately for distress.

In Australia, in relation to the Australian Longitudinal Study on Women's Health, Byles et al. (2008, p. 17) reported that 'Only 67% of women who were claiming

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antidepressants (N06A[4]) reported having been diagnosed with depression'. Also in Australia, McManus et al. (2003) reported that GPs reported prescribing antidepressants for women who did not meet the criteria for which antidepressants were subsidised by the Pharmaceutical Benefits Scheme:

> The most prominent type of depression that GPs believed they were treating was "chronic mild depression", which contrasts with the subsidized indication for all newer antidepressant classes of 'major depressive disorders'(p. 184).

McManus et al. concluded (p. 184):

> most management [with antidepressants] in primary care is not for conditions regarded by the GP as major depression. A significant number of prescriptions for the newer antidepressants may not accord with the Pharmaceutical Benefits Scheme (PBS) restrictions for use.

Sometimes, however, inappropriate prescribing is a result of incorrect diagnosis. In a study of Italian primary care physicians (PCPs), Berardi et al. (2005) found that incorrect diagnosis of depression and resultant inappropriate prescribing of antidepressants were common:

> 45.0% of patients labeled as depressed by the PCPs were not cases of depression according to ICD-10 criteria; 26.9% of false-positive cases received an antidepressant. Globally, 35% of antidepressants for 'depression' were prescribed to false-positive cases. (p. 225)

Often there is no formal assessment of patients prior to prescribing antidepressants. One reason is the time pressure GPs experience. A UK study found that many GP consultations were less than 10 minutes in length, and as many as two-thirds ended with the issuing of a prescription for one or more drugs (Audit Commission 1994, cited by Greenhalgh & Gill 1997). Furthermore, a Scottish study by Stirling et al. (2001) found that shorter consultations were associated with increasing socioeconomic deprivation and higher prevalence of psychological distress.

In Australia in 2000-2001, a sub-study of the BEACH (Bettering the Evaluation and Care of Health) program, a national continuous cross-sectional survey of general practice, found a mean consultation length of 14.8 minutes (Britt et al. 2002). Consultations in which depression is managed have been found in the BEACH survey to be longer than other consultations (Harrison & Charles 2009, pp. 241-242, figure 14.11). Antidepressants were prescribed at a rate of approximately 65 per 100

[4] NO6A is the Anatomical Therapeutic Chemical (ATC) Classification System code number of antidepressants.

depression problems managed, relatively consistently from 1998-99 to 2007-08 (p. 239, figure 14.8). 'Depression problems' included both diagnosed depression and 'problems labelled by the GP as symptoms of depression' (p. 237). It seems likely that antidepressants were prescribed for many of the latter.

Elderly people are often recipients of off-label prescribing of antidepressants and other psychotropic drugs. In a US study of Georgia Medicaid enrollees, Chen et al. (2006) found that the likelihood of receiving psychotropic drugs off-label 'increased remarkably with advancing age', and people aged over 65 were five times as likely to receive off-label antidepressants as their younger counterparts (p. 972). Antipsychotics and anticonvulsants were also commonly prescribed off-label. In a Finnish study of antipsychotic use in long-term institutional care of nonagenarians, Alanen et al. (2007, p. 513) found that there were '*no associations between any psychiatric symptoms or diagnoses* including dementia and the use of antipsychotics' [italics added]. Although 33.8% of residents were prescribed antidepressants, only 11.5% had a diagnosis of depression (p. 510). Drawing on data from the 2007 National Survey of Mental Health and Wellbeing (Australian Bureau of Statistics 2008) and Pharmaceutical Benefits Scheme prescribing data, Hollingworth et al. (2010) found that antidepressant use peaked in people aged 90-94 years (but was higher among women) (p. 516). They concluded:

> It appears that older Australians are receiving antidepressant medications for reasons other than the treatment of conditions for which these drugs have marketing approval or for depressive and anxiety symptoms that do not reach the threshold for a diagnosis. (p. 513)

6.6.2 Antidepressant prescribing is evidence-based

Claims that antidepressant prescribing is evidence-based are common and persuasive. Such claims are frequently used to reassure patients who might be reluctant to take antidepressants. They are also used to justify expenditure of very large amounts of money, because antidepressants are approved by governments and health management organisations, on the basis of evidence from supposedly rigorous clinical trials, for prescription for specific purposes, and this often determines subsidisation or reimbursement.

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However, an increasing number of critics argue that doctors are misled into believing that their prescribing is evidence-based. According to Healy (2009, p. 85):

> Doctors say they consume (prescribe) medication according to the evidence, so marketeers design and run trials to increase a drug's use. They select the trials, data and authors that suit, publish in quality journals, facilitate incorporation in guidelines, then exhort doctors to practise evidence-based medicine. Because 'they're worth it', doctors consume branded high-cost but less effective 'evidence-based' derivatives of older compounds making these drugs worth more than their weight in gold

Rather more charitably, according to Fava (2010, p. 204):

> Prescribers may claim to be following the evidence, but are primarily influenced by the eminence of the authorities they listen to in meetings and read in journals or by the framing of the risk of medication side effects by the pharmaceutical industry. This occurs also because of the control of special interest groups over diagnostic classification and clinical guidelines committees

As discussed in chapter 7, there is considerable evidence to support claims that antidepressant prescribing is unduly influenced by pharmaceutical companies and other players with vested interests.

6.6.3 Antidepressant selection and dosage are evidence-based

Leaving aside the issues of assessment and diagnosis, there is also evidence that the choice *among* antidepressants is often not based on sound criteria. In a US survey, Petersen et al. (2002) found that many psychiatrists had beliefs about the efficacy and adverse effect profile of different antidepressants that were not evidence-based, suggesting that drug choices are determined by factors other than empirical evidence. They suggested that drug marketing and media information have a significant influence. In relation to the former, an Australian study by Ward et al. (2008) found that brand names significantly influenced prescribing patterns:

> the brand name as much as chemical differences influenced the prescription of choice of antidepressants by both general practitioners and psychiatrists. The use of a well-promoted brand name may be an important evaluation shortcut by both groups regardless of detailed training resulting in medical practices, which may undermine the social imperative of affordable medical care for all. The authors suggest that clinical appropriateness of prescriptions for antidepressants by brand name needs further investigation. (p. 274).

Furthermore, there is high variability in psychotropic drug prescribing practices among doctors. In an analysis of prescribing decisions in a US state psychiatric

hospital, Gillis & Moran (1981) concluded that agreement among doctors was generally very low. A similar study by Gillis et al. (1981) reported that:

> psychiatric staff members at various Veterans Administration hospitals …. failed to agree with each other significantly more than would be expected by change [sic]; this was true for their prescriptions of general class of medications, specific drugs, and dose levels. (p. 439)

A cross-national study co-authored by Gillis found that agreement was also low among Swiss psychiatrists (Fisch et al. 1982). It also found that American psychiatrists prescribed much higher doses than Swiss psychiatrists for identical hypothetical patients. In the Netherlands, a study of psychiatrists at two psychiatric hospitals and one academic psychiatric department (Lochmann van Bennekom et al. 2008) found poor agreement in their assessments of the rationality of actual cases of psychiatric polypharmacy (prescribing of multiple psychotropic drugs, including antidepressants).

In an interview with the US Public Broadcasting Service, the Director of the NIMH, Dr Thomas Insel, commented:

> One of the things I think that people struggle with the most is that the treatment they are likely to be given may depend much more on who they call and not on what problem they're dealing with. And that's a bit of a change. That's not as true in cancer. It's not quite as true in heart disease, although there's some of that. But in the case of mental disorders, there's still this huge variation in the treatments that people are given, and a lot of it depends not so much on a thorough understanding of these disorders, [but] much more on what it is the therapist is most comfortable in doing. (Public Broadcasting Service 2008)

6.6.4 Antidepressant guidelines ensure that prescribing is appropriate

There are, of course, clinical guidelines intended to influence prescribing. Guidelines for antidepressant prescribing, and for depression treatment more generally, are common. According to Anderson (2003, p. 11), there are more guidelines for depression than for any other psychiatric disorder. Most notable in Australia are the Royal Australian and New Zealand College of Psychiatrists' (RANZCP 2004b) *Australian and New Zealand clinical practice guidelines for the treatment of depression*.

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However, adherence to guidelines is frequently low. For example, in a case vignette study, Smith et al. (2003, p. 61) found that GPs prescribed antidepressants for around 40% of cases, whereas guideline experts prescribed them for less than 25% of the cases. This is even more problematic given that guidelines tend to be based on evidence from secondary and tertiary treatment, not general practice, According to Kendrick et al. (2008, p. 43): 'Little of the evidence about antidepressants is derived from the type of depression seen more commonly in primary care, which is less severe than major depression and less chronic than dysthymia'.

Furthermore, there is considerable criticism of guidelines, even by some antidepressant advocates. According to Anderson (2003, p. 11), depression guidelines, including the British Association for Psychopharmacology guidelines on the treatment of depression with antidepressants (Anderson et al. 2000), of which he was an author, tend to minimise uncertainties and gloss over difficulties. In Australia, the RANZCP guidelines were strongly criticised by Professor Gordon Parker (2004), Executive Director of the Black Dog Institute, who argued:

> these guidelines are far less precise and informative for clinical practice than they appear and with a disturbing lack of rigour for a document promulgated by a professional college. (p. 885)

Clinical guidelines in general have been criticised for many reasons. A range of Australian guidelines, including the RANZCP (2004b) depression guidelines, were found by Vitry & Zhang (2008) not to adequately address co-morbidity, particularly among elderly people.

More significantly, although depression and antidepressant guidelines are often claimed to be evidence-based (Ellis et al. 2003, p. 34; Anderson et al. 2000, 2008), an increasing number of critics argue that guideline committees are unduly influenced, even seriously corrupted, by pharmaceutical companies (Healy 2009, p. 85; Fava 2010, p. 204). Cosgrove et al. (2009) reported that ninety per cent of the authors of three major APA clinical practice guidelines – for major depressive disorder, bipolar disorder, and schizophrenia – had had financial ties to companies that manufactured drugs that were explicitly or implicitly recommended in the guidelines for the respective mental illnesses. None of these financial links were disclosed in the clinical practice guidelines.

> According to Healy (2006), drug companies 'manufacture' favourable consensus based on biased presentations of evidence. He identified industry-funded medical writing (including ghost-writing) as 'the first and most important piece of advertising for any pharmaceutical product--the randomized controlled trial infomercial'.

Bias in the summary of the Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for depression treatment (Kennedy et al. 2003) was briefly discussed in section 6.5.1. The three authors had extensive financial links to pharmaceutical companies.

6.6.5 Conclusion: Appropriateness of antidepressant prescribing

In summary, claims that antidepressant (and other psychotropic) prescribing is evidence-based and appropriate ignore substantial evidence to the contrary. Off-label prescribing, for indications not approved by regulatory authorities, is common, particularly for older people. Selection and dosage of antidepressants are highly variable, even idiosyncratic.

Guidelines exist, but adherence is poor. Furthermore, the content of guidelines is seriously flawed, and is arguably unduly influenced by pharmaceutical industry funding.

6.7 ANTIDEPRESSANTS DO NOT CAUSE ADDICTION OR DEPENDENCE

> Antidepressants are safe, effective and not addictive.
>
> People often want to stop taking antidepressants quickly because they are concerned they are addictive. This may be because they confuse them with sedatives, a group of medications that are used to help a person feel relaxed and, in some cases, fall/stay asleep.
>
> Unlike antidepressants, sedatives are designed to be used only for a short time. If used for long periods of time, sedatives may be needed in higher doses in order for them to have the same effect. This is not the case with antidepressants. (beyondblue 2008, p. 3)

A key debate about antidepressants has been about whether they can produce dependence (or addiction). Dependence was a pivotal issue in the 1990s. In fact, until the last decade or so, whenever the risks of antidepressants have been discussed, there

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has tended to be a disproportionate focus on dependence, often to the exclusion of other risks.

Opinions about antidepressants' dependence potential have been markedly polarised. Medawar (1997), probably more than anyone else, has vigorously campaigned for SSRIs to be recognised as having significant dependence potential. On the other hand, many psychiatrists and other players have emphatically argued against such claims.

Both sides have focused heavily on definitions of dependence. As briefly mentioned in chapter 2, although some people argue that dependence and addiction are different (e.g. Beers et al. 2005), both have been defined in many different ways that overlap substantially. At the core of both concepts is compulsion experienced by users to continue using a drug (or to continue a behaviour), which is relevant to this discussion. In this thesis, the more scientific and less pejorative term 'dependence' is used, except when referring to sources that use terms such as 'addiction'. However, distinctions between dependence and addiction are particularly relevant in this discussion, because of semantic[5] distinctions made by antidepressant advocates and critics. Diagnostic criteria also figure in the debate, particularly the dependence criteria in the DSM-IV (APA 1994)[6] and the ICD-10 (World Health Organization 1992).

An important contextual issue in the debate is the stigma and moral condemnation associated with dependence on drugs, particularly nonmedical drugs. This has raised the stakes: dependence is no *ordinary* adverse effect.

In addition, the question of antidepressant dependence needs to be viewed in its historical context, particularly in relation to the chequered career of benzodiazepines – 'minor tranquillisers' such as Valium® (diazepam) – in the mass psychotropic market. A key strategy used in the debate has been to compare the dependence potential of antidepressants with that of benzodiazepines. Comparisons have also been made between antidepressants and nonmedical 'recreational' psychotropic drugs such as heroin and other illegal opioids. Antidepressant advocates have emphatically argued that antidepressants are very different from these other drugs; critics have argued that

[5] I do not use the term semantics in the disparaging sense in which it is often used. I believe that language is very powerful in constructions of social problems.
[6] As is the case for major depressive disorder, the DSM-IV-TR (APA 2000) criteria for substance dependence are exactly the same as the DSM-IV (APA 1994) criteria, and most people continue to cite the 1994 DSM-IV criteria.

they are all too similar. Comparisons with nonmedical drugs have strong moral and legal implications, which are beyond the scope of this thesis. Comparisons with benzodiazepines are discussed in some detail below.

Many prominent depression/antidepressant advocates have strongly asserted that antidepressants are not addictive. According to both Mental Health America (2010) and the US National Alliance for the Mentally Ill (2009, p. 8), 'Antidepressant medications are not habit-forming'.

In Australia, SANE Australia (2005) declared 'They are not addictive…. Antidepressants are not addictive and you will not become dependent on them'. Similarly, *beyondblue* and its inaugural Chief Executive Officer Ian Hickie have repeatedly denied that antidepressants are addictive:

> Antidepressants are safe, effective and not addictive. (*beyondblue* 2008)
>
> It is proven scientifically that all new classes of antidepressants are safe, effective and are not habit-forming. (*beyondblue* 2008)
>
> antidepressant drug therapies are non-addictive (Hickie & Scott 2007, p. 10)

In the UK, a key message of the industry-funded five-year Defeat Depression Campaign (discussed in chapter 8), run in the 1990s by the Royal Colleges of Psychiatrists and the Royal College of General Practitioners, was that antidepressants are not addictive:

> Doctors have an important role in educating the public about depression and the rationale for antidepressant treatment. In particular, patients should know that dependence is not a problem with antidepressants (Priest et al. 1996, p. 858)

Haddad (1999) similarly argued that antidepressants were not 'addictive', and emphatically declared: 'Patients prescribed other antidepressants should be told that they are not addictive' (1999, p. 300).

Such claims have often been in response to evidence of public perceptions that antidepressants *do* have significant dependence potential. In the UK, a survey conducted in 1991, just prior to the launch of the Defeat Depression Campaign, found that 78% of the general public believed antidepressants *were* addictive (Priest et al. 1996, p. 858).

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A major reason for such public perceptions was the fact that antidepressants displaced benzodiazepines in the market, largely because of benzodiazepines' dependence potential. According to Healy (2004, p. 6):

> the undoing of the benzodiazepines came not from overcharging[7] or from mass prescribing to mask social ills. It came when the possibility was raised, around the end of the 1970s, that these drugs that had been so relied upon might lead to dependence.

Although antidepressants and benzodiazepines differ chemically, they have overlapping effects. Furthermore, they are used to treat overlapping sets of symptoms (mainly depression and anxiety disorders).

When benzodiazepines were introduced in the early 1960s, they were promoted as a safe alternative to barbiturates, which have significant overdose potential (Buckley et al. 1995). Many barbiturate users have died of overdoses, both deliberate (Barraclough et al. 1971; Crome 1993; Mendelson & Rich 1993) and accidental. Barbiturates have a narrow therapeutic index – the ratio between a toxic dose and a therapeutic dose is small (Doweiko 2008, p. 93). Benzodiazepines have a significantly wider therapeutic index (p. 93).

Like previous sedatives, benzodiazepines were promoted as 'non-habit forming' (Lennane 1986). However, by the 1980s they were known to have significant dependence potential (Petursson & Lader 1981). Although it was claimed early on that they did not cause dependence (Marks 1978, 1980), overwhelming evidence soon made this position untenable.

Many lay people extrapolated concerns about dependence from benzodiazepines to antidepressants (Priest et al. 1996, p. 859). Consequently, it was important for antidepressant advocates to contrast benzodiazepines' dependence potential with that of antidepressants. This has been a key theme in antidepressant advertisements (Healy 2004, p. 282; Healy 2003). For example, a direct-to-consumer advertisement in the *Readers' Digest* in 2001 exhorted readers to 'Talk to your doctor about non-habit-forming Paxil today' (Healy 2004, p. 282).

[7] In the UK in the early 1970s, the drug firm Roche was convicted of anti-competitive practices in relation to its pricing of Valium® (diazepam) and Librium®(chlordiazepoxide) and required to repay the government millions of pounds and limit its promotional activities (Medawar 1992, p. 113).

More recently, discussing treatment of panic disorder, Kjernisted & McIntosh (2007, p. 61) asserted that 'antidepressants are preferred over benzodiazepines as first line treatment because, unlike benzodiazepines, antidepressants treat comorbid depression without risk of dependency'.

The distinction of antidepressants' dependence potential from that of benzodiazepines continues today in Australia, with *beyondblue*'s (2010) assertions that:

> Antidepressants are not addictive. They are sometimes confused with sedatives (for example diazepam). This group of medications is used to help a person feel relaxed and, in some cases, fall/stay asleep. Unlike antidepressants, sedatives are designed to be used for a short time. If used for long periods of time, sedatives may be needed in higher doses in order for them have the same effect. When people are addicted to sedatives and they stop taking them, they crave the effects of the sedatives. This is not the case with antidepressants.

In the UK, the dependence potential of antidepressants was essentially dismissed by the authoritative and widely cited Medicines and Healthcare products Regulatory Agency report on the safety of selective serotonin reuptake inhibitors (Weller et al. 2004), which concluded that 'There is no clear evidence that the SSRIs and related antidepressants have a significant dependence liability or show development of a dependence syndrome according to internationally accepted criteria, either DSM-IV or ICD-10' (p. 152). It is instructive to read the report's analysis of the evidence in relation to those criteria:

> With reference to ICD 10 criteria, SSRIs do not appear to lead to craving in comparison with other drugs of dependence such as opiates, heroin, cocaine and alcohol (criterion 1). There is no clear evidence of impaired control (criterion 2) apart from isolated single case studies in individuals who misuse other substances. There is clear evidence of withdrawal symptoms on discontinuation of SSRIs (criterion 3); also some patients take care not to run out of the drug, possibly to avoid withdrawal symptoms (criterion 3). However, this is not nearly as marked as in typical drugs of dependence. Tolerance does not appear to be significant compared with other drugs such as benzodiazepines (criterion 4). There is some evidence of preoccupation, or rather patients making sure they have a supply of SSRI drugs (criterion 5), but this does not appear to be prominent and may be more a feature of withdrawal avoidance. Finally, there does not appear to be evidence of persistence despite harmful consequences, partly perhaps because the harmful consequences related to SSRI use are relatively minor, and the benefits to the individual greater, compared with other typical dependence-producing drugs (criterion 6). So although SSRIs meet two

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> out of the six ICD 10 criteria (numbers 3 and 5), the evidence for criterion 5 is limited compared with other typical drugs of dependence.
>
> In relation to DSM IV criteria, as stated above tolerance is rare (criterion 1), withdrawal is common (criterion 2), and the substance is sometimes taken over a longer period than intended because of difficulties in stopping SSRIs (criterion 3). Sometimes, a desire to cut down can be unsuccessful (criterion 4). However, it is uncommon for a great deal of time to be spent in obtaining SSRIs (criterion 5), activities are seldom given up in favour of SSRIs (criterion 6), and SSRIs are seldom continued in the face of drug-related problems (criterion 7) in comparison with other typical dependence-producing drugs. Overall, in relation to DSM IV there is evidence that three out of the seven criteria are sometimes met. However, the extent to which SSRIs meet these criteria is much less than with other typically dependence-producing drugs. (p. 146)

Notably, Weller et al. acknowledged that antidepressants *can* cause DSM-IV dependence (by meeting three criteria – withdrawal, taking over a longer period than intended, and difficulty cutting down – of the seven specified criteria), but immediately dismissed the potential as much less than with 'typically dependence-producing drugs'. Those drugs were referred to in the first paragraph of the quote as 'drugs of dependence such as opiates, heroin, cocaine and alcohol', implying that it is only recreational drugs, particularly illicit ones, that cause dependence.

Illicit drugs also featured in Weller et al.'s (2004) very selective literature review of antidepressant dependence and 'abuse', in which a number of cases of antidepressant 'abuse' were discounted because the patients had a history of 'substance abuse' or 'opiate, cocaine or alcohol dependence'. This served both to locate the problem in the person, not the drug (the antidepressant), and to invoke the stigma of illicit drug use as a point of differentiation.

This sort of argument had been used earlier in relation to benzodiazepines. Marks (1978), a doctor employed by Roche, the manufacturer of Valium®, declared that the dependence risk with benzodiazepines was very low, and that the small number of people who were dependent were likely to be dependence-prone individuals.

Another strategy for locating the problem in the person rather than the drug has been to emphasise noncompliance as a factor. Schatzberg et al. (1997, p. 9) claimed, without citing any published evidence, 'Clinical experience indicates that … the phenomenon is more likely to occur in patients with a history of noncompliance to antidepressant medication'.

Tolerance was mentioned only once in Weller et al.'s literature review, in relation to a report of two patients who 'abused' fluoxetine but did not experience 'physical dependence as evidenced by tolerance or a withdrawal syndrome' (p. 145). Totally ignored were multiple published reports of antidepressant tolerance. A recent study by Fava & Offidani (2010) cited a number of other reports of antidepressant tolerance published between 1985 and 2002. For example, Fava et al. (1995) concluded: 'An increase in dose of fluoxetine to 40 mg/day appears to be an effective strategy in the treatment of relapse among depressed patients who had initially responded to fluoxetine 20 mg/day'. This clearly fits the DSM-IV definition of tolerance cited by Weller et al. (p. 143):

> tolerance as defined by either of the following:
>
> a. a need for markedly increased amounts of the substance to achieve intoxication or the desired effect;
>
> b. markedly diminished effect with continued use of the same amount of the substance

Furthermore, there is a longstanding colloquial term for antidepressant tolerance: 'poop-out' (often specifically 'Prozac poop-out') (Lambert 2000). Slater (1998), describing her experience of it to her doctor, said: 'I'm taking my doses every day, and I might as well be swallowing a sugar pill' (p. 119). Her doctor's solution was to increase her dose, which made her nauseous but helped alleviate her resurgent depression (pp. 126-127). This invalidates Weller et al.'s dismissal of the applicability of the tolerance criterion.

However, many other players have also dismissed tolerance, along with compulsive use (difficulty cutting down). For example, according to Haddad (1999, p. 300):

> Withdrawal or discontinuation symptoms have long been recognized with antidepressants but other features of addiction such as tolerance and compulsive use are exceptionally rare. Common clinical problems are patients taking subtherapeutic dosages and prematurely stopping antidepressants.

Haddad is correct that subtherapeutic doses and premature discontinuation are common, but that does not mean that there are not significant numbers of people

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increasing their doses because of tolerance and/or taking antidepressants for longer periods or in larger amounts than intended.

The bias in Weller et al.'s report is amplified in claims such as Ebmeier et al.'s (2006) that 'There is *no* evidence that antidepressants cause actual addiction' [italics added] (p. 161). Ebmeier was a member of the expert working group that produced the report, so he should have had an in-depth understanding of the evidence that informed it.

In Australia, Dean (2002) similarly rejected claims that antidepressants were 'addictive'. She acknowledged the existence of a small number of cases of antidepressant dependence. However, like Weller et al. (2004), she argued that the problem resided largely with the individual, not with the drug:

> Most cases were male (14/21), and had a history of prior substance abuse (14/21) or personality disorders (10/21). These are considered risk factors for substance dependence, reinforcing the importance of individual characteristics, not just the drug, in the aetiology of dependence. (p. 318)

Dean's assessment appears to have been coloured by the research she was conducting at the time into pharmacological treatment of heroin dependence (Dean et al. 2006). Opioid dependent people are on average more deviant than people dependent on prescribed psychotropics, if only because heroin use and supply is illegal and because its cost increases the likelihood of committing crime to obtain it. Some people dependent on prescribed psychotropics also commit crime to obtain those drugs, but this is much less common than with heroin.

Dean argued that 'the essence of dependence is compulsive drug seeking behaviour despite negative consequences' (p. 317). Although many people in the alcohol and other drug field would agree with that, because they work with people who do engage in compulsive drug-seeking with negative consequences, it is not supported by the DSM-IV criteria for substance dependence (APA 1994), only three out of seven of which relate to drug-seeking or negative consequences.

Furthermore, there is evidence of antidepressant drug-seeking (and use for the purpose of intoxication). An Australian study of antidepressant use by injecting drug users reported:

> The median number of antidepressants pills taken on the last-use occasion was two (range 0.5± 19), with 17% reporting that they exceeded the prescribed dose.

> These subjects had been prescribed antidepressants. A further 27% had used antidepressants that were not prescribed for them on their last-use occasion….
>
> Depression was the most common reason given for commencement of antidepressant use, but was nominated by less than half of the subjects (42%). Twelve per cent reported that they first used the drugs to become intoxicated…. 20% of males reported initiating use to become intoxicated…. Reasons for continued use reflected those given for initial use, with depression being the most common reason (46%), and 12% reporting intoxication as their main reason for continued use. (Darke & Ross 2000, p. 410)

Over half (57%) of those who had used antidepressants reported experiencing negative effects (p. 410). However, it is not clear how many of them would have continued using antidepressants despite these negative consequences.

Dean argued that so-called evidence of dependence was really only withdrawal symptoms, which did not qualify as dependence based on DSM-IV (APA 1994) criteria. It is of course correct that withdrawal alone is not sufficient for a diagnosis of dependence. However, a DSM-IV diagnosis of dependence can be made on the basis of any three of these four criteria for which there is significant evidence in relation to antidepressants: withdrawal, tolerance, taking an antidepressant 'in larger amounts or over a longer period than was intended', and 'persistent desire or unsuccessful efforts to cut down or control' its use (APA 1994, p. 181).

Like Haddad (1999), Dean also argued that the fact that: 'lower, or even subtherapeutic, doses still dominate prescribing patterns' (p. 317) indicated that dependence was not common. However, Lader and colleagues had demonstrated years earlier that people could develop physical dependence with normal doses of benzodiazepines (Lader 2005, p. 1059): 'We had to say essentially the textbooks are wrong: one can get a physical dependence at normal dosage'. Escalation of dose is not an essential criterion for dependence.

Basically antidepressant *withdrawal syndrome* (or withdrawal symptoms) has been acknowledged by many antidepressant advocates, but antidepressant *dependence* has

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been strenuously rejected, largely by dismissing other diagnostic criteria of dependence such as tolerance and drug-seeking.

A key move to quell the debate has been the strategic development and popularisation of the euphemistic term 'antidepressant discontinuation syndrome', which basically refers to a range of withdrawal symptoms. Conceding the existence of such symptoms, but putting a more palatable frame around them in order to control their interpretation, has been a very successful strategy. According to Glenmullen (2001, p. 76): 'The sanitized term "antidepressant discontinuation syndrome" is the kind of well-funded obfuscation doctors and patients frequently face when trying to get honest, reliable information on these powerful drugs'.

Eli Lilly, the manufacturer of Prozac® (fluoxetine), masterminded the creation of the syndrome, sponsoring a closed symposium of experts, 'SSRI Discontinuation Events' in Phoenix, Arizona, in 1996. This resulted in a strategic *Journal of Clinical Psychiatry* (1997) supplement titled 'Antidepressant Discontinuation Syndrome: Update on Serotonin Reuptake Inhibitors'. A key article in that supplement proposed a 'hypothetical definition of an SRI discontinuation syndrome to facilitate research into a phenomenon that differs dramatically among the SRIs' (Schatzberg et al. 1997, p. 5). The syndrome it defined was rapidly accepted as real, not hypothetical, largely because of the publication of the supplement and subsequent journal articles funded by Lilly. The following year, Rosenbaum et al. (1998) published a clinical trial for which a Discontinuation-Emergent Signs and Symptoms (DESS) checklist had been developed. The DESS has subsequently been used in other studies (Baldwin et al. 2007), and has given the syndrome further legitimacy. Rosenbaum was a discussant at the symposium, and three of his co-authors were Lilly employees.

According to Ebmeier et al. (2006, pp. 160-161), withdrawal symptoms do not have *any* association with addiction (despite the fact that withdrawal is a criterion for dependence):

> There is no doubt that withdrawal symptoms occur after stopping SRIs and other antidepressants. The neologism discontinuation symptoms essentially means the same as withdrawal symptoms, without having any association with addiction.

In the *Journal of Clinical Psychiatry* supplement, Schatzberg et al. (1997, p. 6) argued that antidepressant discontinuation syndrome was very different from withdrawal

from 'sedative hypnotics such as alcohol[8] and barbiturates' because the symptoms of the latter were different and significantly more severe, and because tolerance, drug-seeking, and continued drug use despite aversive consequences occurred with the latter but not with the former. Like Weller et al. (2004), they ignored published reports of tolerance. Schatzberg et al. lamented: 'Unfortunately, the public often perceives wrongly that antidepressants – like alcohol and barbiturates – are addicting'(p. 6).

Schatzberg et al. (1997) is one of a number of papers criticised by Nielsen et al. (2012, p. 2) for euphemistic terminology influenced by industry ties:

> Strong financial ties between the DSM-IV panel members and the pharmaceutical industry have been revealed, and there are clear conflicts of interests involved in the choice of terms. For example, several psychiatrists deliberately use the term discontinuation reactions as a euphemism instead of withdrawal reactions. They argue that it is important not to foster inadvertently the lay belief that antidepressants are addictive, as this might contribute to undertreatment of depression, and they also claim that discontinuation reactions do not indicate dependence

Nielsen et al. reviewed the evidence about SSRI and benzodiazepine withdrawal and concluded somewhat mildly that the distinction made by Schatzberg and others does not seem rational:

> Withdrawal reactions to selective serotonin reuptake inhibitors (SSRIs) appear to be similar to those for benzodiazepines; referring to these reactions as part of a dependence syndrome in the case of benzodiazepines but not SSRIs does not seem rational. (p. 9)

Notably, discontinuation symptoms seem to be less prominent with Lilly's Prozac than with many other SSRIs. Consequently the construction of antidepressant discontinuation syndrome served a dual purpose for Lilly, both addressing concerns about the possibility of dependence and showing Prozac in a favourable light relative to its competitors, particularly paroxetine:

> the vast majority of the reports of discontinuation symptoms with the selective serotonin reuptake inhibitors involve paroxetine and the fewest are for fluoxetine (Schatzberg et al. 1997, p. 4).

[8] Alcohol is technically a sedative hypnotic but is not usually thought of as such.

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Another issue related to discontinuation symptoms is that they can be confused with relapse symptoms. Surprisingly, this was acknowledged in the *Journal of Clinical Psychiatry* supplement: 'Because the symptoms of antidepressant discontinuation include changes in mood, affect, appetite, and sleep, they are sometimes mistaken for signs of a relapse into depression' (Lejoyeux & Adès 1997, p. 11). High-profile antidepressant user and advocate Brooke Shields, discussing her experience of postnatal depression, provided an unwitting example of this when she reported:

> I prematurely stopped taking [Paxil] and had a relapse that almost led me to drive my car into a wall with Rowan in the backseat. But the drugs, along with weekly therapy sessions, are what saved me – and my family. (Shields 2005)

Like many antidepressant users, Shields was unaware that the symptoms of withdrawal can mimic a depression relapse. Such experiences and reports increase the perceived effectiveness of antidepressants, and support claims that long-term use is necessary.

As mentioned at the beginning of this section, dependence potential has been a key debate about antidepressants, particularly in the 1990s. According to Healy (2004, p. 270):

> a specter stalks the SSRIs. Most people feel that suicide on treatment is not something that could happen to them. But almost all of us believe that we could become dependent on drug treatments. This makes us skeptical of claims by the DART and Defeat Depression campaigns that antidepressants are not addictive.

Healy also commented: 'dependence on SSRIs is more likely to bring this group of drugs into public disrepute than the issue of suicide…. we can readily envisage getting hooked on a drug' (p. 2). That was probably an accurate assessment in 2004. These days, however, the spectre of suicide is competing strongly with the spectre of dependence, and suicide has certainly overshadowed dependence in the public debate. Notably Tint et al.'s (2008) acknowledgement that antidepressant discontinuation can be associated with increased suicidality links the two problems:

> Four patients, all on paroxetine, developed emergent suicidal ideation after taper…. Anti-depressant discontinuation in depressed patients can be associated with worsening depression and increased suicidality.

The potential for antidepressants to increase the risk of suicide, and the significance of withdrawal in relation to suicidality, is discussed in the next section.

The addictiveness or dependence potential of antidepressants has been a hotly disputed debate, particularly in the 1990s. The stakes have been high, because addictiveness is a very emotive issue. Antidepressant advocates, of course, have argued against claims that they can be addictive, often emphatically contrasting them with benzodiazepines and nonmedical psychotropic drugs such as heroin and other illegal opioids.

Definitions of addiction and dependence, including diagnostic criteria, figure prominently in the debate. Tolerance and withdrawal have also been key concepts. A major distinction has been made between withdrawal, which is generally accepted as a reality, and dependence, the term used in the APA's (1994) DSM-IV. Withdrawal is sometimes referred to euphemistically as 'antidepressant discontinuation syndrome', a term strategically promoted by Eli Lilly.

The dependence potential of antidepressants has been a crucial debate topic that has mobilised both advocates and critics of the orthodoxy. However, it has now been overshadowed by the debate about their potential to trigger suicide, which is discussed in the next section.

6.8 ANTIDEPRESSANTS REDUCE SUICIDE

> antidepressants do not cause suicide, but are protective against suicide, as would be expected from a medication that effectively treats depression, which is itself a major cause of suicide (Rothschild 2012)

Currently the most significant controversy about antidepressants is about their potential to decrease or increase the risk of suicide. It has long been assumed that they decrease suicide, and many people continue to believe this. In the last decade or so, however, not only has the protective effect of antidepressants been challenged, but also a strong case has developed that antidepressants may *increase* the risk of suicide (particularly by triggering impulsive suicidal acts). This debate about the potential of antidepressants to increase the risk suicide has overshadowed the dominant 1990s debate about their addiction/dependence potential.

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6.8.1 Antidepressants reduce suicide

It has long been assumed, and is often simply taken for granted, that antidepressants reduce the risk of suicide. This is a prominent belief in Australia (and elsewhere), supported by claims that suicide is caused by depression, for which antidepressants are necessary. Antidepressants are also believed to directly reduce suicide. According to Wright (2003), there is a 'common belief that antidepressants treat both depression and suicidality'. Such beliefs are common among clinicians, who often regard antidepressants as the most appropriate intervention for patients who are suicidal.

In addition, there have been some prominent claims that antidepressants reduce suicide rates at the *population* level. In Australia, Professor Ian Hickie has been a strong proponent of this view. According to Hickie (2007, p. 329), 'Increased treatment of depression reduces suicides'. Although he used the word 'treatment', the titles of the two references he cited for this point are 'Association between antidepressant prescribing and suicide in Australia, 1991-2000: trend analysis' (Hall et al. 2003; Hickie was the fifth author) and 'Anti-depressants, suicide, and drug regulation' (Ludwig & Marcotte 2005). This makes it very clear that he specifically meant that antidepressants reduce suicide.

Hall et al. (2003) concluded that increased SSRI prescribing between 1991 and 2000 in Australia was significantly associated with reduced suicide rates, and that:

> The increase in antidepressant prescribing may be a proxy marker for improved overall management of depression. If so, increased prescribing of selective serotonin reuptake inhibitors in general practice may have produced a quantifiable benefit in population mental health. (p. 1008)

Dr Michael Baigent, *beyondblue* Clinical Advisor, clearly referring in part to Hall et al. (2003), echoed Hickie's claim, albeit in a more qualified form:

> there are large population trials that have shown a correlation between increased rates of prescribing with reduced rates of suicide. Now, you can't actually say necessarily that the antidepressants have caused that and it might be that the prescribing of antidepressants is a marker of treatment, including all the different forms and modalities of treatment for depression and not just the antidepressant medications themselves, but it does show that they are helpful for some people. (Millar 2008)

Baigent's reference to different forms of treatment glosses over the fact that antidepressants are the mainstay of treatment modality (AIHW 2004, p. 211; Wilson et al. 2003, p. 685).

Beautrais (2006) not only claimed a causal relationship between antidepressant use and reduced suicide rate, but also added the common claim that SSRIs are safer than older antidepressants:

> there is growing evidence from population based studies which suggests the recent widespread use of the newer, clinically safer antidepressants (selective serotonin re-uptake inhibitors: SSRIs) may have contributed to a decrease in suicide rates in several countries

Furthermore, it has commonly been claimed that antidepressants are *necessary* in clinical practice to prevent suicide. One Australian example of such claims is:

> Michael Dudley, chairman of Suicide Prevention Australia and a senior lecturer in psychiatry at the University of NSW, says antidepressants are vital for people suffering moderate and severe depression, and steering clear of them is "a grave mistake". (Benson 2008)

Benson's article focused on the debate about whether antidepressants can trigger suicide, so it is clear that by 'grave', Dudley was alluding to the risk of suicide.

However the evidence that antidepressants of any type reduce suicide at either a clinical level or a population level is surprisingly weak. At a clinical level, use of antidepressants is associated with heightened risk of suicide. However, the evidence is strongly affected by confounding by indication and severity (Sondergard et al. 2007): antidepressants are commonly used to treat depression, and are more likely to be used when depression is severe, so it is difficult to determine how much of the increased risk is attributable to antidepressants as opposed to the underlying depression (confounding by indication) and the severity of depression (confounding by severity).

Most claims are based on ecological studies, in which aggregate suicide rates and aggregate rates of antidepressant use are compared. Such studies are very weak methodologically, and cannot demonstrate causal relationships. Nevertheless, they are often cited uncritically as providing evidence of causation.

Furthermore, the conclusions of some of the ecological studies that are cited have been strongly criticised, including Hall et al.'s (2003) analysis of the relationship between antidepressant prescribing and suicide in Australia. According to De Leo & Cerin (2003):

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> The conclusions presented in Hall et al.'s (2003) paper on the association between antidepressants prescribing and suicide are questionable. The authors claim that their findings support the contention that there is a clear association and, perhaps, causal relationship between antidepressant prescribing and suicide, especially in older males and females. Unfortunately, the authors fail to duly acknowledge that their data also indicate a lack of impact of antidepressants on suicide in younger individuals, which, indeed, might have been used to corroborate an opposite standpoint to that presented in the paper. For instance, tables 1 and 2 show that, despite an increase in antidepressant use, both male and female subjects aged 15 to 44 reported an increase in suicide rates.

Also critical was UK psychiatrist Joanna Moncrieff (2003a), according to whom 'Hall et al's data on suicide rates and antidepressant prescribing contradict their own conclusions' (p. 288). Moncrieff's was one of four letters to the editor published in response to Hall et al. All were critical.

The strongest champion of the claim that antidepressants reduce suicide has been Swedish Professor Göran Isacsson, whose landmark 1994 PhD thesis, 'Depression, antidepressants and suicide: A study of the role of antidepressants in the prevention of suicide' was published in soft-cover format and has been cited many times. More recently, Isacsson was lead author of a paper with a title categorically declaring that 'Antidepressant medication prevents suicide in depression' (Isacsson et al. 2010). As well as being the leading advocate of the orthodox antidepressant/suicide position, he has been very influential in the debate.

In 2010 I engaged in a published debate (Isacsson et al. 2010) with Isacsson and another advocate of the position, Dr Charles Rich, who jointly argued in favour of the motion that 'The increased use of antidepressants has contributed to the worldwide reduction in suicide rate'. Professor Jon Jureidini and I opposed the motion. The debate provides a useful synthesis of key evidence commonly used to argue in favour of antidepressants' effectiveness as a suicide prevention strategy, with Jureidini's and my counter-arguments. Consequently I summarise it here, drawing out some key issues.

Isacsson & Rich began by declaring that 'Suicide rarely occurs in the absence of depression' (p. 429), a very common belief, as discussed in chapter 5. Jureidini and I pointed out that the main evidence supporting the belief came from psychological autopsy studies, which are methodologically problematic. Psychological autopsies rely heavily on evidence from relatives and close friends, who often seek relatively

socially acceptable explanations, and may be unaware of or unwilling to disclose shameful problems. We pointed out, furthermore, that having a psychiatric history biases classification towards suicide. We also cited one of Isacsson's own studies, which found only a 36% depression rate in a series of suicide cases (Isacsson et al. 1994).

We did, however, agree with Isacsson & Rich that 'the hypothesis that suicide might be prevented by the treatment of depression is not far-fetched' (p. 429), but we did not agree with their stronger claim that 'treatment with antidepressants prevents suicide' (p. 429). That claim was based partly on ecological studies. Isacsson & Rich did not make the common mistake of presenting ecological findings as causal evidence, but incorrectly claimed that only one ecological study had 'failed to demonstrate a decrease in suicide parallel to an increase in the use of antidepressants' (p. 429) – Jureidini and I cited several such studies (p. 430). We also pointed out the problems in Isacsson & Rich's interpretation of several studies, including ignoring explicit rejections of causal interpretation by Barbui et al. (1999) and Guiana et al. (2005).

Furthermore, in response to our criticism of the use of crude correlations in ecological studies, they revealed a surprising lack of understanding of multivariate analyses, by arguing against adjusting for important covariates such as alcohol use and unemployment that might confound the relationship between antidepressant use and suicide, suggesting that they might 'obscure true "crude" rates' (p. 431). A response to the debate by Riordan & Stark (2010) seconded the importance of controlling for possible confounders, and identified another one, namely the size of the family of origin. They suggested that having elder siblings might be linked with increased risk of suicide. They cited data from two data linkage studies to support this. Data linkage studies link two or more databases so that data on individuals in each database can be linked to data on those same individuals in other databases. This provides much stronger evidence than ecological studies (Raven 2010b).

Isacsson & Rich also cited several data-linkage studies (which they referred to as 'individual-based studies') (p. 429) that were able to analyse individual exposure to antidepressants. However, one of those studies (Angst et al. 2005) was of seriously ill hospitalised patients, 61% of whom had psychosis, and the authors acknowledged that

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it was inappropriate to generalise from such patients to people with depression more generally. Another study (Tiihonen et al. 2006) focused on patients hospitalised because of suicide attempts; furthermore antidepressant use both prior to hospitalisation and during follow-up was associated with *higher* risk of suicide, suicide attempts, and mortality.

Isacsson & Rich also cited post-mortem toxicological studies, another mainstay of their position. We pointed out that such studies, including Isacsson et al. (2009), ignore the possibility of suicide being triggered by antidepressant *withdrawal*, which has been linked to suicidality (Tint et al. 2008). Withdrawal would not be detected in toxicological studies, which are premised on the belief that if antidepressants were to trigger suicide, they would have to be present in the blood-stream at the time of suicide. We also pointed out Isacsson et al.'s (2009) failure to take account of the significance of decreased autopsy rates in some countries (Reseland et al. 2008). Kapusta et al. (2011) have discussed this issue in much more detail, citing our debate, reporting that a decreased autopsy rates 'aligned' with decreases in apparent suicide rates, and concluding that:

> Autopsy rates may spatially and temporally affect the validity of suicide mortality statistics. Caution should be exercised in comparing international suicide rates and evaluating interventions that target suicide rate reduction. (p. 1050)

Isacsson & Rich, however, dismissed decreased autopsy rates as an 'irrelevant' variable (p. 431). Furthermore, they seemed to misunderstand our point that decreased autopsy rates would be likely to reduce official suicide rates (because clinical autopsies sometimes detect previously unsuspected suicides).

In summary, although Isacsson and Rich's defence of the motion was stronger than many such claims, because it did not just draw on ecological studies, it relied on selective citation of studies and findings within studies. Furthermore, Isacsson & Rich dismissed the relevance of a number of important variables that could confound relationships between antidepressant prescribing and suicide rates.

6.8.2 Antidepressants do not increase the risk of suicide

Despite the certainty of Isacsson and other advocates that antidepressants prevent suicide, the possibility that they might actually increase the risk has been taken seriously and hotly debated in recent years. A major focus has been the evidence from

clinical trials of SSRIs (because of their dominance of the market, as well as some specific evidence of suicide risk) and to a lesser extent other newer antidepressants. Evidence from observational studies has also been used in the debate. Much of the evidence relates to suicidality rather than completed suicide, because of the rarity of suicide, but suicidality is clearly a significant risk factor for suicide.

Apart from Isacsson, British psychiatrist Professor David Healy has written probably more about the relationship between antidepressants and suicide than anyone else. Unlike Isacsson, however, he has argued that antidepressants can trigger suicide.

Because of this, Healy famously and controversially had a job offer at the University of Toronto rescinded when he spoke about this possibility:

> In December 2000, the University of Toronto breached a contract it held with me, initiating a sequence of events that has led to a public letter to the University from a large number of senior figures in the psychopharmacology community, protesting against the infringement of academic freedom involved, and a first-ever legal action seeking redress for violation of academic freedom. This case has been intertwined from the start with a longer running debate about the possibility that the SSRI group of antidepressants may have the potential to trigger suicidality or other serious effects in a subgroup of takers. (Healy 2002, p. 250)

More recently, commenting on Healy's claims, Fava (2010, p. 204) provocatively asserted that:

> the denial of the link between selective serotonin reuptake inhibitors and suicidal risk before the publication of a critical review [Healy 2003] in our journal was an example of the 'spectacular achievements of propaganda that took place in psychiatry.

According to Healy (2003, p. 72), the debate about the suicide risk of SSRIs began in 1990 when Teicher et al. reported six cases of intense suicidal preoccupation in patients undergoing fluoxetine treatment. These patients had been 'free of recent serious suicidal ideation' (Teicher et al. 1990, p. 207). In several cases, the suicidality lasted weeks after discontinuation of fluoxetine.

Since then, according to Healy & Aldred (2005), there has been considerable evidence of increased suicidality in published SSRI trials:

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> the combined literature points to an excess of suicidal acts on SSRIs compared to placebo from as early as 1988, even though many early trials failed to report on suicidal acts. (p. 164)

Healy & Aldred further noted many biases acting to reduce the apparent risk:

> First, the trials were not designed to detect suicidality. Second, agitation and anxiety occurring in these trials were commonly treated with benzodiazepines, or with other agents, or by dropout. Third, dropouts were often lost to follow-up, so that the true rate of suicidal acts remains unknown. Fourth, there is evidence of under-reporting of serious adverse events; based on known suicidal acts from the Food and Drug Administration (FDA) reviews, a best estimate is that no more than one in four suicidal acts in antidepressant trials are reported in the scientific literature. Fifth, a large proportion of the trials had dropout rates in excess of 30%, and sample sizes no greater than 50 patients. Sixth, many trials with particularly adverse outcomes, including any specifically designed to investigate the occurrence of suicidality remain unpublished or misleadingly published (p. 164)

Furthermore, some cases of suicides and suicidal ideation during pre-randomisation run-in periods and post-antidepressant follow-up have been inappropriately attributed to placebo (Healy & Aldred 2005, pp. 164-165, figures 1 and 2).

Despite such biases, the evidence of a link between SSRIs and suicidality eventually became impossible to ignore. One particularly significant development was an investigation commenced by the FDA in 2003. A meta-analysis performed by FDA staff was subsequently published in the *Archives of General Psychiatry* (Hammad et al. 2006).

As a result of this investigation, official denial of the link between SSRIs and suicidality dramatically crumpled in 2004 when the FDA mandated a 'black box' warning on antidepressant package inserts (Katz 2004):

> Suicidality in Children and Adolescents
>
> Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Drug Name] is not approved for use in pediatric patients except for patients with [Any approved pediatric claims here]. (See Warnings and Precautions: Pediatric Use)

> Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

This warning generated vociferous criticism at the time and subsequently, both in the media and in the medical literature. It was also controversial among members of the FDA panel that made the recommendation. According to Harris (2004):

> Dr. Matthew V. Rudorfer, a panel member from the National Institute of Mental Health, said that 15 percent of teenagers with untreated depression commit suicide - a much greater risk than that presented by the drugs themselves, he said.

When the US Centers for Disease Control and Prevention (2007) reported that the suicide rate among from young people aged 10-24 increased significantly from 2003 to 2004, a number of prominent antidepressant advocates attributed this increase to the black box warnings. One such critic was the CEO of Mental Health America (Shern 2007).

Further warnings were issued by the FDA and government authorities in other countries including the Netherlands (Gibbons et al. 2007). In Australia, the Adverse Drug Reactions Advisory Committee (ADRAC) issued a warning including:

> Assessment of the published and unpublished data available for SSRI use in children and adolescents indicates that there is evidence of an increased risk of suicidality, including suicidal ideation, suicide attempts and self-harm events, associated with each of the SSRIs. (Topliss 2004)

A number of critics claimed that the warnings resulted in increased suicide by young people. Most notably, Professor Robert Gibbons, from the University of Illinois at Chicago strongly and emotively implied that the black box warning was having dire consequences in terms of increased suicide rates. For example, he was lead author of an article in *Psychiatric Times* that argued:

> Although unintended, the FDA's black-box warning has led to a decrease in the pharmacological treatment of pediatric depression and a decrease in the

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> diagnosis of pediatric depression. At the same time, we have seen the largest increase in child, adolescent, and teen suicide since the CDC began recording these data in 1979. In the event that these results are further confirmed by 2005 suicide rate data, it becomes clear that the black-box warning should be reconsidered and replaced by an effort to improve diagnosis of major depression, improved access to treatment, and more careful monitoring of treatment with antidepressants where indicated. Gibbons (2007b)
>
> A black-box warning has only been rescinded once in history, for the drug omeprazole in 2003, but given the mortality of youth suicide and the need to reverse these alarming trends and loss of life, such a step may prove necessary for antidepressant labeling in children and young adults.

In another article (Gibbons et al. 2007a), he and his co-authors reported that:

> SSRI prescriptions for children and adolescents decreased after U.S. and European regulatory agencies issued warnings about a possible suicide risk with antidepressant use in pediatric patients, and these decreases were associated with increases in suicide rates in children and adolescents (p. 1356)

The appropriate use of the word 'associated' in that statement was eclipsed by the misleading use of the word 'effects' in the title of the article: 'Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents'. Furthermore, according to Jureidini (2007), Gibbons et al. misrepresented the data, because there was no significant drop in SSRI prescribing. The study was also criticised by others in the academic literature and the media (Berenson & Carey 2007).

Prominent among Australian critics of the warnings has been Ian Hickie. In an emotive opinion piece in *The Australian* newspaper, he compared the public health benefits of antidepressants, and their critics, to those of immunisation:

> before mass immunisation, the communities that had witnessed the trauma and loss associated with epidemics of polio or whooping cough had little time for the anti-immunisation lobby. Only when remarkable progress had been achieved did the extremely rare accounts of immunisation causing harm to individual children begin to attract disproportionate media attention. When immunisation rates began to fall sharply in Australia, and new cases of preventable childhood infection were reported, the national government moved quickly to correct the situation.
>
> A similar situation has now been reported with regards to the treatment of young people for depression in the US and parts of Europe. When alarmist media reporting and increased government warnings resulted in a fall in the treatment of depression from 2004 onwards, suicide rates – which had been falling for more than a decade among young people – began to rise again. In

> Australia, we do not yet know whether such distorted reporting has had any similar adverse impact on suicide rates. (Hickie 2008)

Hickie's phrase 'adverse impact' claimed a causal relationship between decreased antidepressant use and increased suicide rates. He cleverly qualified this claim by including the phrase 'in the US and parts of Europe'. He was no doubt aware of a paper published a few weeks earlier, which concluded that that was not the case in *England*:

> The noticeable reduction in prescribing of antidepressants since regulatory action in 2003 to restrict the use of SSRIs in under 18s does not seem to have been associated with changes in suicidal behaviour in young people. Specifically, these data for England do not indicate that reductions in antidepressant use have led to an increase in suicidal behaviour. (Wheeler et al. 2008, p. 542).

An editorial accompanying Wheeler et al.'s paper discussed the limitations of ecological data in elucidating causal relationships, and concluded that 'it would be surprising if antidepressants had any effect—positive or negative—on the risk of suicide in the general population', because 'Sustained use of antidepressants is probably too rare to have much overall effect on risk of suicide in people living with depression' (Simon 2008, p. 515).

Dr Michael Dudley, Chairperson of Suicide Prevention Australia, similarly argued that:

> The black box warnings in the US frightened off a lot of people, which *pushed up their suicide rates*. In Australia, there has been a lot of evidence to suggest decreased suicide rates are associated with increased prescription rates. [italics added] (Benson 2008)

Although the second sentence, which clearly refers to Hall et al.'s (2003) study, appropriately refers to an association, the first sentence makes it clear that Dudley was claiming a causal relationship.

In addition to explicit criticism of official warnings, there have been many attempts to sideline and subvert them. In Australia, as noted by Mansfield et al. (2006), the ADRAC warning (Topliss 2004) was subsequently undermined by a clinical guideline published by the Royal Australian and New Zealand College of Psychiatrists, the

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Royal Australasian College of Physicians and the Royal Australian College of General Practitioners. It asserted:

> Clinicians recognise that antidepressants can be very safe and effective when used as part of the comprehensive management of moderate to severe depression in the young and in many instances they can be life-saving

6.8.3 Conclusion: Antidepressants and suicide

In recent years, the relationship between antidepressants and suicide has become highly controversial. Not only has the taken-for granted assumption that antidepressants *protect* against suicide been strongly challenged, but also the possibility that they may *increase* the risk has been officially validated, most notably by the US FDA, to the chagrin of many antidepressant advocates.

Evidence of increased risk has emerged despite strong biases in clinical trials and suppression of unfavourable results. This has resulted in official warnings in a number of countries. However, these warnings have been criticised by some key advocates of the orthodoxy, and have served to entrench claims of an inverse causal relationship between antidepressants and suicide, both in the media and in the academic literature.

6.9 CRITICS OF ANTIDEPRESSANTS ARE WRONG

As discussed in chapter 4, critics of the orthodox story about depression attract sharp censure. Similarly, people who criticise antidepressants (many but not all of whom also criticise depression orthodoxy) are often fiercely censured, using ad hominem arguments.

They are commonly dismissed as ignorant, callous, and dangerous. They are also accused of having a negative and/or hidden agenda, such as pharmacological Calvinism, doctor or pharmaceutical industry 'bashing', and, more extremely, they are sometimes accused of being Scientologists. Sometimes they are accused of uncritically favouring alternative treatments. Numerous examples of all of these claims could be presented and analysed in detail. However, most attention is given here to claims of dangerousness, bias towards psychological therapies, and claims of links to Scientology.

It is sometimes claimed that criticism of antidepressants is driven by the media. In Australia, leading psychiatrist Ian Hickie publicly criticised health journalist Ray

Moynihan's (1998) book *Too much medicine?* as a source of negative attitudes about antidepressants:

> Media stereotypes disparage the provision of effective treatments[9] and disease management programs. (Hickie 2000, p. 126)

Similarly, in the UK, according to Nutt and Sharpe (2008, p. 3):

> The recent review of the selective serotonin reuptake inhibitors (SSRIs) by the Committee on Safety of Medicines (CSM) and the Food and Drug Administration was *occasioned by media concerns* about the safety of this class of antidepressant. [italics added]

Attributing such attitudes and events to the media is a powerful strategy for discrediting and trivialising valid criticism, and it ignores the fact that many professionals have expressed concerns in the academic literature and the policy arena. Of course the media do play a significant role in (and frequently benefit from) debates about antidepressants, but it is a distortion to emphasise their role to the exclusion of others.

6.9.1 Critics of antidepressants are ignorant

It is common for critics of antidepressants to be accused of being ignorant about the nature and severity of depression, the risk of suicide, the need for treatment, and the benefits and risks of antidepressants. Solomon (2001, p. 81) expressed this particularly forcefully, describing criticisms of antidepressants as 'ludicrous' and 'foolish':

> the ludicrous assertions made in such stridently foolish books as *Prozac Backlash* [Glenmullen 2000] cannot be taken for more than pandering to the cheapest fears of an apprehensive audience

As mentioned in chapter 4, an Australian journalist and self-reported depression sufferer published a 'List Of Ignorant Things People Say About Depression Which Shit Me' (Pryor 2008). One 'ignorant' statement is discussed below as an example of pharmacological Calvinism.

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[9] As discussed in chapter 9, Hickie frequently uses the ambiguous term 'treatments' when he promotes or defends antidepressants, which were the specific focus of Moynihan's criticism.

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6.9.2 Critics of antidepressants are callous, trivialising people's suffering

Critics of antidepressants are often accused of being callous towards antidepressant users. Warner (2008) waxed sarcastic about critics of antidepressants and other psychiatric drugs:

> Most of the critics decrying the over-medicalization of the American mind rest their arguments upon the bedrock assumption that people who have nothing wrong with them – happy-go-lucky types who essentially make a wrong turn on their way to Starbucks or soccer and end up in the consulting room – are being medicated for largely fictitious concerns.

She cleverly twisted criticism of psychiatric drugs into victim-blaming and trivialisation of suffering:

> The psychiatrists I've interviewed over the course of the past four years say that they have yet to be swamped by frivolous patients showing up in their offices looking for pills to help them tweak troublesome little aspects of their personalities.

This is a straw man argument. Few critics of the medicalisation of distress argue that the problem is caused by *frivolous patients*. Instead, they generally argue that doctors prescribe antidepressants too readily, and that drug companies spend millions of dollars trying to persuade people that they have an illness called depression.

Despite criticising inappropriate use of antidepressants, Elliott (2002) acknowledged that many antidepressant users are genuinely suffering: 'none of that means that psychological suffering isn't real. I surely don't want to say anything to demean the experience of psychiatric patients'.

6.9.3 Critics of antidepressants are dangerous

A particularly strong and emotive claim about critics is that they endanger the lives of depressed people. This is based on claims that antidepressants are necessary to reduce suicide risk (discussed in section 7.7). It is a powerful and emotive argument that appeals to the fear of suicide, particularly suicide of young people. There are two overlapping threads to claims of dangerousness:

1. Critics' *general* discouragement of depressed people from using antidepressants (for multiple reasons, including lack of effectiveness, a range of potential adverse reactions, and concerns about medicalisation and reliance on pharmacological solutions) is – it is claimed – dangerous.

2. More specifically, critics' assertions that antidepressants can increase the risk of suicide are claimed to be very dangerous.

One important example of the claim that critics are dangerous is by prominent UK psychopharmacologist Professor David Nutt:

> It seems to me that by minimizing the importance of the underlying disorder (so that, for social anxiety disorder, read shyness; for depression, read unhappiness), the risk/benefit ratio of drug treatments can be shifted against therapy. Hopefully, all of you will share my concerns about this and will work with the British Association for Psychopharmacology to stop this *dangerous* trend. Please try to educate the media, the scientific community and the general public about the suffering these *persistent* and *pervasive* disorders produce and the *safety* and *efficacy* of the drugs used to treat them, and protest appropriately if you encounter further examples. [italics added] (Nutt 2003, p. 251)

Medawar (1997, pp. 27-28) reported being criticised for the 'dangerous' suggestion that antidepressants might have dependence potential:

> A former editor of the *British Journal of Psychiatry* (published by the RCP) went further. Provoked by the suggestion that it seemed folly not to have tested drugs like Prozac for their dependence potential (Medawar, 1994), he argued that it was both mistaken and dangerous to have suggested that the question of dependence arose at all: "It would be regrettable if serious depressive illness, often involving the risk of suicide, remained untreated through people being misinformed about the well-established properties of antidepressants ...".

Similarly, according to Shah & Mountain (2007, p. 375):

> advocating exclusive psychological approaches amounts to 'psychological reductionism' and could harm patients by denying them other effective treatments.

Claims of dangerousness are also voiced in less academic forums. One reviewer of Bremner's (2008) book *Before you take that pill: Why the drug industry may be bad for your health* wrote:

> I really think that this is a VERY DANGEROUS book. Did you know that there is a lot of ignorance regarding diseases and its treatments not only in third world countries but in the USA as well?
>
> If someone for example is taking an SSRI for a mental disorder and reads this book, he/she will think that diet and exercise will cure him/her, and could get off his/her meidcations [sic] without consulting their physician because this

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> book was supposedly written by an MD, and not by an anti-pharmaceutical company guy (like most naturopaths are).
>
> You are really jeopardizing a lot of lifes [sic] by writing this dangerous book. (Aragon 2008)

Those who have argued against antidepressants' dependence potential have frequently argued that their opponents' claims are dangerous. For example, Swinney (2004) reported that a doctor who argued that paroxetine was not addictive was critical of her for reporting on the issue:

> Dunn seemed quite annoyed this article was being written. "What about the benefits of the medication and the harm of someone stopping it because they have read an article stating it's an addictive drug," he queries.

In Australia, Dean (2002) dramatically implied that lives were at stake:

> Inappropriate labelling of withdrawal syndromes as addiction can compromise therapeutic outcomes; given the increasing morbidity and mortality arising from depressive and anxiety disorders, this is the last thing we need. (p. 318)

One person who has attracted particularly virulent criticism is psychiatrist Joseph Glenmullen, whose book *Prozac backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil, and other antidepressants with safe, effective alternatives* (2000) emphasised the risks of antidepressants, including their potential to trigger suicidality. Not surprisingly, Eli Lilly condemned the book:

> The manufacturer of Prozac is condemning Dr. Joseph Glenmullen's new book *Prozac Backlash*, calling it a fear-mongering publication and dangerous. (Associated Press 2000).

The National Mental Health Association (now Mental Health America), which has strong financial links with Eli Lilly (Essential Action 2008), also weighed in:

> The book worries officials at the National Mental Health Association, said Laura Young, vice president of community services.
>
> "My fear with books like this is it scares people away from getting the really important treatment they need ... and they may mess around with herbal alternatives." (Associated Press 2000)

Perhaps the most notable attack on Glenmullen came from another US psychiatrist (Morrison 2000):

> I'm in no position to know what Glenmullen's intentions are. He may well be doing what he thinks is right. So was Timothy McVeigh [the 'Oklahoma City Bomber'].

Particularly significant currently are claims that have emerged in response to the FDA's warnings since 2004 about the risks of suicidal ideation in children and adolescents. As discussed in section 6.8, many critics of the FDA warnings have emphasised their dangerous consequences.

Claims that critics of antidepressants endanger people, particularly children, hinge primarily on the putative ability of antidepressants to prevent suicide. However, as discussed in section 6.8, the evidence for this is very ambiguous and problematic.

6.9.4 Critics of antidepressants are pharmacological Calvinists

Pharmacological Calvinism is a term coined by Klerman (1972, p. 3) to refer to 'a general distrust of drugs used for nontherapeutic purposes and a conviction that if a drug "makes you feel good, it must be morally bad"'. Kramer (1993) repeatedly used the term in relation to critics of prescription and use of Prozac (pp. 259, 274, 275, 365n, 370n), referring to pharmacological Calvinism as 'judgmental and prohibitive' (p. 365n).

One item on Pryor's (2008) list of 'Ignorant Things' accuses antidepressant critics of pharmacological Calvinism:

> *If you're depressed you should face your problems rather than escaping them by popping a pill*. This attitude imagines unmedicated depression as the state of looking at the world in a harsh but accurate light, contrasted with medicated depression as the state of looking at the world with a fuzzy glow. So wrong.

Olsen (2006), in a paper provocatively titled 'Depression, SSRIs, and the supposed obligation to suffer mentally' wrote:

> The strong form of the argument, favored by pop-psychologists like Curtiss or psychiatrists like Breggin, contends that avoiding the suffering of depression is simply immoral, on the grounds that it inhibits the growth of noble character. (p. 285)

This is not an argument that many critics of antidepressants would endorse. Furthermore, many advocate alternative strategies for relieving suffering, for example psychotherapy and/or assistance to overcome problems and stressors. Some critics do

argue that antidepressants can be a form of 'cosmetic psychopharmacology' (Cerullo 2006). However, relief of genuine suffering is not 'cosmetic'. Critics do not generally argue that normal people use antidepressants to boost their mood, rather that unhappy people are prescribed antidepressants, which may provide symptomatic relief, rather than having the causes of their unhappiness appropriately addressed.

Some critics, particularly Scientologists, do object to *all* use of psychiatric drugs. However, many critics do not in principle object to psychiatric drugs. Instead they generally argue that antidepressants are overprescribed and are not nearly as safe and effective as claimed. Furthermore, two prominent critics, Healy and Glenmullen, do themselves prescribe antidepressants, but much more cautiously and judiciously than most prescribers (Goode 2000). And some critics are themselves antidepressant users who have found antidepressants useful but problematic (Spoehr 2004; Slater 2006).

6.9.5 Critics of antidepressants are biased advocates of psychological treatments

Many, but by no means all, critics of antidepressants advocate psychological treatment such as cognitive-behavioural therapy as an alternative. They are sometimes criticised for supposedly believing that psychological treatments are harmless. According to Shah and Mountain (2007, p. 375):

> The parallel assumption that psychosocial treatments are without risk, are holistic and the treatments of choice ignores evidence that some psychological treatments can cause damages.

Similarly, according to Nutt and Sharpe (2008, p. 4):

> many psychotherapy trials have not even considered the possibility that their treatment could harm, perhaps because of the assumption (wishful thinking?) by both therapists and the public that as psychotherapy is only talking (with perhaps a little exposure) no possible harm could ensue.

Nutt and Sharpe bolstered their claim that psychotherapy can be harmful by giving examples of extreme forms of therapy unrepresentative of what is generally advocated for depression:

> One form of psychotherapy is exposure therapy, which is based on the premise that worsening of [anxiety] symptoms during exposure is an absolute requirement for subsequent treatment efficacy. When taken to its logical extreme it becomes flooding therapy, which was once popular. The anxiety induced by flooding can be extraordinarily distressing and there are well recognised examples of patients escaping in fear from their treatment and refusing further sessions. (p. 4)

As they mentioned, flooding therapy is an *extreme* version of exposure therapy. Less extreme exposure therapy has been demonstrated to be effective for a range of anxiety disorders (Nathan & Gorman 2002). Nutt and Sharpe also discussed recovered memories therapy, which has been comprehensively discredited:

> Some effects of psychotherapy can lead to distress to family and others close to the patient. A well recognised example of this is the acquisition of "false memories" usually of abuse by a family member that can seriously disrupt family life and has led to parents being falsely imprisoned. (p. 4)

Nutt and Sharpe also raised the spectre of sexual abuse:

> Perhaps the most important aspect of safety relates to abuse of patients by therapists. An anonymous survey of US psychotherapists some years ago revealed a large minority to have had sexual relations with their patients. Gartrell et al. (1986) found 7% of male and 3% of female psychiatrists reported sexual contact with patients. More recent data from the USA suggest that those engaged in intense psychotherapy are at higher risk of this behaviour (Morrison *et al.*, 2001). (p.4)

This ignores the fact that many cases of patient abuse are perpetrated by doctors (psychiatrists and general practitioners) who have prescribed antidepressants and other psychiatric drugs to their victims. Furthermore, Gartrell et al.'s (1986) study and Morrison and Morrison's (2001) study both focused specifically on psychiatrists. Just as the vast majority of antidepressants are prescribed by doctors other than psychiatrists, so would the vast majority of psychotherapy be provided by therapists other than psychiatrists if the availability of psychotherapy was greatly increased as advocated by many critics (among others).

Indeed Nutt and Sharpe's determination to discredit psychotherapy, using dubious arguments, is striking. More generally, the claim that critics are oblivious to the limitations of psychological treatments is essentially a straw man argument. It ignores the well developed literature in clinical psychology, in particular, about evidence-based practice (Barlow 1984; Stricker & Trierweiler 1995; Nathan & Gorman 2002).

6.9.6 Critics of antidepressants are promoting alternative biological treatments

It is often implied or argued that critics of antidepressants promote alternative treatments, sometimes for their own gain. It is true that many critics of antidepressants advocate alternative treatments, such as St John's wort, and that some vociferous

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critics of antidepressants are themselves in the 'natural' therapies industry, and therefore have potential conflicts of interest. However, this does not affect the validity of the arguments they use against antidepressants, although it does justify extra scrutiny of their claims.

Another argument related to alternative treatments is that critics are gullible. Sometimes such claims are explicit, but sometimes they are merely hinted at. For example, according to Shah and Mountain (2007, p. 375):

> The negative view of psychiatric drugs contrasts with views of drugs in other specialties or alternatives such as homoeopathy.

The mention of homeopathy (unlike drugs in other specialties) could suggest that critics of psychiatric drugs are naïve advocates of homeopathy (which is widely considered to be a form of quackery).

6.9.7 Critics of antidepressants are gratuitous 'pharmaceutical industry bashers'

Criticism of antidepressants very often focuses on the pharmaceutical companies that produce and market them. This provokes defensive responses, including accusations of 'industry bashing'. According to Solomon (2001, p. 13), whose father is Chief Executive Officer of Forest Laboratories, the maker of Celexa® and Lexapro®, 'It is fashionable at the moment to excoriate the pharmaceutical industry as one that takes advantage of the sick'.

However, there are sound grounds for criticism of many practices in the pharmaceutical industry that promote the use of antidepressants and other prescribed drugs. This is discussed in chapter 7.

6.9.8 Critics of antidepressants are gratuitous 'doctor bashers' or 'psychiatrist bashers'

Criticism of antidepressant prescribing also inherently entails a degree of criticism of the people who prescribe them, the vast majority of whom are doctors. Critics of antidepressants and other prescribed drugs are sometimes accused of 'doctor bashing'. However, many critics emphasise that doctors are greatly influenced – often unwittingly – by other players, particularly the pharmaceutical industry (Mansfield 2007).

There are, however, sound grounds for strong criticism of key opinion leader doctors who are paid by pharmaceutical companies to enthusiastically promote antidepressants and influence other doctors, particularly GPs, to prescribe them. In particular, there are serious potential conflicts of interest. Industry influence on doctors is discussed in chapter 7.

In addition, other doctors who promote antidepressants are often ill-informed about depression, suicide, and antidepressants. They are also often unaware of strategies used by pharmaceutical companies to influence doctors, and/or convinced that they are not susceptible, even if other doctors are.

Many critics of antidepressants are themselves doctors. Examples include David Healy, Joanna Moncrieff, Jon Jureidini, Peter Mansfield, Peter Breggin, and Joseph Glenmullen, all of whose work is cited in this thesis. Furthermore, with the exception of Mansfield, all of these are psychiatrists. In addition, members of organisations that criticise inappropriate promotion of drugs more generally, for example Healthy Skepticism, are doctors.

6.9.9 Critics of antidepressants are Scientologists

As mentioned in chapter 4, critics of depression orthodoxy are sometimes accused of being Scientologists. People who criticise antidepressants (and other psychiatric drugs) are even more likely to attract this charge.

Scientologists are very strong critics of psychiatry and psychiatric drugs. Much of their criticism is channelled through the Citizens Commission on Human Rights (CCHR). For example, CCHR has produced and distributed a DVD called 'Psychiatry: An Industry of Death' (CCHR 2006). CCHR was founded by Scientology and Thomas Szasz, a very prominent critic of psychiatry, particularly notable because he is a psychiatrist himself.

Antidepressant advocates often respond to criticisms of antidepressants by referring to Scientologists, implying that they are the main critics, and hinting that *any* critic may be a Scientologist, or at least be influenced by Scientology:

> Recent years have seen a sustained media campaign of misinformation about the value of certain psychiatric treatments that has rarely been seen before, with the

> possible exception of the anti-ECT campaign of the 1970/80s. This campaign began with the Scientologists attacking Prozac in the early 1990s and, at least in the UK, has gained new momentum recently. (Nutt 2003, p. 251)

Responding to a newspaper story (Davies 2008) about Australian children, including pre-schoolers and babies, being prescribed antidepressants, several people dismissed the validity of Commonwealth Department of Health and Ageing statistics because they had been *obtained* (not generated) by the CCHR. One responder accused other responders of being Scientologists because they endorsed the concerns raised. 'Jeremy of Brisbane' wrote:

> Although not a scientologist, giving drugs that essentially do no more than placebos is ridiculous. These drugs are in actual fact proven to do more harm than good. And what of scientologists presenting these facts? I may or may not agree with their beliefs but I for one think [it's] great they are educating society about the dangers of psychiatric drugs.

'Anon of Everywhere' responded, accusing Jeremy and another person of being Scientologists:

> The Key word here is Scientology. They are anti psychiatry. And I wouldn't put it pass them to make up numbers. clearly these posters are Scientologists Abigail of Victoria Jeremy of Brisbane (Very obvious by him starting off with "I am not a Scientologist!)

According to Levine (2008), the media are largely responsible for perceptions that all critics of psychiatry are linked to Scientology:

> For many Americans who gain their information solely from television, all critics of psychiatry are Scientologists, exemplified by Tom Cruise spewing at Matt Lauer, "You don't know the history of psychiatry. . . . Matt, you're so glib." The mass media has been highly successful in convincing Americans to associate criticism of psychiatry with anti-drug zealots from the Church of Scientology, the lucrative invention of science fiction writer L. Ron Hubbard.

Levine did not really explain *why* the media have tried to persuade the public to associate criticism of psychiatry with Scientology. However, he commented that psychiatry and Scientology are both orthodoxies that rely on well funded public relations, but that 'psychiatry is the more *prevailing orthodoxy*, and, as George Orwell explained, the mainstream press does not challenge a prevailing orthodoxy'.

Another contributing factor, of course, is that conflict makes for good copy. For example, high profile Scientologist Tom Cruise's public criticism of Brooke Shields' use of antidepressants (Shields 2005) generated many thousands of media reports

criticising Cruise, strengthening the perception of links between Scientology and critics of antidepressants.

More provocatively, Robert Whitaker, author of *Anatomy of an epidemic* (Whitaker 2010) has suggested that the pharmaceutical industry may actually have strategically *encouraged* Scientology to criticise them, in order to tarnish perceptions about critics collectively:

> Big Pharma and their partners in establishment psychiatry have smartly used Scientology to defuse criticism of their medications. I honestly believe that if Scientology weren't around, then our society could have a much more rational discussion about our drug-based paradigm of care. (p. 281)

Although Scientology has a high public profile in its criticism of psychiatric drugs and psychiatry more generally, many people who are critical of antidepressants are also highly critical of Scientology (e.g. Levine 2008). However, many critics of antidepressants (myself included) would agree that many of the *evidence-based* claims made by CCHR about antidepressants (and psychiatric drugs more generally) are valid.

6.9.10 Conclusion: Critics of antidepressants

Antidepressant critics are accused of negative traits such as ignorance and callousness, and bias towards alternative treatments. They are also accused of having vested interests, including benefitting from promotion of alternative treatments such as psychotherapy and 'natural therapies', and being Scientologists.

Many of the charges levelled at critics, in the media and in academic literature, would seem valid to many people. The emotive language (e.g. 'dangerous') that is commonly used makes these charges more powerful, particularly when they are articulated by high-profile doctors and consumer/community organisations. However, these accusations often misrepresent what critics actually think and say, and there is little evidence to support them.

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6.10 CONCLUSION

There is considerable evidence to challenge the orthodox claims that antidepressants are safe, effective, and necessary, that they are evidence-based and are appropriately prescribed. In fact, it is fair to say that antidepressants have long lost their 'wonder-drug' status among people familiar with current research about them. Unfortunately, however, most of the public and the media lack good knowledge of the evidence.

There is substantial and increasing evidence of significant risks, both short and long-term. Much of this evidence has emerged from observational studies, despite inadequate post-marketing surveillance. Some evidence has also emerged from clinical trials, despite biased methodology and reporting.

In relation to effectiveness, there is mounting evidence that the apparent efficacy of antidepressants in clinical trials has been enhanced by methodological manipulations in the design of clinical trials, including the use of placebo washout. This has been compounded by reporting biases, including suppression of negative trials.

Despite claims of massive under-treatment of depression and under-prescription of antidepressants, there is considerable evidence that antidepressants are prescribed to a majority of patients diagnosed with depression, and to many people who do not satisfy diagnostic criteria. However, dramatic increases in antidepressant use at a population level have not reduced the prevalence and impact of depression.

In the 1990s, the key debate about antidepressants focused on their dependence potential, described by Healy (2004, p. 270) as a 'specter stalk[ing] the SSRIs'. Antidepressant advocates have used biased definitions of dependence/addiction and biased interpretations of diagnostic criteria to argue that antidepressants do not have dependence potential. That debate has subsided since, but is still important. Antidepressant advocates have grudgingly admitted the possibility of withdrawal symptoms and syndromes; claims that antidepressants are not 'addictive' continue but are less common now than they used to be.

More recently, safety concerns have focused primarily on suicide. According to orthodox beliefs, antidepressants reduce the risk of suicide by depressed people. However, paradoxically and controversially, there is some evidence that use of antidepressants can increase the risk of suicide. This is the subject of the most heated and polarised current debate about antidepressants, particularly in relation to young

people. The evidence wielded by both sides of the debate is complex and ambiguous and, from an epidemiological perspective, weak.

As with depression and suicide, weak and sometimes manipulated empirical evidence and faulty logic are being used to support the current orthodoxy about antidepressants. Much of this is orchestrated by the pharmaceutical industry, as discussed in the next chapter.

Not surprisingly, critics of antidepressants are themselves strongly criticised. This includes accusations of ignorance, callousness, dangerousness, vested interests, and prejudice against doctors and pharmaceutical companies. Notably, ad hominem arguments are much more common than reasoned evidence-based responses to issues raised by critics.

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Chapter 7

Pharmaceutical industry practices and issues

7.1 INTRODUCTION

As outlined in chapter 3, the pharmaceutical industry is a key player in the antidepressant story. Pharmaceutical companies have made enormous profits from the sale of antidepressants, one of the most lucrative classes of drugs for many years (Shelley 2009).

There has been increasing criticism of the pharmaceutical industry on many fronts in recent years. There is considerable concern about a number of industry practices that directly or indirectly promote drug sales and profits. In the main part of this chapter, promotional strategies used in the marketing and promotion[1] of antidepressants are discussed. The most significant strategies are drug representatives, gifts, drug samples, medical journal advertisements, research funding, ghost-writing, and key opinion leaders (KOLs), all of which primarily target doctors, direct-to-consumer advertising, which targets patients, and strategic relationships with government entities and consumer organisations. Where possible, Australian examples related to antidepressants are given.

Next is a detailed case study of the marketing and promotion of one antidepressant, Lexapro® (escitalopram), a chemical variant of Celexa® (citalopram). Numerous strategies have been used to promote it, both internationally and in Australia, with considerable effectiveness. The case study reveals both how common strategies such as samples are used and how unusual circumstances can be exploited.

[1] In this thesis, the terms marketing and promotion are used as partial synonyms, as is often the case in the literature and the media. Marketing generally refers to strategies paid for by drug companies, either externally (e.g. medical journal advertising) or internally (e.g. employment of drug representatives). Promotion is broader than this, and includes marketing, but it is often referred to as a separate category of activities, often not directly paid for by drug companies. However, the boundaries are blurred. For example, many doctors are paid by drug companies for specific activities such as presenting workshops that discuss drugs in a favourable light. Such doctors are referred to in the industry as 'key opinion leaders', and such payments routinely appear in marketing budgets. However, those same doctors are likely to also refer to the relevant drugs favourably in other contexts (e.g. in clinical teaching, collegial discussions, and media encounters). This is more likely to be categorised as promotion than as marketing.

Before discussing specific promotional strategies, some general comments are in order. The pharmaceutical industry spends huge amounts of money on prescribed drug marketing (including advertising), significantly more than on research and development (Ballance 1996, p. 97; Angell 2000; Nader 2001). US expenditure on marketing was approximately $15.7 billion in 2000 (Frank et al. 2002, p. 6). Nearly $3 billion of that was for advertising. In 1998-1999, approximately one billion dollars was spent on promotion by drug companies in Australia (Jureidini & Mansfield 2001, p. 96). All promotional strategies are aimed at increasing sales and profits, in keeping with drug companies' fiduciary duty to maximise profit for shareholders (Shah & Finucane 2007, p. 1009; Jureidini & Mansfield 2001, p. 96), and there is clear evidence of the effectiveness of many strategies (Wazana 2000).

Pharmaceutical promotion has multiple key target groups, including: doctors and medical students, hospitals and other institutions, managed care organisations, patients/consumers, consumer organisations, journalists, and governments and regulatory authorities. Different strategies are used for different target groups.

Traditionally, most marketing has been directed at doctors, via medical journal advertisements and promotional materials and samples provided by drug representatives, because doctors are the gatekeepers to patients' access to drugs. Doctors are trained in diagnosis, pharmacology, and therapeutics, but patients generally have negligible knowledge in these areas. The doctor is therefore a 'learned intermediary' (Drazen 2002).

This can create problems because doctors do not pay for the drugs they prescribe (Jureidini & Mansfield 2001, pp. 97-98) and because there can be financial incentives for them to prescribe and promote drugs that other people pay for and use. However, it is repeatedly claimed that doctors are too ethical to prioritise such incentives over the best interests of their patients. Another issue is whether doctors are misled by pharmaceutical promotion. In response, it is often claimed that doctors are too intelligent to be misled by the pharmaceutical industry. Some examples of claims about both these issues are given in the main part of this chapter in relation to specific

Common acronyms in this chapter: ACCC Australian Competition and Consumer Commission; APA American Psychiatric Association; CGP clinical practice guideline; DSM Diagnostic and Statistical Manual (of Mental Disorders); DTCA direct-to-consumer-advertising; FDA Food and Drug Administration; KOL key opinion leader; NAMI National Alliance for the Mentally Ill; NARSAD National Alliance for Research on Schizophrenia and Depression; NIMH National Institute of Mental Health; PhRMA Pharmaceutical Research and Manufacturers of America; ROI return on investment; SSRI selective serotonin reuptake inhibitor; SNRI serotonin and noradrenalin reuptake inhibitor; TCA tricyclic antidepressant; TGA Therapeutic Goods Administration

promotional strategies. Then at the end of the chapter there is a consolidated analysis of the effectiveness of industry influence, particularly on doctors.

Medical journals play a very important role in drug marketing, and in recent years they have attracted considerable criticism for publishing advertisements and articles that promote prescribing. Most medical journals are financially dependent on pharmaceutical advertising. In addition, industry-sponsored supplements and article reprints are a lucrative source of income for journals. There is evidence of industry-favourable bias in journal policies and practices, for example, not publishing criticism of the industry, and publishing biased and methodologically weak articles in journal supplements. Many of these supplements report the opinions and decisions of industry-funded meetings and advisory groups. According to the ex-editor of the *BMJ*, 'Medical journals are an extension of the marketing arm of pharmaceutical companies' (Smith 2005, p. 364). Richard Horton, editor of *The Lancet*, has also been very critical of the relationships between medical journals in general and the pharmaceutical industry (Horton 2005). Obviously advertisements in medical journals are very important, but journal supplements and reprints of articles are also powerful marketing tools that generate revenue for journals and create potential conflicts of interest.

Medical students, as doctors-in-waiting, are also targets of promotion, using many of the same strategies that are used with doctors. Hospitals are also targets, particularly in relation to their pharmaceutical formularies (the drugs they stock to dispense to patients). Similarly managed care organisations in the US are very important because they control what drugs doctors can prescribe to patients.

Government agencies and regulatory authorities are also important, because of their power to control marketing and prescription of drugs. In the US in particular, enormous sums of money are spent by pharmaceutical companies on lobbying politicians in order to influence decisions that affect the industry.

Numerous guidelines and codes of conduct have been introduced to regulate industry practices. Some have been developed by industry bodies (e.g. the US Pharmaceutical Research and Manufacturers of America (PhRMA), the Association of the British Pharmaceutical Industry, and Medicines Australia). Others have been developed by government agencies, most notably the US Food and Drug Administration (FDA).

There are also guidelines developed by health professional organisations (e.g. the American Medical Association and the Royal Australian College of General Practitioners that stipulate what sorts of interactions with pharmaceutical companies are appropriate for doctors. Several of these guidelines and codes are mentioned in this chapter. However, a comprehensive analysis of their content and effectiveness is beyond the scope of this chapter.

Another important issue is evidence-based medicine, which supposedly governs doctors' clinical practice, including prescribing. According to an increasing number of critics, pharmaceutical companies are adept at distorting evidence to their advantage while paying lip service to evidence-based medicine. Healy (2006) has provided a detailed analysis of this in relation to the marketing of SSRI antidepressants for adolescent depression, concluding:

> Evidence-based medicine (EBM) is portrayed by its advocates as a value-free approach to the problems of clinical practice. In its early days, the appeal of EBM lay in the promise that the assessment of all available clinical trial data rather than judgments based on selected data sets would deliver clinical facts that should trump the values of individual clinicians, academic or nonacademic, which were all too often at risk of subversion by the free meals on offer from pharmaceutical companies. But … there are grounds to think that pharmaceutical companies have effectively subverted the process. (p. 151)

Several strategies used to subvert evidence-based medicine are briefly discussed in this chapter.

Another important issue is that pharmaceutical promotion selectively focuses on more profitable drugs, which in most cases are newer drugs. New drugs are claimed by the industry to be more effective, safer, and more cost-effective. There is considerable evidence that challenges such claims (Lexchin 2004; Moulds 2004; Rolan et al. 2006), but a detailed discussion of this is beyond the scope of this thesis.

One particularly significant category of newer drugs is analogues or 'me-toos' – drugs that are minor variants of profitable existing drugs, rather than innovative drugs (Jewesson 2002). Newer antidepressants are good examples of me-too drugs (Angell & Relman 2001, p. A27) particularly SSRIs developed since the blockbuster Prozac was released in the US in 1988.

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7.2 DRUG REPRESENTATIVES

Pharmaceutical sales representatives ('drug reps') play a very important role in drug marketing. Drug companies outlay very large amounts of money on drug reps. In the US in 1999, in a very useful analysis of return on investment (ROI) of pharmaceutical promotion, expenditure on drug reps was estimated at nearly $5 billion (Neslin 2001, p. 6).

Reps spend vast amounts of time visiting doctors in their clinics and other workplaces. This face-to-face contact and relationship building is often referred to as 'detailing', and drug reps have often been referred to as 'detailers' and 'detail men' (Sapira 1973), although these terms (particularly the gendered latter) are losing currency. The pharmaceutical industry often uses the inaccurate term 'medical representative' instead.

Drug reps first emerged in the mid to late nineteenth century (Elliot 2006; Davis 1997, p. 93). Their ranks have swelled dramatically in recent years, doubling in the US between 1996 and 2001 to a total of 90,000 (Elliot 2006). In the US, according to Shaughnessy & Slawson (1996), there was one drug rep for every 15 practising physicians in 1996. According to Moynihan (2003), 80-95% of doctors regularly see drug reps.

According to a marketing plan by Forest (2003), manufacturer of Celexa® and Lexapro®, 'The anti depressant market is the most heavily detailed category in the pharmaceutical industry' (p. FCA0017722[2]). US reps promoting six SSRIs had well over three million contacts with doctors in 2002:

> IMS audits reported Lexapro to have 374,000 detailing contacts in 2002 while Celexa had 611,000. Zoloft was the market leader in this category with a little over 1 million detailing contacts. Paxi1/CR and Effexor XR and [sic] were second and third behind Zoloft with 983,000 and 653,000 detailing contacts, respectively. (Forest 2003, p. FCA0017701)

These days, many drug reps are attractive young women (Elliot 2006). Indeed, some are recruited as college cheerleaders (Saul 2005). Male reps are also often attractive. Successful reps have very good communication skills, and are good at building

[2] The page numbers are those assigned by the United States Senate Committee on Finance. No original page numbers are apparent on the document pdf.

rapport with doctors. In addition, drug reps are sometimes accompanied by doctors employed to promote specific drugs because they are more likely to be perceived as credible. This is discussed in section 7.5.

Drug reps use different strategies based on their assessment of doctors' personalities:

> the best reps tailor their messages constantly according to their client's reaction. A friendly physician makes the rep's job easy, because the rep can use the "friendship" to request favors, in the form of prescriptions. Physicians who view the relationship as a straightforward goods-for-prescriptions exchange are dealt with in a businesslike manner. Skeptical doctors who favor evidence over charm are approached respectfully, supplied with reprints from the medical literature, and wooed as teachers. Physicians who refuse to see reps are detailed by proxy; their staff is dined and flattered in hopes that they will act as emissaries for a rep's messages. (Fugh-Berman & Ahari 2007, p. 621)

In fact, staff are targeted more broadly than suggested in the last sentence. They are gatekeepers to doctors, literally – by controlling doctors' appointment books, and presiding over waiting rooms – and figuratively – by giving reps clues about how to establish rapport with doctors (Elliot 2006) and by influencing doctors' opinions of individual reps.

Drug reps also categorise doctors according to their attitudes towards prescribing. In relation to antidepressant prescribing, this also includes attitudes towards depression. Berliner (2002) identified three types of doctors: 'Deniers' who 'do not screen for depression and avoid treating it'; 'Dabblers' who 'recognize the importance of depression and its treatment, but feel somewhat inadequate in their ability to treat it'; and 'Diligent and determined', who 'fully realize that depression is an important problem that must be addressed like any other condition they treat'.

The goal of drug reps' interactions with doctors is to increase prescribing of their companies' drugs:

> An official job description for a pharmaceutical sales rep would read: Provide health-care professionals with product information, answer their questions on the use of products, and deliver product samples. An unofficial, and more accurate, description would have been: Change the prescribing habits of physicians. (Fugh-Berman & Ahari 2007, p. 623)

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Drug reps are highly trained to achieve this goal by skilfully and subtly influencing doctors, who are not trained to resist. A former drug rep reported:

> While it's the doctors' job to treat patients and not to justify their actions, it's my job to constantly sway the doctors. It's a job I'm paid and trained to do. Doctors are neither trained nor paid to negotiate. Most of the time they don't even realize that's what they're doing (Fugh-Berman & Ahari 2007, p. 624)

Australian researchers Roughead et al. (1998, p. 306) discussed how drug reps used Cialdini's (1988) six key techniques of influence: reciprocity, friendship/liking, commitment/consistency, social validation, authority, and scarcity. They commented that doctors 'may not be aware of the potential effect these techniques can have on their prescribing practices' (p. 306).

According to the industry, drug reps play an important role in doctor education, particularly about new drugs. According to Spilker (2002, p. 243).

> Sales representatives perform valuable functions that promote better patient care. At a time when doctors are bombarded daily with new information and are finding it increasingly difficult to keep up to date, sales representatives provide information to physicians on new treatments, new approved uses for existing medicines, contraindications, new dosages, drug interactions, and new ways to monitor patients.

Decades ago, when there was no internet and little continuing medical education, there was considerable truth in such claims, but now there are much better ways of educating doctors:

> There may have been a time when representatives were the easiest source for finding out about pharmaceutical developments, but now there is ready access to a plethora of non-promotional, evidence based information in simple and digestible form on all the major therapeutic advances. Drug information departments additionally supply detailed advice on such matters as new formulations and interactions. There seems little or no need to see representatives in order to keep abreast of drug developments. (Griffith 1999, p. 69)

Industry advocates sometimes claim or suggest that drug reps are compelled to give doctors good information:

> Jeff Trewhitt, a spokesperson for the Pharmaceutical Research and Manufacturers of America, says detailers provide important expertise that is of great use to doctors. "Yes, they are trying to draw attention to a product, but if they are going to do it, they are going to have to maintain their credibility and show that they are knowledgeable, and be able to answer important technical questions." (Black 2004, p. 1656)

In addition, the industry claims that drug reps are ideal for providing other information. For example, Gowdy (2006), a UK pharmaceutical company employee with a National Health Service background, argued that drug reps can do a better job than health authorities of disseminating guidelines to GPs.

Bizarrely, the Australian Federal Government contracted in 2002 with industry to educate doctors about Pharmaceutical Benefits Scheme restrictions:

> In a bid to cut the rising costs of government subsidised drugs – a rise partly caused by inappropriate prescribing – the Australian government has opted to enlist the sales force of pharmaceutical companies.
>
> The decision has astonished consumer groups but been welcomed by its proponent, the Australian Pharmaceutical Manufacturers Association.
>
> According to last week's Budget papers, savings will be achieved by ensuring that restrictions on the government's pharmaceutical benefits scheme, under which the government subsidises the costs of approved drugs, will be communicated to doctors through drug company representatives. (Burton 2002)

This is ironic given that the industry has a strong track record of promoting off-label (non-approved) prescribing (Kravitz et al. 2005; Steinman et al. 2006).

More generally, the quality of information provided by drug reps is problematic. In 1997, Greenhalgh wrote: 'Pharmaceutical "reps" do not tell nearly as many lies as they used to (drug marketing has become an altogether more sophisticated science), but they have been known to cultivate a shocking ignorance of basic epidemiology and clinical trial design when it suits them' (1997a, p. 480). Possibly they tell fewer lies again these days, because of heightened scrutiny and somewhat stricter regulation, but more recent studies have found that both written and verbal information provided by reps is often inaccurate, as well as being biased in favour of their companies' products.

However, it is often claimed that doctors are too intelligent to be misled by industry promotion. Surprisingly, however, Medicines Australia (2007) acknowledged that doctors are not too intelligent to be misled by drug reps:

> members were of the view that EBM [evidence-based medicine] is a skill that needs to be constantly practiced to be maintained and it is not reasonable to assume that an average GP is trained and able to assess this information in a 5 – 10 minute detailing by a medical representative.

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Doctors themselves tend to believe that they have the skills they need to judge the validity of claims made by reps (Steinman et al. 2001). More generally they believe that they are not susceptible to influence by reps. In a survey of psychiatrists in training, Hodges (1995) found that many dismissed the potential of interactions with reps to influence their prescribing. Tellingly, the more money and promotional items they received from reps, the more likely they were to have this belief.

However, many doctors believe that *other* doctors are susceptible to influence. In a US study, Steinman et al. (2001) found that, although 61% of internal medicine residents said they themselves were unaffected by drug reps, only 16% said that other physicians were immune to influence (p. 554).

There is clear evidence that doctors are often unable to detect inaccuracies in reps' claims. In a study by Ziegler et al. (1995, p. 1296) in a US teaching hospital, the accuracy of statements made by reps who provided lunch and made short presentations was analysed, as was doctors' ability to assess their validity. Both reps and doctors were found wanting:

> Eleven percent of the statements made by pharmaceutical representatives about drugs contradicted information readily available to them. Physicians generally failed to recognize the inaccurate statements.

Not surprisingly, all the inaccurate statements were favourable to the drug being promoted by the rep (p. 1297). One statement judged inaccurate by the researchers was about antidepressants:

> "We are the only SSRI that has long-term data."
>
> …. One of the competing drugs had much-longer-term clinical and research data. The company's drug had been on the market for 3 months while a competing drug had been marketed for 5 years. (p. 1298)

Studies show that prescribing is significantly influenced by contact with reps (Roughead et al. 1998; Caudill et al. 1996; Lexchin 1993). In relation to antidepressants specifically, Griffith (1999, p. 70) argued that:

> Increased costs of prescribing are likely to be a further consequence of contact with representatives. Selective serotonin reuptake inhibitors are just one example where promotion by drug companies has boosted sales far beyond levels that might have been expected if non-promotional literature had been heeded. Despite a widely available and authoritative review counselling caution in their use – a policy subsequently born [sic] out by later evidence – sales of selective serotonin reuptake inhibitors soared, with consequent increases in

> spending. As has been pointed out before, these resources could perhaps have been better used elsewhere.

Also in relation to antidepressants, the Deputy Director of the Royal College of Psychiatrists research unit expressed a view that drug reps influence antidepressant prescribing:

> *Dr Kendall*: I personally, as a psychiatrist, have never seen, maybe once or twice in my youth, a drug rep, but I am very aware that there are physiatrists [sic] whose prescribing is obviously influenced by those relationships.
>
> ….
>
> *Dr Kendall*: No, the problem in an area like psychiatry is that it is full of me-too drugs, so that when prescribing an anti-depressant you have a choice of a whole range of them, but all doing much the same type of thing. I believe whichever drug rep becomes your closest friend does have an influence on you. (House of Commons 2005b, p. Ev 117)

Some academics and clinicians advocate exposing medical students to drug reps and teaching them skills that will help them avoid being influenced in the future (Wofford & Ohl 2005). However, the effectiveness such 'innoculation' is questionable (Mansfield 2006).

Furthermore, the information flow between drug companies and doctors is two-way:

> [Drug reps] also are an important channel of information from physicians to drug companies about the use of their products, particularly about any adverse reactions physicians may have observed. (Spilker 2002, p. 243)

Spilker's assertion about the value of the information flow from doctors to drug companies is ironic for several reasons. Firstly, drug companies often actively suppress information about adverse reactions and about unfavourable findings more generally; this is discussed in section 7.11.

Secondly, drug companies are extremely interested in information from doctors, but it is primarily information about prescribing habits, and potential influences, that they want, rather than reports of adverse reactions. Drug reps are 'trained to assess physicians' personalities, practice styles, and preferences, and to relay this information back to the company' (Fugh-Berman & Ahari 2007, p. 621). In addition, US drug companies buy prescription data from market research companies, which obtain the

data from pharmacies and hospitals (Elliot 2006). Generally such information is de-identified, but drug companies also pay the Federal Government and professional organisations such as the American Medical Association and the American Psychiatric Association for additional information that allows them to identify doctors (Whitney 2006). Consequently, drug reps have dynamic data about individual doctors' prescribing, enabling them to individually tailor their strategies and evaluate their effectiveness (Carlat 2007).

The return on investment (ROI) per additional dollar spent on drug reps is very high, amply justifying the high expenditure. Using 1995-1999 data, Neslin (2001) reported:

> Our overall findings: for detailing, there is an overall ROI of $1.72, suggesting that detailing pays off even at very high levels of expenditure. The range of this variable is the largest, going from $1.27 to $10.29, depending on brand size and launch date. There is a particularly high ROI for large and more recently launched brands. (p. 20)

Many antidepressants would at that time have fitted into the category of large and more recently launched brands, suggesting that the large expenditure on promotion by drug reps – between four and twelve million dollars in some months for Celexa® (citalopram) alone, according to Neslin (2001, p. 12) – made good business sense.

7.3 GIFTS

Drug reps provide doctors with many gifts, of varying types. Many of the gifts, particularly pens, self-adhesive notes, and other stationery items, are relatively cheap and functional. Doctors also receive computers and items of medical equipment. Two key categories of functional gifts are drug samples (discussed in section 7.4) and journal article reprints (discussed in section 7.8) and other potentially educational resources such as textbooks.

The Royal Australian College of General Practitioners (1999) guidelines on acceptance of gifts state that 'The patient should be the primary beneficiary of any gift accepted by the general practitioner and the gift should be related to the general practitioner's work'. Similarly the Association of the British Pharmaceutical Industry (2006) code specifies that gifts should be 'relevant to the recipient's work' such as pens and diaries (pp. 6-7). However, reps sometimes dispense gifts that are clearly intended for doctors' personal benefit, for example silk ties and golf bags (Fugh-

Berman & Ahari 2007, p. 623), rather than plausibly being tools of the trade or products that directly benefit patients.

More ambiguous, and more broadly dispensed, is hospitality, ranging from mundane sandwiches at work to luxury international travel and accommodation that sometimes extends to spouses/partners. Hospitality is an important strategic category of gift because of its apparent insignificance in many instances. Its ephemeral nature (particularly in the case of lunches) makes its influence more insidious than that of more substantial gifts. Furthermore, hospitality is usually provided in conjunction with educational events (and vice versa), which makes it both easier for doctors to justify accepting industry largesse, and harder for them to avoid it.

Inappropriate industry hospitality has attracted considerable criticism in several countries, including Australia. In the US, Brubaker (2002) highlighted one egregious example which involved both lavish hospitality and payment for sham consultation:

> A week ago last night, about two dozen doctors gathered for cocktails and dinner at the Plaza Hotel in New York, guests of a pharmaceutical company that planned to solicit their "advice" and "feedback" on the treatment and management of depression.
>
> The doctors didn't have to rush home after dinner. Forest Laboratories Inc. treated them to an overnight stay at the Plaza, where even the least desirable rooms – those without Central Park views – go for about $250 a night.
>
> Saturday morning, after a free breakfast, the doctors participated in a four-hour discussion about depression, which can be treated with Forest's best-selling product, Celexa. Then, after a free lunch, each doctor was offered a token of Forest's appreciation: a check for $500.

In Australia in 2009, Wyeth sponsored a $1 million 'antidepressant overview weekend meeting' as part of its launch of a new SNRI (serotonin and noradrenalin reuptake inhibitor) antidepressant, Pristiq® (desvenlafaxine) (Kollmorgen 2010). As discussed in section 7.20, Pristiq is a chemical reformulation of Efexor® (venlafaxine).

Leading doctors often provide naïve justifications for accepting hospitality. One example is the then President of the Australian Medical Association, responding to criticism of industry-funded meals for doctors and their personal partners:

> the AMA's Haikerwal maintains that drug companies funding restaurant meals for doctors is acceptable and that they are there to "oil the wheels". He argues that company-sponsored events give doctors an opportunity "to critically question the companies' products" and that "no patient harm comes from this process". He says he regularly accepts drug company-sponsored hospitality. (Moynihan 2006)

Haikerwal also defended *upmarket* hospitality:

> AMA national president Mukesh Haikerwal strongly defends the $200-a-head dinner at the Opera House. "It's understandable why it's done there, rather than doctors slumming it somewhere in a budget chain motel," he says. (Moynihan 2006)

A member of the American Medical Association's working group on ethical guidelines similarly argued that gifts more generally do not affect prescribing: 'Others say the perks don't influence them at all. "Doctors will do what's best for their patients," the AMA's Thomas said' (Brubaker 2002).

However, there is substantial opposition within the medical profession itself to inappropriate hospitality and other gifts, regardless of size. As mentioned in chapter 3, No Free Lunch is a New York based organisation of doctors and other healthcare providers who believe that pharmaceutical promotion is frequently biased and that accepting gifts from drug companies adversely influences clinical practice.

Its website (http://www.nofreelunch.org/)[3] carries the slogan 'Just Say No to Drug Reps', and it features a tongue-in-cheek modification of the CAGE alcohol dependence test (Ewing 1984; Ewing & Rouse 1970). The original CAGE test consists of four questions that assess different aspects of dependence:

1. Have you ever felt you ought to **C**ut down your drinking?
2. Have people **A**nnoyed you by criticising your drinking?
3. Have you ever felt **G**uilty about your drinking?
4. Have you ever had a drink first thing in the morning as an "**E**ye opener"?

The No Free Lunch CAGE also consists of four questions (Yamey 2001):

- Have you ever prescribed **C**elebrex?
- **A**nnoyed by people who complain about drug lunches & free gifts?
- Is there a medication lo**G**o on the pen you're using right now?

[3] In April 2011, Healthy Skepticism announced that No Free Lunch was merging with. it (Healthy Skepticism 2011). However, the No Free Lunch website is still online.

- Do you drink your morning **E**ye-opener out of a Lipitor coffee mug?

Health professionals were encouraged by No Free Lunch to take the pledge to refuse gifts, seek unbiased information, and avoid conflicts of interest. No Free Lunch also offered a 'pen amnesty', in which doctors could swap drug company pens for No Free Lunch pens (Yamey 2001).

According to Jureidini & Mansfield (2001), gifts create a sense of reciprocal obligation, and it is a mistake to dismiss small gifts as unimportant:

> Even small gifts are a way of creating obligation, either consciously or sub-consciously. Gifts are different from contracts, where the obligation is known and overt. On the whole, corporations get better return from the sense of obligation that is induced by gifts than they would from overt agreements to exchange services for money. Cheap gifts should not be thought of as harmless indulgences, but as low cost, highly cost effective advertising. (p. 97)

However, many doctors believe that they are immune to any sense of obligation. In a study of US radiation oncologists, Halperin et al. (2004) found that 'although only 4% felt that their recommendations concerning purchases of medical equipment are affected by gifts, 19% felt that other physicians would be influenced' (p. 1477).

Not surprisingly, pharmaceutical industry spokespeople deny the influence of gifts. In particular, small inexpensive gifts are strongly defended. For example, Black (2004, p. 1656) quoted Jeff Trewhitt, a spokesperson for the US peak industry organisation Pharmaceutical Research and Manufacturers of America (PhRMA):

> Trewhitt thinks critics are over blowing the influence of gifts given to physicians by drug company representatives. "We believe that when you give a modest gift that helps promote the medical practice of the health care professional involved, you are simply acknowledging that you are taking valuable time from a busy health care professional. Quite often all they are is pens and pads. It is entirely possible that a physician is going to have a pen and a pad from one company and then a pen and a pad from that company's main competitor. It's probably an insult to the vast majority of doctors to think they are going to be unduly influenced by a $1·18 pen with somebody's name on it

Similarly, responding to claims that it is not appropriate for hospital residents (junior doctors) to be given free lunches and other gifts by industry (Brody 2002; Jung 2002), Spilker (2002, p. 243) argued:

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> Howard Brody and Paul Jung fear that physicians are so weak and lacking in integrity that they would "sell their souls" for a pack of M&M candies and a few sandwiches and doughnuts…. I find it hard to imagine that any of my colleagues would compromise professional concern for their patients. Certainly the vast majority of physicians are able to resist this temptation and make decisions solely based on the best medical interests of their patients.

A standard industry tactic is to speak positively about rules and guidelines, implying that they are effective, as in this quote from Spilker (p. 244), also in response to Brody and Jung:

> the authors fail to note that sales representatives are subject to certain rules and guidelines. Drug representatives are governed by rules and guidelines of the US Food and Drug Administration (FDA), and the relationship of representatives and physicians is spelled out in position statements of the American College of Physicians (ACP) and the American Medical Association (AMA) that have been adopted by the Pharmaceutical Research and Manufacturers of America (PhRMA). The ACP specifies that gifts should not be accepted if they might influence or appear to influence the objectivity of clinical judgement. The AMA guidelines state that gifts are appropriate if they serve a genuine educational function.

This is analogous to discussing laws governing driving speeds, implying that the existence of those laws means that speeding is not a problem.

This quote about American Medical Association guidelines on gifts almost farcically highlights their ineffectiveness, and the absurdity and hypocrisy of industry involvement in management of relationships between doctors and drug companies:

> Last summer, the AMA launched a campaign – funded largely by the pharmaceutical industry – to reeducate the nation's 700,000 doctors on ethics.
>
> The guidelines offer some wiggle room. Doctors who have been deemed "advisers" to drug companies, if only for a few hours, can accept honorariums and travel perks, for example. Forest Laboratories calls its advisers "advertising/marketing consultants" in the confidentiality agreements they are asked to sign. (Brubaker (2002)

As mentioned in chapter 3, Healthy Skepticism, an Australian-based international organisation, has a significant role in combating inappropriate advertising and marketing more generally, including gifts. Healthy Skepticism intermittently publishes *AdWatch*,[4] which 'illuminates the logical, psychological and pharmacological techniques used in drug advertisements' (Healthy Skepticism 2010).

[4] I am a member of the four-person *AdWatch* editorial team.

The September 2006 *AdWatch* (Healthy Skepticism[5] 2006) focused on packs of sweets used by Wyeth[6] to promote Efexor®[7] (venlafaxine):

These sweets were clearly not directly related to doctors' work, nor were they of benefit to patients, in contravention of the Royal Australian College of General Practitioners (1999) guidelines for gifts. Furthermore, the sweets and their brightly coloured tetrahedron packaging would have been appealing to children, and it is likely that many of the sweets would have been eaten by child patients and children of doctors and their staff. Notably, Efexor is not approved for prescription to children.

As a promotional strategy, these sweets are somewhat similar to candy cigarettes, which have been used effectively for decades to encourage children to start smoking. The tobacco and confectionery industries colluded for their mutual benefit, suppressing evidence of the effectiveness of candy cigarettes in promoting cigarettes to children (Klein & St Clair 2000; Cancer Council NSW 2002). They also ridiculed people who advocated bans (Klein & St Clair 2000). Candy cigarettes are now prohibited in several Australian jurisdictions and a number of other countries.

[5] I was the primary author of this *AdWatch*.
[6] Wyeth is mentioned repeatedly in this chapter. However, its promotional strategies are probably no worse than those of other antidepressant manufacturers.
[7] In the US, venlafaxine is marketed as Effexor®.

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According to child psychiatrist Jon Jureidini (then Chair of Healthy Skepticism), the sweets 'trivialised the issue of someone going on quite serious medication':

> I don't think a kid who picks this up is going to want to take antidepressants, but it sends a message that there's something kind of nice about it — like taking 'happy pills' (Hingston 2006).

Predictably, however, Wyeth rejected the criticism, and the Australian Medical Association defensively dismissed it:

> Chairwoman of the AMA ethics and medicolegal committee Dr Rosanna Capolingua dismissed the lollies as a "trivial marketing gimmick".
>
> "Promotions like this do not affect prescribing choices – a doctor will choose the drug best suited for the patient," she said. (Hingston 2006)

7.4 DRUG SAMPLES

Drug samples are a very important category of gifts. Drug reps give large quantities of samples (sometimes referred to as 'starter packs') to doctors, to dispense as they see fit. In 2005, the US industry gave away samples with an estimated retail value of over $18 billion, representing 11.2% of sales (Donohue et al. 2007, p. 676) and 62% of promotional spending. Doctors' sample cupboards are often overflowing with competing samples.

Samples are particularly clever gifts, because they can be used by well intentioned doctors for supposedly good purposes. It is argued that they are beneficial to impoverished patients, who would otherwise have to pay for drugs (Chew et al. 2002). This argument is particularly salient in the US, where many patients lack health insurance and are unable to afford medications, but it is also relevant in countries such as Australia.

In addition, samples are considered useful to patients and doctors because they can trial a drug without a prescription (Symm et al. 2006). Samples can also encourage patient compliance in taking drugs, including antidepressants (Bastiaens et al. 2000). According to Dudley (2007), they can also give patients hope. In a surprisingly candid article, Dudley, a family physician in Seattle, described giving a sample box of antidepressants to an elderly patient for his dying wife:

> I suggest that I think we may be able to help his wife with one of the new pills, an antidepressant. It works great and just may help perk her up.

> My patient reaches for the little box of pills as earnestly as if it were a life ring from the Titanic. He turns it over and over clumsily in his calloused hands, examining it every which way, this new little talisman. His face brightens. His tears dry up. He has hope. And I have played a part. I'm a hero. I like that.
>
> What I don't tell him is that it's not much different than older drugs, just newer and sexier — and pricier, once the free samples run out. We'll deal with that later.

Dudley also explicitly linked his use of samples to his receipt of gifts for himself, implying that the former justified the latter:

> As a doctor, he takes the free lunches and free pens. In turn, he gives out free samples – and hope.

However, there is increasing criticism of sample drugs, which often distort subsequent prescribing (Patounas & McGuire 2007). Both patients and doctors tend to prefer to continue drugs that they have already tried, unless there is a compelling reason to change, so whatever is dispensed as a sample is more likely to be prescribed in the future than it would otherwise have been.

Chew et al. (2002) found that many US physicians reported that they would dispense samples of drugs other than their preferred drug choice to uninsured patients, and would subsequently prescribe the same drugs. In relation to antidepressants specifically, most doctors were willing to dispense samples; nearly half were willing to compromise on the choice of antidepressant:

> For an uninsured woman with depression, 108 (82%) respondents reported that they would dispense a drug sample; 53 (49%) of 108 sample users indicated that they would dispense a drug sample that differed from their preferred drug choice. (p. 478)

The reported sample dispensing rate was much higher for antidepressants than for urinary tract infection drugs and hypertension drugs. However, the proportion of dispensers who reported willingness to dispense a drug other than their preferred drug, although high (49%), was much lower than for urinary tract infection drugs (95%) and hypertension drugs (91%). This relative reluctance to prescribe something other than the preferred drug is probably attributable to widely accepted claims that SSRIs are superior and safer.

Common acronyms in this chapter: ACCC Australian Competition and Consumer Commission; APA American Psychiatric Association; CGP clinical practice guideline; DSM Diagnostic and Statistical Manual (of Mental Disorders); DTCA direct-to-consumer-advertising; FDA Food and Drug Administration; KOL key opinion leader; NAMI National Alliance for the Mentally Ill; NARSAD National Alliance for Research on Schizophrenia and Depression; NIMH National Institute of Mental Health; PhRMA Pharmaceutical Research and Manufacturers of America; ROI return on investment; SSRI selective serotonin reuptake inhibitor; SNRI serotonin and noradrenalin reuptake inhibitor; TCA tricyclic antidepressant; TGA Therapeutic Goods Administration

Despite the evidence of the influence of samples, many doctors claim to be immune to the influence of samples (Symm et al. 2006). However, a recent industry survey found that US physicians reported that samples influenced their prescribing more than any other promotional activity (Verispan 2006). Furthermore, the pharmaceutical industry could not justify spending billions of dollars on production and distribution of samples if they were not effective marketing tools. According to Coyle and Brenner (2005, p. 26), 'One of the most powerful promotional tools in the industry is the distribution of product samples', and there is clear evidence of sharply increased prescribing when marketing campaigns are launched (Glogowski 2003). In addition, allied marketing companies such as IMS Health monitor the effect of samples not only on aggregate sales but also on individual doctors' prescribing, helping drug reps to customize the provision of samples to individual doctors (Sadek & Henderson 2004).

Doctors are likely to dispense the most recent samples they have received, for multiple reasons. Samples are usually accompanied by promotional materials such as pens and reprints, and substantial advertising in medical journals, so doctors are more likely to think of newer samples (Fugh-Berman & Ahari 2007, pp. 621-622). Storage issues also increase the likelihood of newer samples being dispensed, because they are at the front of storage cabinets (or still waiting to be stored). Samples can therefore help to drive fads in prescribing.

Samples are rarely generics, and are generally newer and more expensive than alternative drugs, particularly generics. An Australian study found that generics were rare in GPs' sample cupboards (Hall et al. 2006). In the US, some health insurers have started providing generic samples to doctors in an effort to reduce drug costs (Japsen 2006). One drug targeted for replacement by generics was the blockbuster antidepressant Zoloft® (sertraline).

Samples also discourage prescription of recommended first-line drugs. Boltri et al. (2002) compared antihypertensive prescribing in a family practice residency program before and after samples were prohibited, and found that prohibition of samples resulted in an increase in first-line drug use from 38% to 61%.

Samples are sometimes inadequately labelled (Hall et al. 2006) and dispensed without adequate information for patients about dosage, administration, and possible adverse

reactions and interactions (Patounas & McGuire 2007). Another issue is that drug samples are commonly used by physicians and office staff and drug reps for their personal and family use (Hall et al. 2006; Westfall et al. 1997).

7.5 KEY OPINION LEADERS

It is commonplace for drug companies to use senior doctors promote their drugs (Moynihan 2008b). Key opinion leaders (KOLs) (also referred to as thought leaders) are usually senior academics and specialist clinicians who are paid by the industry for participation in educational events, clinical trials, advisory groups, etc. They are often quoted in the media supporting favourable claims and/or disputing unfavourable claims.

The use of KOLs is a very important marketing strategy (Moynihan 2008b; Raven & Parry 2012). According to BusinessWire (2004), 'The average brand allocates nearly $40 million to support thought leader activities throughout the development cycle'.

KOLs' value is their blend of status and credibility. According to Elliot (2010):

> The KOL is a combination of celebrity spokesperson, neighborhood gossip, and the popular kid in high school. KOL's do not exactly endorse drugs, at least not in ways that are too obvious, but their opinions can be used to market them – sometimes by word of mouth, but more often by quasi-academic activities, such as grand-rounds lectures, sponsored symposia, or articles in medical journals (which may be ghostwritten by hired medical writers). While pharmaceutical companies seek out high-status KOL's with impressive academic appointments, status is only one determinant of a KOL's influence. Just as important is the fact that a KOL is, at least in theory, independent.

Burnside (2010) unflatteringly likened them to talkback radio hosts whose voices are for hire:

> Key Opinion Leaders are the medical profession's equivalent of talk back radio hosts. They are the people whose voices are powerful and there is no doubt whatsoever that the pharmaceutical industry courts them, flatters them, coaxes them and nourishes them with feelings of goodness and virtue expecting that they will pass on favourable messages about the sponsor's products.

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Moynihan (2008b) referred to KOLs as 'drug representatives in disguise' (p. 1402). He quoted a former highly experienced and successful US drug rep:

> drug companies desperately need key opinion leaders. "There are a lot of physicians who don't believe what we as drug representatives say. If we have a KOL [key opinion leader] stand in front of them and say the same thing, they believe it." (p. 1403)

One such KOL has described – years afterwards – how he was employed to persuade other doctors to prescribe Effexor XR® (Carlat 2007). He deprecatingly referred to himself as 'Dr Drug Rep', and described his discomfort with his role:

> Regardless of how I preferred to think of myself (an educator, a psychiatrist, a consultant), I was now classified as one facet of a lunch helping to pitch a drug, a convincing sidekick to help the sales rep. Eventually, with an internal wince, I began to introduce myself as "Dr. Carlat, here for the Wyeth lunch."

Specialists have considerable influence on GPs' prescribing habits (Florentinus et al. 2009). In Australia, Robertson et al. (2003) found that GP prescribing was influenced more strongly by specialists than GPs realised:

> Although GPs thought specialists had only a small influence on their prescribing overall, it was substantial in some clinical areas, in complex conditions and conditions seen infrequently. Specialists were seen as authoritative and unbiased. Local specialists were particularly influential. Specialist influence came from seeing how specialists managed patients, clinical meetings, and specific verbal advice. It influenced the prescribing of new drugs, selection of drugs within a class and sometimes changed established prescribing practices (p. 573)

Robertson et al. noted: 'This influence is well recognised by the pharmaceutical industry which uses visiting and local specialists as opinion leaders to promote new drugs' (p. 576). An industry survey of drug companies' use of KOLs (Cutting Edge 2009, p. 162) found that all 'tier 1' KOLs (the most influential and well remunerated) were specialists, sub-specialists, or had 'expert-in field' status. Only in tier 3 were there some (25%) KOLs who were primary care physicians.

KOLs also lend their names and reputations for payment by participating in industry-funded expert panels that develop treatment guidelines and algorithms (Raven & Parry 2012, p. 513). Industry influence on guidelines is discussed in section 7.13.

One very influential US KOL is Professor Michael Thase. According to Carlat (2007), Thase 'single-handedly put Effexor on the map with a meta-analysis'. That meta-analysis (Thase et al. 2001) was co-written by two Wyeth employees, and was

described by Wright (2002, p. 82) as 'a commercially valuable paper'. It has been criticised as biased (Warner 2001) and methodologically weak (Smith et al. 2002, p. 402).

Another important US KOL who has promoted Effexor is Professor Martin Keller, who toured Australia in 2002 at Wyeth's expense (Hughes & Minchin 2003). He had previously been found to have concealed hundreds of thousands of dollars of drug company payments (Bass 1999). Similarly, Professor Charles Nemeroff was found to have concealed from his employer, Emory University, large amounts of income from the pharmaceutical industry (Carlat 2009).

KOLs also play a crucial role in disease awareness campaigns. This is discussed in section 7.14. Two KOLs who have played very important roles in the Australian depression/antidepressant arena, Professor Graham Burrows (who participated in Keller's tour (*SA Medical Review* 2002)) and Professor Ian Hickie, are discussed in chapter 9.

7.6 MEDICAL EDUCATION

Much continuing medical education is provided and/or funded by pharmaceutical companies (Davis 2004; Elliot 2004). Postgraduate training is also often industry-funded (Sadun & Dunn 2008), as is some medical student education (Coombes 2009).

According to the pharmaceutical industry, drug companies play a very important role in doctor education, particularly about new drugs. For example, anticipating criticism on the eve of the release of the first ACCC report into industry relationships with doctors, Ian Chalmers, then Chief Executive of Medicines Australia, declared: 'We believe doctors' participation in such educational events is legitimate and in the best interests of patients' (AAP 2008).

Chalmers was seconded by the then President of the Australian Medical Association, Rosanna Capolingua, who was quoted as saying that:

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> "Pharmaceutical companies who research and develop medicines have the most extensive information about a therapeutic drug, including its benefits and possible side-effects, and pass on this information at education seminars.
>
> "It is a great advantage for doctors who attend these education seminars to be able to interrogate the manufacturers of the medicine, discuss and look at the data, and gain knowledge before prescribing it for their patients." (AAP 2008)

As mentioned in section 7.3, educational events have attracted criticism because of inappropriately lavish hospitality. More important, however, is bias in the content.

Medical education provided by pharmaceutical companies is first and foremost a form of public relations. This is clearly enunciated in industry publications. Elliot (2004, p. 18) quoted one insider:

> What's the difference between medical education and pharmaceutical public relations? Not much, according to the people who do it. "(T)he broad distinction between healthcare PR and medical education is becoming obsolete," writes Neil Kendle, chief executive officer of Lowe Fusion Healthcare, in a recent issue of Pharmaceutical Marketing magazine. So slender is the difference between education and PR than that Kendle cannot even say for certain which business he is in. "Sometimes I describe Lowe Fusion as a 'PR consultancy', sometimes as a 'healthcare communications agency'. Sometimes I just cop out and list the things we do."

Another industry insider explained that the purpose of health professional education is to support marketing:

> Medical communications can be defined as the strategic planning and development of educational programmes that serve to influence the behaviour of healthcare professionals and positively impact health outcomes for patients. Put another way, effective medical communication helps to build the reference and opinion framework that will form the basis of all promotional activities for a brand. (Roos 2009)

Neslin (2001, p. 21) reported a return on investment of $3.56 per additional dollar spent on physician meetings and events, second only to medical journal advertising.

Unfortunately, there is widespread naïvete about the motivation for, and effects of, industry involvement in medical education. Avorn (2007) gave this example:

> Years ago, an administrator at a community hospital explained to me how well his institution's grand-rounds program worked. "The drug companies find the speakers, pay their honoraria, and provide free food for the doctors, which helps a lot with attendance," he said. "It works well for us, especially with our budgets so tight." Yet those lunches were actually quite costly for the hospital: attendees at such events predictably go on to prescribe the products promoted there –

> which is precisely why the drug companies so willingly pay for these programs. (p. 1697)

Predictably, some doctors vociferously object to suggestions that they might be misled by industry education:

> It is insulting to think that doctors who are ostensibly smart enough to save one's life are in fact so stupid, or merely gullible enough, to be swept away by what is in actuality only a very weak potion of sales-presentation intermixed with and embedded within generally informative and pharmaceutical-balanced subject-focused medical lectures. (Bock 2010)

Of particular relevance to antidepressants in Australia, several pharmaceutical companies have been approved as providers of training that qualifies GPs for access to payments under the Australian Government funded Better Outcomes in Mental Health Care program. One industry training program, Wyeth's 'Time Efficient Mental Health – solutions for time poor GPs' (Rural and Remote Medicine Education Online 2008), received a marketing award in the 2008 Australian Pharmaceutical Research, Innovation & Marketing Excellence Awards, reflecting industry awareness that it is an effective *marketing* strategy. More significant is the SPHERE program, which is funded by Pfizer Australia. According to Lifeblood, an 'independent communications company' that combines pharmaceutical advertising and marketing with medical education, SPHERE 'assisted in restoring the market share and growth of the Pfizer antidepressant Zoloft®, restoring it to the Number One product in this market' (Lifeblood 2007). SPHERE is discussed briefly in chapter 9.

7.7 MEDICAL JOURNAL ADVERTISING

As mentioned earlier, medical journal advertising is a key marketing strategy. Doctors are the primary focus of prescribed drug advertising (Frank, Berndt, Donohue, Epstein, & Rosenthal 2002, p. 2), and medical journals are the most important channel for advertisements, which focus primarily on new and expensive drugs (Newby & Henry 2002, p. 285). Neslin (2001, p. 21) reported a return on investment of approximately $5.00 per additional dollar spent on journal advertising, higher than for drug reps, direct-to-consumer advertising, or physician meetings and events.

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Journal drug advertisements have been described by Smith (2003, p. 1202) as 'often misleading' and by Newby & Henry (2002, p. 285) as 'truths, half-truths and few statistics'. However, most medical journals are financially dependent on pharmaceutical advertising (Smith 2003, p. 1202). This creates potential conflicts of interest for journal editors, who are not oblivious to problematic content in advertisements but often turn a blind eye to it.

People tend to pay little conscious attention to advertisements (Ogilvy 1995). This reduces the likelihood of critical analysis. According to Keizer (1996, p. 67) drug advertisements exert their effect at a subcortical level. Medical journals, he argued, 'are filled with advertisements about medication in which the doctor is approached on the level of the housewife and her washing powder'. This is vividly expressed in this mock Prozac advertisement (http://www.dysthymia.com):

A detailed analysis of a 2008 *JAMA* advertisement for Pristiq® (desvenlafaxine; Wyeth) revealed multiple problems (Healthy Skepticism[8] 2010). Pristiq, a serotonin and noradrenalin reuptake inhibitor (SNRI) antidepressant, is an example of the use of chemical reformulation as a marketing strategy. It is a metabolite of Effexor®/Efexor® (venlafaxine), an established SNRI, which is approaching the end of its patent life in several countries. This is discussed briefly in section 7.20.

The main photograph shows a middle-aged man and an attractive younger woman smiling at each other while shopping together, or perhaps encountering each other while shopping separately. The meaning of the photo is ambiguous, but it is likely to be interpreted as an 'after' picture, showing not only successful treatment of depression, but also beneficial effects on relationships. However, no evidence is provided in the advertisement of Pristiq's effectiveness and safety relative to Effexor's.

The advertisement states: 'PRISTIQ may help your patients with depression – emotionally, physically, and functionally'. This claim widens the indication to

[8] I was the secondary author of this *AdWatch*.

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depression more generally rather than just major depressive disorder. Three references are given to support this claim:

1. Product information (which contains no information about comparative efficacy and safety except versus placebo).
2. Data on file. This suggests that relevant information has not been published.
3. A review of the Sheehan Disability Scale in a textbook published in 2000. This review does not mention Pristiq. Its use as a reference for this point is misleading, suggesting that it provides evidence of Pristiq's effectiveness. This book would not be readily available to most primary care practitioners, who prescribe the majority of antidepressants, so it would be hard for them to check what it says.

Predictably, many doctors deny being influenced by advertisements. Sidney Bloch, Editor of the *Australian and New Zealand Journal of Psychiatry*, responding to a comment about the intrusiveness of an antidepressant advertisement enveloping the journal, asserted that it was not a problem because doctors were neither stupid nor gullible:

> We've had wrap-around ads, we've had bookmarks in the journal, every drug company's marketing house will be thinking of some dodge or strategy to win the attention of the reader. My usual response is that our doctors are not stupid, and they will simply rip the wrap-around and dispose of it. They will take the bookmark and either use it or throw it in the bin. Nobody is gullible, and frankly it's never bothered me, because ultimately when you open the journal that's where it counts. (Australian Broadcasting Corporation 2002)

A letter to the journal (Jureidini & Mansfield 2003, p. 495) challenged Bloch's response, arguing that doctors' intelligence did not make them immune to the effects of advertising:

> We agree that your readers are intelligent. However, few of us have the advanced training in logic, statistics, advertising psychology, and evaluation of evidence or the time that critical appraisal of drug advertisements requires. Even if we did, there is no guarantee that critical appraisal skills would be enough to protect us from potential adverse influences acting outside of our awareness. Drug advertisements do not fool all of the doctors all of the time, but they are known to be effective enough on average to provide good return on investment otherwise drug companies would not pay for them. Wrap advertisements are designed to work during the seconds it takes to pick up a journal and rip them off. The fact that they are usually not given much attention enhances their influence by getting the message into our brains under the radar of critical appraisal.

Bloch (2003) responded to this challenge by asserting that 'our readers have the capacity to evaluate advertisements'. He further argued that the journal's independence

was not compromised because 'the advertising material is entirely separated from the editorial material' (p. 495). Such reasoning is commonly used by editors to justify the acceptance of drug advertisements.

7.8 JOURNAL ARTICLE REPRINTS

Reprints of journal articles are a very important promotional strategy for the pharmaceutical industry. As mentioned earlier, reprints are commonly given to doctors by drug representatives. They are also commonly distributed via the exhibit booths of pharmaceutical companies at conferences (Lurie et al. 2005). Reprints are usually accompanied by advertising materials, along with drug samples and gifts, and they are usually part of a coordinated campaign for a particular drug.

Reprint articles are selected by pharmaceutical companies for their potential to show company products in a favourable light. Not surprisingly, they are often reports of clinical trials funded by the companies themselves. There are substantial biases in industry-funded studies, as discussed in section 7.11, and reprints are a key channel via which the industry uses supposedly evidence-based medicine as a marketing tool. According to Smith and Roberts (2006, p. 1), reprints are a key vehicle for 'Publishing Partial and Biased Reports from Trials'.

Reprints come from a wide range of journals. However, two types of source journals are particularly noteworthy: highly prestigious generalist journals such as the *New England Journal of Medicine*, which has a much higher impact factor than any other medical journal (Smith 2006), and specialist journals whose editors have strong connections to manufacturers of drugs relevant to particular medical specialties. In the latter case, reprints are often from industry-funded supplements rather than regular issues of the journal. Supplements are discussed in section 7.9.

Reprints of supposedly high quality journal articles are viewed much more favourably by doctors than advertising materials (Spiller & Wymer 2001), whether or not doctors read them. Such reprints are probably also more likely to be filed away for future reference.

As mentioned earlier in relation to drug reps, reprints are most likely to be given to doctors who are regarded as skeptical (Fugh-Berman & Ahari 2007). Such doctors are likely to regard clinical trials as methodologically rigorous, but they often lack the critical appraisal skills necessary to analyse sources of bias, which makes reprints a potent marketing tool.

In fact, many of the reprints given to doctors do not support the claims made in the accompanying advertising materials. A Spanish study by Rivera Casares et al. (2005) found that 44.5% of advertising messages given to family doctors were not based on the studies that were claimed to support them. This suggests that doctors are not expected to carefully read the journal articles, and/or not expected to understand them sufficiently to realise that the claims are not supported.

Reprints are a very important source of revenue for journals (House of Commons 2005a, p. 56). Reprints are very profitable. For example, Merck bought 900,000 reprints of one article from the *New England Journal of Medicine*; Smith (2006) estimated that they cost between US$700,000 and $836,000, of which he estimated that $450,000 would have been profit (he commented that reprints have a very high profit margin). This creates potential conflicts of interest for journals, by giving them an incentive to publish industry-funded research studies with favourable results. The better a drug is claimed to be, the more likely an article is to be reprinted.

Publishers openly market their reprints to drug companies. The website of Lippincott Williams & Wilkins, the publisher of many psychiatric journals, promoted reprints in this way:

> The dedicated Pharma Solutions team provides a standard of care second to none. At a time when pharmaceutical and medical device brand loyalty is still flexible, our aim is to match your clients' blockbuster products with our world-leading titles….
>
> **Commercial Reprints**
>
> Promote your product with article reprints, from any published journal or supplement….
>
> Reprints can be used as:
>
> - High quality access tools that are economical and are produced to high professional standards
> - Reward for booth attendance at conferences
> - Educational door-openers for sales reps

- Support for new product launches and product development
- Vehicles to update target audiences with your key messages
- Custom marketing tools that disseminate information on your product to a wider audience
- Leave behinds for "hard-to-see" physicians

http://web.archive.org/web/20070416022547/http://www.lww.com/resources/healthcare/capabilities.html (25 August 2010).

Reprints also enhance the careers of the authors who write (or are credited with writing) the articles, boosting their profile and increasing the chance of citation of their articles. This gives authors greater credibility as key opinion leaders and consequently enhances their value to the industry.

Reprints played an important role in the market success of rofecoxib (Vioxx), a blockbuster nonsteroidal anti-inflammatory drug. Vioxx was released onto the market in 1999. In 2000, a *New England Journal of Medicine* article (Bombadier et al. 2000) was published, claiming that Vioxx users had fewer gastrointestinal side effects than people using an established alternative, naproxen. The manufacturer, Merck, bought 900,000 reprints of the article. In 2005, the *NEJM* published an 'expression of concern' about the article, detailing significant problems of omission, and concluding: 'Taken together, these inaccuracies and deletions call into question the integrity of the data on adverse cardiovascular events in this article' (p. 2814).

Smith (2006) argued that the *NEJM* was not only negligent in not publishing its concerns about the trial for several years, but also disingenuous for arguing that it was not their responsibility: 'The editors also point out that the correct data were on the FDA website; but there is a world of difference between data on a website and data included in the world's leading medical journal and being circulated in nearly a million reprints' (p. 2). Smith estimated that the *NEJM* made approximately US$450,000 profit from the reprints. As an ex-editor of the *BMJ*, he was well aware of both the power of reprints as a marketing tool and their value as a source of revenue to medical journals.

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In relation to antidepressants, Medawar (2003, p. 49), discussing the prominent UK psychiatrist and key opinion leader Stuart Montgomery, noted:

> Montgomery is also editor of a learned journal, *International Clinical Psychopharmacology,* itself a major source of information on prophylactic antidepressant use. The journal carries no drug advertisements, though many papers are by research staff from pharmaceutical companies and no doubt many reprints are purchased.

7.9 JOURNAL SUPPLEMENTS

Just as pharmaceutical companies commission reprints of medical journal articles to use for marketing purposes, they also commission supplements. Many medical journals, including some of the most prestigious ones, publish themed supplements at irregular intervals, funded by external sponsors. Journals obtain substantial revenue from supplements (Smith 2005, p. 0365).

Most medical journal supplements are funded by pharmaceutical companies, and they often publish the proceedings of industry-sponsored symposia to promote particular drugs (Bero et al. 1992). However, according to Rochon et al. (1994), individual articles in supplements frequently do not acknowledge industry links. This is particularly problematic when reprints of articles from supplements are distributed separately, as is often the case.

Unlike regular issues of journals, in which authors have had to compete to have their articles published, commissioned supplements are essentially commercial products with a relatively easy passage into print, provided the requisite fees are paid. Editorial standards for supplements are lower than for regular issues of journals:

> Journals' supplements to support the new release of a drug are a common practice; the fact that their articles are rarely peer reviewed and of lower scientific standard than those that are published in the regular issues of the journals, and that authors often received a fee for them, is not always appreciated and may mislead readers. (Fava 2003, p. 12)

Notably, randomised control trials published in journal supplements are generally of inferior quality to those published in the parent journals (Ellard 2001; Rochon et al. 1994). Open-label studies, which are much more prone to bias than blinded studies, are common in supplements.

In relation to antidepressants, Shorter and Tyrer (2003, p. 158) commented:

> The industry exerts a major influence through publication of sponsored supplements to journals, which are often poorly peer reviewed and promote unapproved treatments. Such supplements are particularly common for drugs for anxiety and depression as these are the most common treated conditions. Worldwide sales of antidepressants dwarf sales of drugs for all other psychiatric disorders.

7.10 THROWAWAY JOURNALS

Throwaway journals, sometimes referred to as 'controlled circulation journals' or 'tabloids', if they are in newspaper format (Frank 2004), or 'ephemerals', are very common in medicine. Most are funded by pharmaceutical companies and distributed free to doctors.[9] They are usually relatively thin and easy to read. Like supplements, throwaway journals are often used to promote new drugs. However, supplements have received more academic scrutiny than throwaway journals, partly because they are often held by medical libraries and so are more accessible to researchers.

Throwaway journals differ significantly from mainstream academic subscription journals in several important respects. In particular, they generally do not publish new research (Rennie & Bero 1990); instead articles tend to be opinion pieces and non-systematic reviews. Articles are rarely peer-reviewed in the normal academic sense, although throwaway journals often have distinguished editorial boards. According to Rennie and Bero (p. 891): 'Without exception [throwaway journals] have large collections of distinguished folk on their editorial boards'. However, such boards are often illusory: '[one member] writes that he was on the editorial boards of three throwaways and was never called upon to review anything' (p. 891). Rennie and Bero were scathing about such boards:

> No self-respecting physician should agree to be on the editorial boards of throwaways. They should be told by their friends that they are merely being used and that the honorarium is not worth the disgrace. (p. 892)

[9] A different and relatively new type of 'throwaway journal', not relevant to this discussion, is open access online journals of questionable quality that use spam emails to persuade authors to contribute articles, for which they are required to pay publication fees (Eysenbach 2008).

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The articles in throwaway journals are often very short and simple in structure. They are rarely cited in the medical literature, and are often not included in authors' curricula vitae. Throwaway journals, as their name implies, tend to be rapidly discarded and tend not to be included in medical libraries.

Nevertheless, the influence of these journals should not be underestimated. According to Key et al. (1979, p. 21), 'the controlled circulation journals we surveyed are read by and seem to fill some immediate reading needs for their targeted constituencies'. Furthermore, there is evidence that throwaway journals are 'more widely read than some peer-reviewed journals in the same subject areas' (Rochon et al. 2002, p. 2853). One reason for this is their very large circulations. In 1976, of 28 US medical publications with circulations of more than 70,000 physicians, 26 were throwaways (Dornette 1976, p. 14).

According to Rochon et al. (2002, p. 2853): 'Although lower in methodologic and reporting quality, review articles published in throwaway journals have characteristics that appeal to physician readers'. These characteristics include more photographs, more colour, larger print sizes, and appealing titles. Rochon et al. also found that throwaway journal articles required lower level reading skills and were judged by physicians as being more relevant to clinical practice. According to Kaplan (1991, p. 1109), 'if we are looking for easy-to-read review articles, information on primary patient care, or practical tips on improving practice, then we should look to the throwaways'.

In marketing industry parlance, throwaway journals are a form of 'strategic medical education' or 'strategic healthcare communications'. They are recognised as being potentially very valuable drug marketing tools. With large circulations, they are expensive commodities, but they clearly provide a good return on investment. Discussing a major psychiatric throwaway journal in the US, Carlat (2008) commented:

> *Psych Times* is a "controlled circulation" journal. This means that doctors don't have to subscribe to get it. In fact, every month it is sent for free to over 40,000 psychiatrists. Just about every last dime of the journal's income comes directly from the pharmaceutical industry. Companies pay extremely high prices for their ads … precisely because the journal can guarantee that ads will be viewed by 40,000 sets of prescribing eyes.

Criticism of throwaway journals has a long history. According to Key et al. (1976, p. 21):

> There has been mounting concern on the part of some that the pharmaceutical industry support of controlled circulation journals through advertising exerts undue influence on these publications – that they buy bias for their products; control or influence what is or is not written, as well as the content for articles published; and in general for glutting the printed word market with nonscholarly patter.

Such issues are not unique to throwaway journals and supplements. Medical journals in general have been criticised by many, including current and former editors (Horton 2005; Smith 2005). However, throwaway journals are generally considered worst of all. Rennie and Bero (1990, p. 889), two of the most strident critics of throwaway journals, described them as:

> Glossy journals that stuff up the mail of physicians; journals that academics sniff off as being harmless because they think no one reads them, or at any rate, takes them seriously. Well, they are very big business and a great many people outside medicine, who are trying to sell pharmaceuticals to doctors, take them very seriously indeed.

A number of editors of throwaway journals have defended their journals against such criticisms. Siwek (1992) emphasised 'the important role that review article journals play in meeting the continuing medical education needs of most practicing physicians'. Siwek also accused Rennie and Bero of insulting the intelligence of doctors, as did Kaplan (1991, p. 1109): 'It is clear from their recommendations that Rennie and Bero think that the average practitioner is a dumb boob who believes everything that is in a throwaway and blindly accepts the advertising'.

Dornette (1976, p. 16) argued that his *Journal of Legal Medicine*, a notably high-circulation throwaway journal, had a rigorous editorial process, and he challenged anyone 'to show any paucity of scholarship, lack of independence, bias, or need for governmental control' in it. It seems plausible that drug advertisements in his journal might have been less related to the content of articles than the advertisements in more clinically oriented journals. However, he revealed a degree of naivety in his statement that 'The advertising agency and pharmaceutical manufacturer hope the physician will read through the publication, note the advertisements, and consider prescribing or

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employing the drug the next time he [sic] needs one for that purpose' (p. 14). His use of the word 'needs' implies that doctors only prescribe drugs when there is a genuine need, and ignores the possibility that doctors might be encouraged to prescribe unnecessary drugs.

Rubin (1976, quoted by Key et al. 1976, p. 20) also defended the throwaway journal he edited (*Family Practice News*), saying 'If you thought that we were using our news columns to push the products being advertised, you'd stop reading us'. However, he acknowledged the value of his journal to advertisers:

> We're offering you useful and interesting information in exchange for your time and attention. In turn we sell advertising space to manufacturers who want to use the attention we have traded for to get you to see their ads. They advertise in our paper because they are convinced that you find … [it] interesting and that you read it regularly.

Whether or not the news columns 'pushed' drugs, clearly drug companies believed that his journal was effectively promoting their brands.

Throwaway journals are used strategically by drug companies. They play an important role in the promotion of drugs. Advertising and articles in throwaway journals are often used early in a brand's lifecycle, as part of an intensive launch campaign. Strickland-Hodge and Jepson (1982) found that throwaway journals were more highly rated by doctors who were 'early adopters' – those who start prescribing new drugs earlier than their peers. Throwaway journals are also used to promote off-label prescribing (Fugh-Berman & Melnick 2008; Loder 2005; Uretsky 2004).

In addition, throwaway journals are sometimes used to address concerns about the safety of medications. In Australia in 2002, Merck used a 'fake' journal, the *Australasian Journal of Bone and Joint Medicine*,[10] to reassure the medical profession about the safety of the blockbuster nonsteroidal anti-inflammatory drug Vioxx, which was withdrawn from sale in 2004 because of its potential to cause heart attacks and strokes (Rout 2009; Moynihan 2009). The journal was published by Elsevier, a mainstream academic publisher that has a sideline producing company-sponsored journals as strategic medical education.

[10] Issue 1(1) was published as the *Australasian Journal of Musculoskeletal Medicine*.

In summary, throwaway journals have inferior content to that of mainstream medical journals but they are appealing to many doctors and they are an important marketing tool for drug companies.

7.10.1 *Managed Care* magazine

The monthly throwaway magazine *Managed Care* is very prominent in the US managed care industry. The content of the magazine varies from chatty news items to relatively academic referenced articles. In addition to the magazine, the publishers produce themed supplements, which undergo a 'peer review' process that adds to their credibility. Some are eligible for continuing education credit for doctors and/or pharmacists.

A number of supplements have focused on depression. Not surprisingly, they have been sponsored by antidepressant manufacturers, particularly GlaxoSmithKline. Generally the pharmaceutical company sponsors a panel or meeting of key opinion leaders. The proceedings are written up by marketing professionals such as The Zitter Group, which 'helps life sciences and medical product manufacturers work more effectively with managed care companies' (http://www.zitter.com).

The supplements have a moderately academic appearance, with references, tables, and figures. However, they are more strongly rhetorical than most academic publications. Among the article titles are:

- Depression Is Prevalent and Pernicious, Costing Employers Billions Each Year
- Depression's Ripple Effect on Health Status and Costs
- Depression: Underdiagnosed, Undertreated, Underappreciated
- Advances in Drug Therapy Have Improved Outcomes

Not surprisingly, given that antidepressants are one of the most costly drug classes (IMS Health 2007), economic issues feature prominently in these supplements. An important strategy used by GlaxoSmithKline was the establishment in 2002 of the 'Economic Working Group', which comprises 'professionals from managed care, behavioral health, psychiatry, pharmacy, academia, health care policy and accreditation, primary care, health economics and outcomes research, and the

employer sector' (Zitter Group 2005, p. 2). The Economic Working Group has been involved in the production of several supplements, including one unsubtly titled 'Undertreatment of Depression and Comorbid Anxiety Translates Into Costly Mismanagement of Resources and Poor Patient Outcomes' (Zitter Group 2005).

Another of GlaxoSmithKline's Economic Working Group supplements is titled 'Diagnosing and Treating Depression In a Managed Care Environment: Concerns, Perceptions, and Misperceptions' (Zitter Group 2004). One of the 'misperceptions' addressed head-on is overuse of antidepressants: 'A large percentage of my patients who are prescribed antidepressants never complete their course of therapy. Perhaps they did not need the drugs in the first place'. The response begins: 'No MEDLINE studies documenting overdiagnosis or overtreatment of depression could be located' (p. 7). However, only on the back of the title page of the supplement (p. 2), less likely to be read by clinicians and HMO managers, is it explained that only studies published within the previous three years were included in the literature review. As discussed elsewhere in this thesis, there is documented evidence of overdiagnosis of depression (chapter 4) and overuse of antidepressants (chapter 6). Three relevant studies that were not published within the arbitrarily chosen three-year period are Klinkman et al. (1998), Tiemens et al. (1999), and Ornstein et al. (2000). Furthermore, an important study suggesting overuse of antidepressants (Zimmerman et al. 2002) was published *within* the three-year period. This is a clear case of biased literature search and selective and misleading reference citation.

7.11 RESEARCH FUNDING AND RESEARCHER FINANCIAL TIES

In the US, the majority of biomedical research is funded by industry (Institute of Medicine 2009, p. S-2). Most drug trials are funded by pharmaceutical companies.

Many researchers personally receive industry funding (Yank et al. 2007, p. 1), and they often have additional financial ties to drug companies (Henry, Doran et al. 2005). In a systematic review of the scope and impact of financial conflicts of interest in biomedical research, Bekelman et al. (2003, p. 456) reported that:

> Studies suggest that 23% to 28% of academic investigators in biomedical research receive research funding from industry. A 1998 survey found that 43% of investigators also receive research-related gifts, including biomaterials and discretionary funds. Approximately one third of investigators at academic

> institutions have personal financial ties with industry sponsors. Earlier studies have shown that 37% of investigators in the National Academy of Sciences had "dual affiliations" with both universities and companies. A 1992 analysis of 789 articles from major medical journals found that 34% were written by lead authors with relevant personal financial interests in their research (ie, company patents, equity, or advisory board, or director positions).

Bekelman et al. concluded that 'the financial ties that intertwine industry, investigators, and academic institutions can influence the research process' (p. 463).

Many studies have found that industry-funded research is significantly more likely to produce results favourable to the sponsors. This is the case in terms of efficacy (Davidson 1986; Cho & Bero 1996; Yaphe et al. 2001; Kjaergard & Als-Nielsen 2002), safety (Stelfox et al. 1998), and economics (Friedberg et al. 1999) across a broad range of drug classes. This has implications not only for clinical practice but also for subsidisation via mechanisms such as the Australian Pharmaceutical Benefits Scheme.

Industry-favourable results are not necessarily attributable to inappropriate research conduct. They could be due to selective funding of drugs likely to be effective (Bekelman et al. 2003, p. 463). However, there is abundant evidence of significant biases in the methodology and reporting of industry-funded trials (Schott et al. 2010; Sismondo 2008; Bhandari et al. 2004), including psychiatric drug trials (Heres et al. 2006; Tungraza & Poole 2007).

Heres et al. (2006) found that 79% of head-to-head comparison trials of atypical antipsychotics were sponsored by industry. In 90% of those trials, the overall outcome favoured the sponsor's drug. This resulted in conflicting conclusions in studies comparing the same drugs for different sponsors, reflected in the paper's humorous title, 'Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine'.

Heres et al. (2006, p. 185) reported that most sources of bias were 'subtle rather than compelling'. They included dosage and dose escalation, participant inclusion criteria, statistical analyses, reporting of results, and wording of findings. However, according

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to Heres et al. (p. 190), industry-funded trials were often methodologically superior to non-industry-funded trials.

A more recent review of trials by Schott et al. (2010) similarly found that the methodological quality was no worse in industry-funded trials, but protocols were often advantageous to sponsors' drugs, for example by comparing them to placebo rather than an active control (p. 284). Overall, industry-funded trials were more likely to have findings favouring the sponsor's drug than independently funded trials, and the results were more likely to be *interpreted* favourably (p. 279).

Another important factor is publication bias, particularly suppression and selective reporting of results (Bekelman et al. 2003, p. 463; McGauran et al. 2010; Jureidini et al. 2008). In an Australian study by Henry, Kerridge et al. (2005), significant numbers of medical specialists involved in industry-funded research reported delayed publication or non-publication of key negative findings (6.7% and 5.1% respectively), and concealment of results (2.2%). Overall, 8.6% reported at least one event that could represent a breach of research integrity.

A more extreme problem is the active suppression of unfavourable research findings against the wishes of researchers. Shuchman (2000) documented the cases of several medical researchers who were harassed and threatened by pharmaceutical companies attempting to suppress their research findings.

One important strategy for addressing some of these problems is mandatory registration of clinical trials at inception, to prevent post hoc manipulation of outcome measures and so on. Since 1 July 2005, the International Committee of Medical Journal Editors (ICMJE) has required that trials published in ICMJE journals (including the *Medical Journal of Australia*) be registered (De Angelis et al. 2004). However, an analysis of randomised controlled trials published in 2008 in leading (high impact factor) journals (Mathieu et al. 2009) found that only 45.5% were adequately registered and selective outcome reporting was prevalent.

Not surprisingly, pharmaceutical companies selectively fund research that is ultimately likely to demonstrate the efficacy and/or cost-effectiveness of their drugs (Fried et al. 2008, p. 60), so many potential avenues of research (particularly non-pharmacological interventions) are ignored.

According to Jureidini & Mansfield (2001), much industry-funded research is little more than a marketing exercise:

> many so-called research studies seem designed to familiarise doctors with drugs and encourage their use, rather than to contribute to scientific knowledge. This may be particularly the case where doctors are flattered (and financially rewarded) by invitations to participate in international, multicentred trials. In such cases, invited centres are not required to make any scientific contribution to the process. The first author was recently approached with a request to participate in a multicentre trial of an SSRI drug for Obsessive-Compulsive Disorder. He was offered the status of 'chief investigator' if he could provide patients, even though he has no particular expertise in the area being researched, or in drug trials. (Jureidini & Mansfield 2001, p. 97).

Researchers' industry ties influence a wide range of their publications, not just reports of clinical trials:

> A high and increasing proportion of biomedical researchers have financial ties to the pharmaceutical industry. Such researchers are more likely to publish articles—economic analyses, reviews, opinion pieces, and even randomised controlled trials—that support products produced by the industry. (Yank et al. (2007, p. 1)

In support of these claims, Yank et al. analysed 124 meta-analyses (about hypertensive drugs), and found that they were influenced by industry funding. Although meta-analyses with financial ties to one drug company were no more likely to have *results* favouring that company's drugs, they were more likely to have favourable *conclusions*. Furthermore, peer reviewers and journal editors allowed publication of biased conclusions.

Industry funding also influences the policies and practices of universities and teaching hospitals. David Healy, a prominent British psychiatrist, was offered a job at the Centre for Addiction and Mental Health, a teaching hospital of the University of Toronto. The job also carried with it a teaching appointment at the University. When he spoke at a seminar organised by the Centre about the potential for antidepressants to cause suicide, he controversially had the job offer abruptly withdrawn and also consequently lost the teaching appointment. The Centre had received substantial funding from Eli Lilly (the manufacturer of Prozac), SmithKline Beecham, and other pharmaceutical companies (Healy 2002).

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It is often argued that industry funding of drug trials is necessary because only the industry has the resources to fund them. For example, according to Sidney Bloch, Professor of Psychiatry at the University of Melbourne, and Editor of the *Australian and New Zealand Journal of Psychiatry*:

> I think we have to go hand in hand, because there's no way that any other institution on earth can produce new good drugs. It has be these gigantic big pharmaceutical houses, because it is so expensive to put out a drug. (Australian Broadcasting Corporation 2002).

This argument overlooks the fact that drug companies' huge resources are determined by the profitability of their drugs, which the public pay for, often via governments. It also glosses over the fact that much early drug research is actually publicly funded (Angell 2010). Much less often, it is argued that industry funding of pharmaceutical trials should not occur at all (Doucet & Sismondo 2008).

Industry spokespeople frequently endorse guidelines that are intended to regulate researchers' relationships with industry. For example, Spilker (2002) declared on behalf of Pharmaceutical Research and Manufacturers of America:

> We support the policies set forth in September by thirteen journal editors to ensure the independence of academic researchers who participate in industry-sponsored trials, and we encourage all authors to abide by them. (p. 244)

Such assurances are dishonest, given drug companies' ongoing manipulation of research (Henry, Kerridge et al. 2005; Gøtzsche 2005; Sismondo 2008).

7.12 GHOST-WRITING

Ghost-writing – writing by people who are not revealed as the authors of publications – is common practice in the medical literature. Ghost-writing is a form of plagiarism, but one to which the actual authors generally consent. It is an important means by which pharmaceutical companies arrange for favourable information about their drugs to be published in influential arenas.

Ghost writing is also common in non-medical literature, particularly autobiographies. Sometimes an elite sportsperson or other celebrity engages and pays a professional writer to write their life story as if it was in their own words, but generally much more literate than they would be capable of, and polished to suit the target public audience. Alternatively, a publisher will offer the celebrity a contract and provide the

ghostwriter(s). In a high-profile case in 2006, the then 20-year-old Manchester United striker Wayne Rooney signed a five million pound deal with HarperCollins for five 'autobiographical' books (Adams 2006). Ghost-written fiction is also quite common (Adams 2006), and ghost-written music has a history centuries old, with Wolfgang Amadeus Mozart believed to have written music for wealthy patrons to pass off as their own (Wikipedia 2010).

There are degrees of ghost-writing. At one extreme, the nominal authors have not written the piece at all. In most such cases in the medical literature, the actual authors are employees of pharmaceutical companies, or employees of industry-affiliated communication companies, or freelance writers working for such companies. Alternatively, the nominal authors may be given a fairly comprehensive draft and asked to contribute a small amount of extra content. This may help to make their authorship more plausible, by putting their 'stamp' on it, and no doubt it also makes it easier for nominal authors to justify their role to themselves. Most nominal or semi-nominal lead authors are key opinion leaders (KOLs) with significant publication records who will nevertheless benefit from additional publications, particularly in high-profile journals.

In some much milder cases, the stated authors have done most of the writing, but undisclosed other people have made substantial contributions to the content. Such cases blur with unattributed editing and helpful advice from colleagues, students, and other non-industry players. Ghost-writing also overlaps to some extent with honorary authorship – the routine listing of a person in power, such as an academic supervisor, laboratory head or department chair, as a co-author (sometimes lead author) of all papers emanating from a research group or laboratory or department, regardless of whether or not that person has met accepted criteria for authorship.

What is most relevant is journal articles largely or entirely written by pharmaceutical company employees or contractors. According to Healy (2004), approximately half of the published articles on medicinal drugs are ghost-written, and pharmaceutical companies are likely to have had a 'determining role' in writing most of the other half.

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Ghost-writing is a win-win situation for pharmaceutical companies and KOLs. Pharmaceutical companies get carefully crafted articles, favourable to their drugs, published in reputable medical journals, in the name of respected experts who are generally regarded as unbiased. Such articles are vastly more effective marketing tools than anything openly penned by the companies. These articles are efficiently distributed to doctors and medical libraries. They are often publicised by journalists. They are regarded as credible and authoritative. The selectively disclosed findings take their place in the jigsaw of evidence-based medicine; once there, they are difficult to dislodge.

Nominal authors also benefit significantly. They gain additional publications on their curricula vitae, which are very important for tenure and promotion and when applying for research funding. They also boost their academic profiles, and sometimes also their public profiles, if the articles attract significant media attention. In addition, they are often paid honoraria by the pharmaceutical company.

Pharmaceutical companies have been caught out over ghost-writing on a number of occasions. Madsen (2006) found drug company commentaries in a paper he was reviewing for publication when he turned on Track Changes. Fugh-Berman (2005) reported having turned down the opportunity to have an industry-written paper published in her name, then being asked by a medical journal to review that same paper some time later, with another clinician's name on it. The pharmaceutical company, AstraZeneca, unconvincingly argued that it was a mistake (they had inadvertently sent a completed paper written by a genuine author) rather than a case of ghost-writing.

7.13 CLINICAL GUIDELINE DEVELOPMENT

Many clinical guidelines have strong links to the pharmaceutical industry. At a minimum, it is likely that the majority of experts who develop treatment guidelines and algorithms will be key opinion leaders (KOLs) with financial ties to industry. Very often, drug companies pay KOLs to participate on guideline panels, their names and reputations providing credibility. Healy (2006, p. 145) referred to industry-manipulated guideline development as a form of 'manufactured consensus'.

Fried et al. (2008, pp. 60-61) provocatively questioned whether guidelines should be evidence-based, in part because of the industry's capacity to subvert evidence-based clinical trials:

> Large trials mean high costs, and this means that the decision to perform a trial depends heavily on the resources of the pharmaceutical industry which, not surprisingly, therefore, sets the agenda. The priorities of the pharmaceutical industry, in terms of disease targets and the entities that are chosen to test, might not reflect the needs of patients or the community. The goals of industry can, therefore, become the hidden agenda behind the generation of much of the evidence that is used to construct guidelines. The profusion of clinical trials in lucrative diagnostic categories is testament to this phenomenon. (pp. 60-61)

Sometimes the tactics used by drug companies to influence guidelines are overtly aggressive. As mentioned earlier, Shuchman (2000) has documented cases of pharmaceutical companies using intimidation to attempt to prevent researchers from releasing their own research findings. Similar tactics sometimes occur in relation to development of clinical guidelines:

> From 1997 to 1999, Anne Holbrook, MD, PharmD, MSc, a physician and pharmacist based at McMaster University in Toronto, Ontario, Canada, led a panel preparing guidelines for treatment of peptic ulcer disease and reflux. The panel concluded that three different proton-pump inhibitors could be used interchangeably in affected patients. Holbrook sent draft guidelines to all of the pharmaceutical companies that marketed products in this field and asked them to comment. In reply, she received an intimidating letter from a large Toronto law firm representing AstraZeneca, the makers of omeprazole (Prilosec or Losec). (p. 1013)

One very important and influential case of industry-funded guideline development related to antidepressants is the US industry-funded TMAP (Texas Medication Algorithm Project). TMAP commenced in 1995, funded initially by Janssen Pharmaceuticals (Johnson & Johnson), the manufacturer of the atypical antipsychotic Risperdal (Healy (2006, p. 137). Other psychotropic manufacturers subsequently provided further funding. Many of the consultants on the expert panel had financial links to Janssen and the other drug companies. The guidelines and algorithms developed were endorsed by the Texas legislators, and became mandatory in the Texas public mental health system. They were also marketed to other US states. According to Healy, TMAP 'endorsed the use of SSRI antidepressants for treating

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childhood nervous disorders, largely on the basis of a series of unpublished trials' (pp. 144-145).

More recently, Cosgrove et al. (2009) analysed the financial links between authors of American Psychiatric Association clinical practice guidelines (CPGs) for major depressive disorder, bipolar disorder, and schizophrenia. They reported that:

> Ninety percent of the authors of 3 major CPG in psychiatry had financial ties to companies that manufacture drugs which were explicitly or implicitly identified in the guidelines as recommended therapies for the respective mental illnesses. None of the financial associations of the authors were disclosed in the CPG. (p. 228)

Financial ties included receipt of research funding, consultancies, membership of corporate or advisory boards, receipt of honoraria, participation in company speakers bureaus, and equity holdings. Furthermore, multiple ties were the norm, representing intertwining of interests rather than incidental convergence.

7.14 DISEASE AWARENESS CAMPAIGNS

Pharmaceutical companies are increasingly using disease awareness campaigns as a marketing strategy. Such campaigns aim to increase public awareness of and concern about diseases or disorders. They encourage people who think they might suffer from these disorders to seek treatment. In essence, disease awareness campaigns 'sell' diseases or disorders in order to sell drugs.

Disease awareness campaigns often include direct-to-consumer advertising (DTCA). However, unbranded advertisements – which do not mention a drug (but often mention a drug company, if only in the form of small print or a logo) – also play a major role. This is a form of de facto DTCA, which is less strictly regulated because it does not mention specific drugs.

The main target audience of disease awareness campaigns is the general public, who are accessed via mainstream media and, increasingly, social networking. Many people are receptive to disease awareness campaigns. This is certainly the case with depression: patients are often happy to accept the construction of depression as a disease (Shooter 2003, p. 325).

Doctors and other health professionals are also targeted, particularly via key opinion leaders (KOLs), who play a crucial role in disease awareness campaigns. As mentioned in chapter 2, a key strategy used early on to develop a viable antidepressant market was the drug company Merck's purchase and distribution to GPs of 50,000 copies of Ayd's (1961) monograph, *Recognizing the depressed patient* (Healy 2004, p. 8). This was an early example of using a KOL in a disease awareness campaign (probably before the term was invented) to sell a disorder in order to sell a drug.

More recently, disease awareness campaigns have been used to promote SSRIs. In the US:

> Manufacturers of SSRIs encouraged doctors to watch for depression, and the reduced stigma afforded by the new medications induced patients to seek help. As a result, diagnosis and treatment for depression doubled over the 1990s. (Cutler & McClellan 2002, p. 21)

Governments are also targeted by disease awareness campaigns, both directly and via the influence of the medical profession and the media and public opinion. In Australia in the 1990s, leading psychiatrist Professor Graham Burrows and other KOLs, in conjunction with the Mental Health Foundation of Australia, very effectively promoted depression as a disease and as a major neglected social problem. They simultaneously promoted two antidepressants, using the *Depression Awareness Journal*, an industry-funded throwaway journal, as a powerful marketing tool that sold depression as well as antidepressants, and ultimately influenced government mental health policy. This is discussed in detail in chapter 9.

Like key opinion leaders, consumer/community organisations play an important role in disease awareness campaigns (Moynihan, Heath, & Henry 2002, p. 886; Weinstein (2004, pp. 136-138). The role of consumer/community organisations is discussed in section 7.19.

A key critic of disease awareness campaigns has been Australian health journalist Ray Moynihan. According to him, disease awareness campaigns often involve inappropriate medicalisation of everyday problems: shyness is transformed into social phobia, to be treated with antidepressants; baldness and erectile dysfunction are similarly turned into diseases to be medicated (Moynihan et al. 2002).

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Disease awareness campaigns are usually part of a larger marketing strategy that involves multiple players:

> Within many disease categories informal alliances have emerged, comprising drug company staff, doctors, and consumer groups. Ostensibly engaged in raising public awareness about underdiagnosed and undertreated problems, these alliances tend to promote a view of their particular condition as widespread, serious, and treatable. Because these "disease awareness" campaigns are commonly linked to companies' marketing strategies, they operate to expand markets for new pharmaceutical products. (Moynihan et al. 2002, p. 886)

Doctors are not always happy with medicalisation of problems such as distress. According to Mike Shooter, President of the Royal College of Psychiatrists and a 'patient with a recurrent depressive disorder myself' (Shooter 2003, p. 824), doctors are often pressured into prescribing as requested by patients, who are influenced by the pharmaceutical industry:

> [patients] are equally susceptible to social and commercial pressures…. an increasing number of people seek a pill from their doctor as a panacea for social distress. The pharmaceutical industry, with fewer diagnoses than it needs to absorb its products in a competitive market, is only too willing to oblige. Doctors, standing at the gateway between illness and non-illness, could resist this medicalisation of unhappiness. But time constraints on consultation, the insidious advertising of new preparations, and a need to be seen to be doing something quickly, all increase the pressure to diagnose and treat. (p. 825)

Disease awareness campaigns are referred to by Australian health journalist Ray Moynihan as 'disease mongering' – 'the selling of sickness that widens the boundaries of illness in order to grow markets for those who sell and deliver treatments' (Moynihan et al. 2008, p. 06894). Not surprisingly, the disease-mongering label is strenuously rejected by industry (Pharma in Focus 2010; Lush 2007).

Other terms related to disease awareness campaigns include 'condition branding' and 'disease branding' (Angelmar et al. 2007). Viewed from the perspective of Wiener's (1981) 'arena analysis', disease/condition branding can be used to 'redefine the scope' of a condition, as a way of 'legitimizing the problem' (p. 21), This long quote from Parry (2003) describes a striking example of this process (and the pivotal roles of a KOL and a cooperative government agency):

> No therapeutic category is more accepting of condition branding than the field of anxiety and depression, where illness is rarely based on measurable physical symptoms and, therefore, open to conceptual definition….

> A legendary example of this condition branding strategy was the development of Xanax (alprazolam) for panic disorder in the 1970s [when] panic disorder fell under the broad category of anxiety neurosis. Without a well-branded condition, patients experiencing panic attacks often went to cardiologists, thinking their problem was a heart condition, only to be labeled "cardiac complainers" and hypochondriacs due to a lack of physical pathology.
>
> Dr. David Sheehan, a pioneering thought leader in the field of panic, helped characterize the condition and push for a new way to diagnose and treat it. Upjohn, the makers of Xanax, helped fund this early research, as well as publications and speaking tours to cardiologists to help raise awareness of the heart-brain connection in the minds of panic disorder patients. Xanax was the only benzodiazepine to be studied that showed clear evidence of effectiveness. Through an unrestricted grant to the National Institute of Mental Health, a three-day thought leader conference resulted in a published consensus on the diagnostic criteria of panic disorder and how best to treat it.
>
> Xanax was the first to receive an exclusive indication, thereby maintaining its leadership in anxiety disorders. Since the release of DSM-III in 1980, which first recognized panic disorder as a distinct condition, its incidence has grown 1,000-fold, and newer antide-pressants have stepped in to foster expanding ideas about panic.

Angelmar et al. (2007, p. 345) provided an example of condition branding being used to redefine depression as a *chronic* condition, citing Scott's (2006) pointedly titled *BMJ* article, 'Depression should be managed like a chronic disease':

> The time course of the condition can be defined as acute, intermittent/cyclic or chronic. How the time path is defined influences when and for how long the condition should be treated. For example, depression can be defined as an acute condition requiring temporary treatment. Alternatively, it can be seen as a chronic condition requiring life time treatment. [Scott 2006] (Angelmar et al. 2007, p. 345)

7.15 DIRECT-TO-CONSUMER ADVERTISING[11]

As discussed earlier in this chapter, doctors are the primary focus of prescribed drug advertising, because patients cannot legally obtain prescribed drugs without a prescription. However, controversially, direct-to-consumer advertising (DTCA) – advertisements for prescribed drugs published or broadcast in mass media – has become big business. DTCA is a potent marketing strategy skilfully utilised by the

[11] This section draws heavily on Raven (2004).

Common acronyms in this chapter: ACCC Australian Competition and Consumer Commission; APA American Psychiatric Association; CGP clinical practice guideline; DSM Diagnostic and Statistical Manual (of Mental Disorders); DTCA direct-to-consumer-advertising; FDA Food and Drug Administration; KOL key opinion leader; NAMI National Alliance for the Mentally Ill; NARSAD National Alliance for Research on Schizophrenia and Depression; NIMH National Institute of Mental Health; PhRMA Pharmaceutical Research and Manufacturers of America; ROI return on investment; SSRI selective serotonin reuptake inhibitor; SNRI serotonin and noradrenalin reuptake inhibitor; TCA tricyclic antidepressant; TGA Therapeutic Goods Administration

pharmaceutical companies, which in recent year have spent huge amounts of money on advertisements in mainstream media to raise public awareness of particular drugs. Prescribed drug advertisements now appear in many newspapers (both print and web editions) and magazines, and on websites, radio, and particularly television.

7.15.1 Which drugs?

DTCA focuses on a relatively small number of drugs (Frank et al. 2002, p. 2). Many of them are so-called 'lifestyle drugs' (Lexchin 2001; Gilbert, Walley, & New 2000), rather than drugs with demonstrated public health benefits. Commonly advertised drugs include impotence drugs, weight-loss drugs, baldness drugs, antidepressants and anxiolytics (anxiety-reducing drugs), arthritis drugs, and heartburn/ulcer drugs.

Another common focus of DTCA is me-too drugs. Usually these are expensive new drugs touted as superior replacements for established drugs. One prominent example is newer nonsteroidal anti-inflammatories (NSAIDs) such as Celebrex®, which have been claimed to be safer than older, cheaper NSAIDs and other analgesics, a claim not supported by the evidence (Lexchin 2004).

Antidepressants are prominent in terms of DTCA: In 2000, Paxil (paroxetine, GlaxoSmithKline), an SSRI, the eighth largest selling drug in the US, had the fourth highest DTCA expenditure (US$91.8 million) (National Institute for Health Care Management (NIHCM) 2001, p. 7) and US$1808.0 million in sales (p. 8). Antidepressants are advertised extensively in magazines (particularly women's magazines) and on television. According to the NIHCM:

> Paxil and Prozac compete against each other in the antidepressant market. Paxil was the 8th largest selling drug in 2000. Its sales were up 25%. That made it the 13th largest contributor to the overall spending growth in 2000. Prozac was the 4th largest selling drug in the retail market but its sales were up only 5%. That relegated it to 49th place as a contributor to spending growth. The difference in the two drugs sales growth was perhaps related to their DTC promotion. Paxil's maker, GlaxoSmithKline, spent $91.8 million promoting the drug to consumers. In contrast, Eli Lilly spent only $23.3 million promoting Prozac to consumers in the last full year the drug had patent protection.

In recent years several antidepressants including Paxil have been promoted for the treatment of social phobia and other anxiety disorders. A major reason is that many of the best-selling antidepressants have reached or are approaching the limits of their patent protection. It is not unusual for drugs at that stage be promoted via DTCA for new indications (Frank et al. 2002, p. 3). A prominent case of DTCA promotion for a

new indication is the reformulation of Prozac as Sarafem for premenstrual dysphoric disorder (PMDD). Prozac's patent protection ended in 2001; Sarafem is patent protected until 2007 (Rebensdorf 2001).

7.15.2 Content of DTC advertisements

The content of DTC advertisements includes many tried and true persuasion techniques, including many of the same strategies as used in advertisements in medical journals, as well as some distinctive other strategies. The target behaviour is not the direct purchase of drug products, but the persuasion of doctors to prescribe them. This is more challenging than advertising directly to doctors. However, drug companies are able to tap into powerful emotional factors, including the value of health (one's own or that of loved ones), the fear of disability, self-consciousness, and shame.

Statistics are sometimes quoted. They generally focus on the prevalence of disease, and the prevalence of untreated disease, but rarely on the effectiveness of drugs (as is the case with medical journal advertisements (Loke et al. 2002)).

Many advertisements encourage people to consult their doctors. Sometimes materials (e.g. symptom quizzes) are provided for people to take to their doctor to discuss. For example, Eli Lilly's Prozac.com website offers the opportunity to 'Take a self-assessment test', which is based on Zung's (1965) self-rating depression scale. The website advises:

> If your score is 50 or higher, consider printing the results of your test to show it to your doctor. Ask him or her to evaluate you for depression.
> Please Note: Only a health care professional can actually diagnose clinical depression. (http://www.prozac.com/common_pages/quiz.jsp, accessed 18 July 2005)

Advertisements in medical journals often depict patients as passive, needy, even annoying people, in need of doctors' expert help. DTC advertisements, however, portray consumers more positively. They may be in need of treatment, but they are often active decision-makers taking responsibility for their own health in partnership with their doctor. In keeping with principles of market segmentation, the models and

actors used are carefully chosen not only for their relative attractiveness, but also to fit particular demographics, for example mothers with school-age children.

7.15.3 History and legal status

According to Davis (1997, p. 93) advertising has historically been a key issue in the status of drugs:

> In contrast to the patent medicine sector promoting remedies to the public at large, pharmaceutical companies were concentrating on selling higher quality medicines to doctors. Such medicines were known as 'ethicals'. This originally meant that they were honest – in their therapeutic claims – but came to mean that they were advertised only to the medical profession and not directly to the public.

DTCA therefore violates the traditional meaning of 'ethical' drugs. However, that term is still used for drugs that are advertised to the public, for example Prozac:

> Eli Lilly and Co., a leading maker of prescription drugs, is well known for its popular Prozac antidepressant drug. It also produces a wide variety of other ethical drugs and animal health products. (BusinessWeek 2005)

DTCA is banned in many countries, including Australia. The only industrialised countries in which DTCA is allowed are New Zealand and the United States (Toop et al. 2003, p. iii). However, the pharmaceutical industry is exerting considerable pressure on governments to legalise it. Also, in many countries, including Australia, the industry is also increasingly engaging in de facto DTCA, including unbranded advertisements in which in high-profile drugs are not mentioned by name but are obvious to many people.

United States

In the United States, the first DTC advertisements emerged in the early 1980s. However, in 1983 the Food and Drug Administration (FDA) declared a voluntary moratorium on it. Since the moratorium was lifted in 1985, and particularly since the FDA issued draft guidance allowing broadcast advertising in 1997 (Palumbo & Mullins 2002, p. 430), DTCA has burgeoned into a multi-billion dollar per annum industry. DTCA spending has dramatically increased in recent years: a nine-fold increase in DTCA between 1994 and 2000 (Frank et al. 2002, p. 1). Pharmaceutical industry journals trumpet the effectiveness of DTCA and celebrate its 'nonstop acceleration' (Morais 1998) and the 'legendary successes' produced by nearly US$7 billion expenditure in the five years to 2001 (Lieberman & Dunnan 2001, p. 22).

DTCA is regulated by the FDA, but violations of the regulations are common and monitoring is under-resourced (Toop et al. 2003, pp. 33-34).

In the US, according to Frank et al. (p. 1), 'Surveys have shown that over 90 percent of the public reports seeing prescription drugs advertisements'. According to Drazen (2002, p. 523), 'It is now practically impossible to read a major newspaper or a nationally circulated magazine, to watch television, or to listen to the radio without coming across an advertisement for a medical product or procedure'. In 2000, television advertising accounted for 60 per cent of US DTCA (Frank et al. 2002, p. 1). Many US websites also carry DTCA. Some state vacuously that they are intended for use by US residents only (e.g. the Prozac.com website, http://www.prozac.com/index.jsp).

New Zealand

New Zealand is the only industrialised country with both DTCA and a comprehensive publicly funded drug subsidy scheme (Toop et al. 2003, p. 1). It has permissive legislation and relies on self-regulation through the Therapeutic Advertising Pre-vetting System (p. 28), for which there is no regular prospective monitoring.

DTCA was never prohibited in New Zealand, but pharmaceutical companies did not take advantage of its legal status until recent years. However, it has increased rapidly in recent years. In 2001, NZ$4.9 million was spent on DTCA for four prescription-only medications (Toop et al., p. 3).

DTCA was reviewed in 2000 by the Ministry of Health (2000), which recommended tightening of the regulations. However, according to Toop et al. (2003, p. v), this has not happened. Toop et al.'s report is highly critical of DTCA and has generated significant controversy. Lynne Clifton, Executive director of the Communication Agencies Association of New Zealand, reportedly stated:

> We believe that this latest research from the Christchurch School of Medicine is a highly emotive attempt to stir unfounded concerns. (Ralston 2003)

In addition, several high-profile Massey University academics have criticised Toop at al., including Associate Professor Janet Hoek and Professor Philip Gendall

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(Department of Marketing) (Massey News 2003a), and Dr Lynne Eagle (College of Business) and Associate Professor Kerry Chamberlain (Psychology) (Massey News 2003b).

The New Zealand pharmaceutical market is very small, but it is significant to the international pharmaceutical industry because of the legality of DTCA. It provides opportunities to test DTCA marketing strategies and to conduct research that purportedly demonstrates the value and acceptability of DTCA. Furthermore, as noted by Calfee (2002, p. 7, note 6), 'The New Zealand experience is of obvious interest not just because DTC ads are permitted but also because they are regulated by the Advertising Standards Authority, a self-regulatory body'. One example of international interest in New Zealand DTCA is a report in the Australian *Financial Review* on 1 July 2005 that the New Zealand Government would ban DTCA from 2006. Pharma in Focus (2005b), a prominent Australian industry publication, responded, saying that the report was 'premature' – no decision had been made. As of August 2010, DTCA remains legal in New Zealand.

Australia

Prescribed drugs in Australia are regulated by the *Therapeutic Goods Act 1989*, administered by the Therapeutic Goods Administration (TGA), part of the Commonwealth Department of Health and Ageing. DTCA is prohibited in Australia by the *Therapeutic Goods Act*. This was reviewed in 2000/2001 as part of the review of all State and Territory drugs, poisons and controlled substances legislation against the Principles of National Competition Policy, commissioned by the Council of Australian Governments in 1999 (Galbally 2000/2001). The report recommended that:

> the prohibition on advertising prescription medicines is retained, except that publication of the Consumer Medicine Information should be permitted as should advertisements which only provide information about the price of medicines or general information about disease states, in accordance with a code of practice underpinned by legislation to promote the informational nature of these advertisements (p. xiii)

DTCA is also prohibited by the Medicines Australia (previously Australian Pharmaceutical Manufacturers Association) Code of Conduct (Medicines Australia 2009, p. 92):

> 12.3 Promotion to the general public

> The promotion of products covered by the Code of Conduct to the general public would breach the Commonwealth therapeutic goods legislation and this Code which stipulate that prescription products must not be promoted to the public.
>
> Prescription products may be promoted only to healthcare professionals. Any information provided to members of the general public must be educational. Any activity directed towards the general public which encourages a patient to seek a prescription for a specific prescription only product is prohibited.

The Code, which is approved by the Australian Competition and Consumer Commission (Medicines Australia 2009, n.p.) and is reviewed triennially (p. 1), sets out a formal process for dealing with breaches. However, 'education', including online information, is permitted (even required):

> The industry also has an obligation to provide appropriate non-promotional information on prescription products to members of the general public. The Code provides the standard for the provision of this information. (Medicines Australia 2009, p. 1)
>
> Medicines Australia supports the right of companies to use the internet as a means of providing accurate and scientifically reliable information on products in a responsible manner for the benefit of members of the general public. (p. 98)

Furthermore, de facto DTCA occurs in the form of unbranded advertisements about specific diseases and conditions. Celebrex (celecoxib, Pfizer (previously Pharmacia)), a nonsteroidal anti-inflammatory (NSAID), was the subject of a major de facto DTCA campaign in Australia, with television advertisements showing middle-aged people running then hobbling along a beach. According to Harvey (2002):

> following an extensive promotional campaign by the manufacturer, Celebrex cost the PBS [Pharmaceutical Benefits Scheme] $100 million in the first five months alone… and pharmacists commented that it was being prescribed for a variety of minor complaints including strains, sprains and sports injuries.

The use of Celebrex for minor complaints is a striking case of 'leakage' (prescribing for patients without PBS authorised indications) clearly driven by DTCA (Harvey 2002).

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European Union

In 2002, there was intense lobbying of the European Parliament about a proposal to allow DTCA of prescription medicines in the European Union. However, the proposed amendment was rejected (by a 12 to 1 majority) (Toop et al. 2003, p. vi).

7.15.4 Key players in the DTCA debate

Not surprisingly, the main advocates of DTCA are the pharmaceutical industry and associated industries, particularly the advertising industry. These industries produce a considerable volume of papers, report, and submissions in support of DTCA. Three notable US organisations are the Pharmaceutical Research and Manufacturers of America (PhRMA) (e.g. PhRMA 2002), the IPI Center for Technology Freedom (e.g. Matthews 2001), and The American Enterprise Institute (e.g. Calfee 2002).

The main groups objecting to DTCA are health academics and lobby groups primarily comprised of health professionals. Many doctors object to DTCA (Kravitz 2000; Handlin, Mosca, Forgione, & Pitta 2003), as do some US health insurance organisations (West 1998), and many consumer health advocates (Mintzes 1998; Sasich 1999). Consumer groups also participate in the debate, but some argue for and others against DTCA. Many consumers reportedly view DTCA positively (Handlin et al. 2003; Kravitz 2000). However, it depends on what they are asked and in what context. Mintzes et al. (2001, p. 35) found that only a minority of patients regarded media advertisements as accurate. Governments express conflicting views, and respond in contradictory ways, partly because of competing health and economic agendas.

7.15.5 Arguments for DTCA

Advocates of DTCA tend to argue that it is a win-win situation in terms of both health and economic outcomes (e.g. Calfee 2002; Block 2007). They claim that it provides valuable consumer education about medical conditions and treatments (Moser 2002).

However, this argument is not supported by the content of DTCA (Hollon 2005). Information about non-pharmaceutical treatments is generally omitted, as is information about potential causes of disorders that might be amenable to intervention. Information about side-effects is also poor.

DTCA encourages people to consult doctors (West 1998), so advocates often cite research about people's (particularly men's) reluctance to consult doctors. For example, Dow (2003) alluded to an Australian Institute of Health and Welfare's report (Bayram, Britt, Kelly, & Valenti 2003) documenting men's under-utilisation of GP services. Advocates also argue that DTCA can improve doctor-patient relationships by increasing communication (Matthews 2001, Executive summary).

Opponents of DTCA are often characterised as paternalistic (e.g. Matthews 2001, p. 15). Civil libertarian arguments are also used. Ralston (2003) quoted a communications industry spokesperson: 'Quite simply, it comes down to a patient's rights to choose and to have access to information'.

Advocates (and advertisements) sometimes often cite statistics about the prevalence of diseases, and the number or percentage of untreated cases. However, these statistics are often questionable, exaggerating the severity and/or frequency of conditions to expand markets (Moynihan et al. 2002, p. 886). In addition, the sources of statistics are often obscure. For example, according to Moser (2002):

> Ads for one drug may lead patients to receive treatment for other illnesses. Since drug advertisements for erectile dysfunction have appeared, millions of men have visited their doctors for a prescription and have learned they had other serious health issues needing treatment. For every million who asked for the medicine, it was discovered that 30,000 had untreated diabetes, 140,000 had untreated high blood pressure, and 50,000 had untreated heart disease (PhRMA, 7/24/01)

The internet link provided for the PhRMA reference is obsolete (as is the link for Moser's 'fact sheet'), making it difficult to assess the validity of the claim. This is common in pro-pharmaceutical industry publications.

Implicit in such statements are concerns about not only the public health significance of untreated illnesses, but also the economic costs. However, the selection of drugs for DTCA is clearly linked much more strongly to commercial imperatives than to consumer health needs (Frank et al. 2002, p. 3).

Advocates also use other economic arguments, particularly that DTCA reduces drug prices. This statement, 'The average price of brand-name prescription drugs with DTC

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ads is $78.19, while unadvertised drugs average $90.65 (Pfizer 2002)', used by Moser (2002), warrants several comments. Firstly, average prices are often highly unrepresentative (hence the use of median prices in real estate reporting). Secondly, it is not just the unit cost that matters in economic terms, but also the volume. Many DTCA drugs are for chronic conditions (Frank 2002, p. 5; Vogt 2005, p. 5). Thirdly, the source cited was a 'Pfizer, Inc. Conference Presentation' – there is presumably no written public record, so it is not possible to check the data sources and methodology.

Not surprisingly, a key argument is that DTCA increases competition and therefore, following purist economic logic, improves efficiency. According to Matthews (2001, Executive summary):

> As long as patients are insulated from the cost of medical care and doctors stand between patients and their prescriptions, the health care marketplace cannot work exactly like a normal market. But it still can be competitive. Advertising will play a major role in expanding that competition. We have no reason to fear advertising; what we should fear is the people who want to control it.

The rhetoric of democracy and freedom of speech is also invoked:

> DTCA is part of the rich fabric of a well functioning democracy and market economy, where consumers and business are free to talk with each other through the mass media. (Association of New Zealand Advertisers 2004, p. 1)

The rhetoric of destigmatisation and equal rights for people with mental illnesses has been used to support antidepressant DTCA:

> Frederick K. Goodwin, M.D., director of the Center on Neuroscience, Medical Progress and Society, and professor of psychiatry, George Washington University Medical School, told Psychiatric Times that if prescription drug advertising is going to be allowed, there should be no distinctions drawn between medications for physical and mental illnesses.
>
> "I generally don't like policies that differentiate mental health from the rest of health," said Goodwin, the former head of the National Institute of Mental Health and a long-time proponent of efforts to destigmatize mental illness. "[I]f the public has accepted direct advertising of drugs for hypertension, drugs for prostate and drugs for infections, then they should also be available to inform the public about psychiatric medications." (Grinfeld 1997)

Another argument in favour of antidepressant DTCA is that it can encourage screening:

> Lydia Lewis, the newly appointed executive director of DMDA said that what's more important than any concern over commercialism is that the message about mental illness get out to consumers.

> "If the Prozac ad is going to get people to see their doctor to be screened for depression, then it's a good thing," she said. (Grinfeld 1997)

Notably, the National Depressive and Manic-Depressive Association convened an influential consensus statement on the undertreatment of depression, which was sponsored by Bristol-Myers Squibb (Hirschfeld et al. 1997). As discussed in chapter 8, that statement was based on questionable epidemiology.

One particularly notable advocate of antidepressant DTCA has been economist Adam Block (2007), who used economic modelling to estimate that it provided a net social benefit of over US$72 million per year. He acknowledged that DTCA led to unnecessary treatment, but argued that 'the costs of treating non-depressed people may be vastly outweighed by the much larger benefit accruing to treated depressed individuals' (p. 511). He further argued that the 'benefit cost ratio is so high that treating everyone in the country with an SSRI would also provide a net benefit' (p. 519). Together with colleagues, I published a critique (Jureidini et al. 2008) detailing three major problems with Block's modelling: failure to incorporate antidepressant-induced harms; exclusion (and explicit denial) of costs other than drug costs, and unrealistic estimation of benefits.

Doctors may be pleased to see previously passive patients actively engaging in their own health care by requesting prescribed drugs. Also doctors may believe in the power of the placebo: if a patient has already been convinced that a drug is effective, this belief may make it effective. Furthermore, doctors are under significant pressure to maximise their throughput of patients. A patient requesting a specific drug is likely to be satisfied very quickly by a prescription for that drug. The latter two arguments are not generally publicly aired, but probably have some influence on doctors' attitudes.

7.15.6 Arguments against DTCA

Objections to DTCA also fall into two main categories: the potential impacts on health, and the economic impacts. There is also concern about the effect on doctor-patient relationships. A joint statement by the Health Action International Europe and European Public Health Alliance (2002) argued that:

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> advertising of prescription medicines is a grave threat to public health and puts the profits of the pharmaceutical industry ahead of public health…. it clearly places undue stress on public health budgets, increases the amount of misleading and unhelpful health information and increases the inappropriate and unnecessary use of medicines.

Negative health impacts include direct harms from unnecessary use of drugs (all drugs have potentially harmful side-effects), and reliance on drugs rather than safer and more effective nonpharmaceutical treatment and prevention strategies such as exercise and diet modification, which often play a role in the prevention and control of multiple diseases, not just the one targeted by the drug. Such strategies are rarely mentioned in DTCA (Kravitz 2000; Moynihan et al. 2002, p. 889).

There are significant problems with the quality of information in advertisements and promotional materials targeting doctors (Loke et al. 2002; Stryer & Bero 1996; Wilkes, Doblin, & Shapiro 1992). In particular, benefits of drugs are overstated, and risks understated. Despite their medical education, doctors need training in 'separating the wheat from the chaff' (Shaughnessy, Slawson, & Bennett 1994). It therefore seems unrealistic to expect consumers to be able to make genuinely informed choices.

Defending Prozac DTCA, Goodwin conceded that advertising does present risks to those unable to sort out the information by themselves, but argued that "in some ways the drug advertising is the safest of all in terms of comparing that with advertising of other products, because it's very heavily scrutinized by the FDA" (Grinfeld 1997). As discussed in section 7.18, serious questions about the fallibility of the FDA are gaining momentum.

In a stark illustration of the risk of over-promotion of over-the-counter (OTC) psychotropic drugs, Hennessey (1993) documented an epidemic of deaths, predominantly female, due to kidney failure resulting from long-term use of compound analgesics such as Bex and Vincents in Australia from the mid-1950s to the 1970s. Although the damage was directly caused by the combination of phenacetin and aspirin, the high caffeine content of these products (APCs – aspirin, phenacetin, caffeine) fostered the dependence that led to the cumulative effects (p. 6). Advertising in influential Australian women's magazines also played a major role in encouraging and indeed normalising use. Compound analgesics were constructed as the solution to everyday stresses experienced by women (particularly housewives).

The OTC status of these drugs made them much more accessible than prescription psychotropics.

APCs were promoted for many purposes, including relief of headache, pain, fatigue, and boredom. However, as the text of one Zans (Nicholas) advertisement (reproduced in Hennessy 1993, p. 71) reveals, one of the purposes for which APCs were promoted was relief of depression and anxiety:

> When molehills seem like mountains; when you're jaded and nervy and feel you just can't carry on . . .that's the time to take a couple of 'ZANS,' those amazing little APC tablets.
>
> 'ZANS' tablets have a double action against headaches and pain: they soothe the nerves and they give you a pleasant 'lift' from that depressed feeling.

Several US studies have investigated the effects of antidepressant DTCA on prescribing. Kravitz et al. (2005) investigated the effect on primary care physicians of patients' requests for antidepressants that were advertised directly to consumers. They found that such requests profoundly influenced prescribing, including off-label prescribing of antidepressants. Kravitz et al. concluded that DTCA 'may have competing effects on quality, potentially both averting underuse and promoting overuse' (p. 1995).

Donohue and Berndt (2004a) found that antidepressant DTCA appears to affect whether patients are prescribed antidepressants, whereas detailing affects which antidepressants are prescribed. Drawing on the same data, Donohue et al. (2004b) found that antidepressant DTCA was associated with an increase in the number of people diagnosed with depression who initiated antidepressant therapy. It was also associated with a small increase in the number of patients who received the 'appropriate' duration of antidepressant therapy.

Direct negative economic impacts of DTCA include costs to the consumer, potentially at the expense of adequate food, housing, and other factors that affect health, and costs to the government or insurance provider. With the escalating costs of drugs threatening the viability of public subsidy schemes such as the PBS (Goddard, Henry, & Birkett 2001), economic costs also potentially translate into health costs. A

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particular concern is 'leakage' – prescribing for patients without indications for which drugs have been listed on the PBS (Henry & Birkett 2001; Harvey 2002).

According to Mintzes and Baraldi (2001, p. 2), the impact of DTCA on prescribing may have been very substantial:

> In the U.S., prescription drug spending increased from US $50.6 billion in 1993 to $93.4 billion in 1998, an 84% increase over a five-year period. Four categories of drugs accounted for 30.8% of this increase: oral antihistamines used to treat allergy, antidepressants, cholesterol-lowering drugs and ulcer treatments. These categories include seven of the ten drugs most heavily advertised to the public in 1998. That means that direct-to-consumer advertising could have added more than $13 billion to the US drug bill in 1998. In 1999, two thirds of the increase in spending on prescription drugs in the US was for 25 drugs with the most intensive DTC advertising campaigns.

In relation to doctor-patient relationships, as mentioned above, DTCA encourages people to consult doctors. However, it also encourages them to ask for specific drugs (Kravitz 2000). According to Mintzes et al. (2002, p. 279):

> Patients' requests for medicines are a powerful driver of prescribing decisions. In most cases physicians prescribed requested medicines but were often ambivalent about the choice of treatment. If physicians prescribe requested drugs despite personal reservations, sales may increase but appropriateness of prescribing may suffer.

Doctors are trained as medical experts, but they are also trained to empathise with patients. When they encounter patients requesting specific drugs, either by name or by implication (e.g. 'that new arthritis drug'), they can experience significant conflict, particularly if they have previously developed positive relationships with patients (and often their families). A survey by Weissman et al. (2004) of US physicians about patients' requests for advertised drugs found that physicians reported mixed feelings about DTCA. Furthermore, five per cent of doctors who prescribed DTCA drugs requested by patients thought that other drugs or treatment options might have been more effective but wanted to accommodate the patients' requests (p. 226). One reason may be to avoid losing patients, who sometimes change doctors if their requests are refused (Bell, Wilkes, & Kravitz 1999), which can lead to disruptions in ongoing medical care.

Weissman et al. (2004) found that in 39% of consultations, the advertised drug was prescribed. In 5% of those cases, this was against the doctor's judgement of the best treatment option (drug or otherwise). In 22% of total cases, a different drug was

prescribed. In many instances, this would have been a similar drug. According to Rosenthal et al. (2002, p. 1), DTCA is effective primarily by promoting growth within entire drug classes (including antidepressants). This is sometimes referred to as a 'class effect' (Bradford et al. 2006; Jones 2007).

The ten most common conditions for which advertised drugs were requested were:

> impotence (10.9 percent of all DTCA visits), arthritis (10.5 percent), allergies (9.6 percent), high cholesterol (8.7 percent), heartburn (8.4 percent), depression (5.8 percent), anxiety (5.6 percent), pain (3.8 percent), diabetes (3.6 percent), and menopausal symptoms (3.3 percent). (pp. 224-225)

Twenty-five per cent of the consultations resulted in new diagnoses, of which the ten most common were:

> impotence (15.5 percent of new diagnoses), anxiety (9.0 percent), arthritis (6.8 percent), menopausal symptoms (6.6 percent), allergies (6.0 percent), depression (5.7 percent), hypertension (4.7 percent), pain (4.6 percent), heartburn (4.1 percent), and high cholesterol (3.4 percent). (pp. 224-225)

Given that antidepressants are commonly prescribed for both depression and anxiety, and are sometimes prescribed for menopausal symptoms, they were therefore relevant to 14.7% of conditions and 21.3% of new diagnoses. This shows that antidepressants are a key class of drug in which DTCA encourages patients to request drug treatment and also increases the likelihood of diagnosis and prescription.

Neslin (2001, p. 20) reported a return on investment of $0.19 per additional dollar spent on direct-to-consumer advertising in general. As with drug reps, there was a significantly higher return ($1.37) for large and more recently launched brands, a category into which blockbuster antidepressants would fit. DTCA played a very important role in the marketing of one such blockbuster, Lexapro® (escitalopram). This is discussed in the case study at the end of this chapter.

7.16 DEPRESSION DISEASE MANAGEMENT PROGRAMS

Pharmaceutical companies are strongly linked to disease management programs (DMPs), which are prominent in the US health system, and have a smaller but growing presence in many other countries, including Australia. Definitions of disease

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management programs vary. According to Krumholz et al. (2006, p. 1442), DMPs should include 'a coordinated system of care, delivery system support, support for patient self-care, identification of at-risk populations, a continual feedback loop between patients and care providers, measures of clinical and other outcomes, and the goal of improving overall health'. US DMPs are population-based in the sense that they focus on a defined population such as employees (and family members) of a large corporation or Medicaid recipients in a particular state jurisdiction. The main diseases targeted are chronic diseases, particularly heart disease, diabetes, and asthma. Depression is a less common but significant focus.

Medication is central to DMPs. According to Bodenheimer (2000, p. 563), the concept of disease management 'was initiated by pharmaceutical companies because they feared that health maintenance organisations would cut the amount that they paid for drugs just as they had reduced payments to physicians and hospitals'. Some DMPs evolved directly from pharmacy benefit management organisations (PBMs). Pharmaceutical companies purchasing PBMs gained access to prescription data that could be used to identify patients with specific conditions (Glabman 2005).

Increasingly, however, disease management programs are run not by pharmaceutical companies but by commercial firms that have lucrative contracts with employers, health maintenance organisations, and hospitals (Bodenheimer 2000, p. 563). Such companies and pharmaceutical companies have substantial common interests, and tend to be supportive of one another. For example, a favourable evaluation of the effectiveness of DMPs was partly funded by TAP Pharmaceutical Products (Weingarten et al. 2002, p. 930). The fact that this paper was published in the *BMJ* is an indicator of how successfully DMPs have been mainstreamed.

A number of pharmaceutical companies have set up DMPs focusing specifically on depression, including Merck-Medco's *Transitions to Better Health* and Pfizer's *Prime-MD Today* (National Pharmaceutical Council 2003, pp. 8-9). Interestingly, Merck-Medco received financial support for *Transitions to Better Health* from Pfizer Health Solutions (Fulop et al. 1999, p. 61), illustrating recognition by both Merck and Pfizer of the value of co-operation.

Not surprisingly, DMPs are biased towards pharmacological treatment of depression, as this quote reveals:

> The goals of the program are to optimize detection, diagnosis, and *medication* management of a depressed patient population, and to promote improved health outcomes and reduce costs. The central feature of the program is that it leverages a prescription database, a core resource of a pharmacy benefits manager (PBM), and incorporates medical care utilization data when available. We use these data to identify an at-risk patient population for undiagnosed depression, and help enhance appropriate *antidepressant drug therapy* through individualized patient monitoring. [italics added] (Fulop et al. 1999, p. 61)

Other pharmaceutical companies, including Eli Lilly and Forest Laboratories, have produced depression disease management resources. Increasingly these are internet based, often supplemented by physical resources such as videos and booklets for patients.

More generally, the pharmaceutical industry is an enthusiastic advocate of depression disease management programs. Indeed, its enthusiasm is reflected by a glossy 20-page review published by the National Pharmaceutical Council (2003). Among the powerful messages it reinforces are:

- depression is common (p. 2)
- depression is serious (p. 2)
- depression is a chronic disease (p. 2)
- depression imposes substantial economic costs (p. 4)
- depression is a risk factor for suicide (p. 4)
- the centrality of antidepressants in treatment (p. 4)

A favourable evaluation of the effectiveness of depression DMPs was partly funded by TAP Pharmaceutical Products (Badamgarav et al. 2003, p. 2088); one of the authors was a TAP employee; another has subsequently become an employee of another pharmaceutical company. Notably, the evaluation found much bigger effect sizes (i.e. much stronger relationships between variables) for measures of detection of depression and treatment processes (e.g. compliance with prescribing guidelines) than for measures of depression outcomes and broader health outcomes.

In Australia, there are no depression DMPs equivalent to those in the US, largely because of the dominance of Medicare and the absence of health maintenance organisations and employment based healthcare. However, a number of less

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comprehensive depression management programs have been developed for use by GPs. Much of the funding has been provided by pharmaceutical companies. A prominent Australian industry-sponsored depression management program, SPHERE, is discussed briefly in chapter 9.

The Commonwealth Department of Health and Aged Care and Australian Institute of Health and Welfare (1999, p. 107) uncritically reported:

> Pharmaceutical companies have contributed significantly to the management and treatment of depression. Most pharmaceutical companies have developed consumer support programs to encourage adherence to ongoing medication regimes (Eli Lilly – Breakthrough, Pfizer – Rhythms). Smithklein [sic] Beecham has also supported the development of primary care support personnel with mental health expertise. Additionally, the INSIGHTS program, conducted over the last five years by the Roche pharmaceutical company, in association with psychiatrists and general practitioners, is estimated to have reached almost half of the general practitioner workforce. Pfizer pharmaceuticals actively promoted the PRIME-MD diagnostic program in Australia and has recently provided extensive support for non-pharmacological treatments developed at the University of New South Wales.
>
> The Focused Educational and Psychological Therapy Program (FEPP) is being funded by the pharmaceutical industry to provide a practical, focused, psychological therapy approach for use by general practitioners in the treatment of depression. FEPP comprises strategies based on principles of CBT and interpersonal therapy combined with consumer education materials. General practitioners will be trained in the use of FEPP by video instruction together with face to face workshops. FEPP is designed for both acute treatment (six weeks) and maintenance therapy (12–18 months).

The above discussion of FEPP implies that antidepressants were not a component of it. However, the only published trial of FEPP compared venlafaxine plus FEPP with venlafaxine plus usual psychosocial treatment, and was sponsored by Wyeth (Judd et al. 2001). Sponsorship of such trials is a win-win strategy for a pharmaceutical company: regardless of the outcome, there is no risk of their antidepressant being seen to be less effective than a competitor's antidepressant (as in a head-to-head trial of two antidepressants), and it bolsters industry claims to support non-pharmacological treatments.

7.17 RELATIONSHIPS WITH PROFESSIONAL ORGANISATIONS

Pharmaceutical companies have strong relationships with professional organisations. Most important in relation to depression and antidepressants are relationships with psychiatric organisations, particularly the American Psychiatric Association (APA).

Pharmaceutical companies provide substantial funding to the APA (Carey & Harris 2008). Similarly, in Australia, the Royal Australian and New Zealand College of Psychiatrists receives considerable industry funding (Moynihan 2008a).

Much of the funding is for conferences. It is commonly argued that medical conferences would not be viable without pharmaceutical industry sponsorship. In Australia in 2008, the South Australian organising committee of the 2009 Congress of the Royal Australian and New Zealand College of Psychiatrists decided to seek non-pharmaceutical industry sponsors for naming rights. However, they were over-ruled by the national Council of the College. Several members of the committee resigned in protest. One of them (Jon Jureidini) attributed the decision to conflict of interest: 'In my opinion the college got freaked by the possible consequences of offending the pharmaceutical industry' (Moynihan 2008a).

Industry publications and spokespeople frequently emphasises the role of the industry as a partner to the medical profession. For example, according to Medicines Australia (2005, p. 63), 'the additional marketing activities undertaken by the industry are becoming aligned (both in content and delivery) with broader educational programs involving other partners such as the specialist colleges'.

As mentioned above (section 7.2), pharmaceutical companies buy prescribing data from the APA (Whitney 2006). The APA and other US health professional organisations also participate with industry-funded consumer organisations in joint advocacy activities such as lobbying for 'mental health parity' (discussed briefly in section 7.18).

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7.18 RELATIONSHIPS WITH GOVERNMENT ENTITIES

In many countries, the pharmaceutical industry has very strong links to government. There are multiple reasons for this. Firstly, the industry is important to many economies, providing substantial employment and export revenue. As mentioned in chapter 3, one of the objectives of the Australian *National Medicines Policy 2000* (Commonwealth Department of Health and Aged Care 1999b) is 'maintaining a responsible and viable medicines industry' (p. 1).

Another economic reason is that regulation of drugs is increasingly industry-funded. Most notably and controversially, the US FDA is dependent on industry fees for processing of licensing applications. This is discussed below. The Australian Therapeutic Goods Administration is also dependent on industry fees (Vitry 2008, p. 114).

Another reason is the substantial compatibility and synergy between industry and government agendas. Both benefit from the medicalisation of social problems. In relation to depression and other psychiatric disorders, neuroscientific explanations locate endemic distress within the brains of individuals, making it easier for governments to rationalise lack of action on social disadvantage and inequalities. As manufacturers and purveyors of drugs that act on neurotransmitters, drug companies directly benefit from (and actively promote) neuroscientific explanations. This shared neuroscience agenda is discussed below in relation to the US National Institute of Mental Health.

In the US, enormous sums of money are spent by pharmaceutical companies on directly lobbying politicians in order to influence decisions that affect the industry (Public Citizen 2001). This also occurs in Australia (Crabb 2008), but on a much lesser scale.

In addition, just as drug companies harness the credibility of key opinion leaders to deliver their messages, so too do they use other organisations for lobbying purposes. The industry skilfully uses key players such as health professional organisations and consumer groups, and the mass media, to lobby governments in the interests of pharmaceutical companies, particularly regarding decisions about licensing and subsidisation of drugs. In relation to depression, another key lobbying issue, which is discussed briefly below, is promoting mental health parity legislation that would

increase prescribing of psychiatric drugs. As mentioned in section 7.14, a detailed Australian example of industry use of other players to influence government mental health policy is given in chapter 9.

7.18.1 US Food and Drug Administration

The US Food and Drug Administration (FDA) administers the Federal Food, Drug, and Cosmetic Act, regulating human and veterinary drugs, biological products, medical devices, food, cosmetics, and products that emit radiation. In recent years, the FDA has attracted considerable criticism for not adequately protecting public health, partly because of its relationships with the pharmaceutical industry (Furberg et al. 2006).

The FDA's mission statement includes 'helping to speed innovations that make medicines and foods more effective, safer, and more affordable'. Unfortunately, the emphasis is on the strategy of speeding rather than the goals of effectiveness, safety, and affordability. A major reason for this is the fact that, since the Prescription Drug User Fee Act was passed in 1992, drug companies have paid fees for assessment of new drugs. According to Angell (2007):

> In effect, the user fee act put the FDA on the payroll of the industry it regulates. Last year, the fees came to about $300 million, which the companies recoup many times over by getting their drugs to market faster.

Similarly critical, Avorn (2007) likened the dependence of the FDA on industry funding to the reliance of a community hospital on drug companies that funded and organised the hospital's grand-rounds:

> This penetration of commerce into the province of science isn't limited to continuing medical education. Since 1992, the United States has relied heavily on the pharmaceutical industry to pay the salaries of Food and Drug Administration (FDA) scientists who review new drug applications. The Prescription Drug User Fee Act (PDUFA) is now up for its periodic 5-year renewal, and Congress seems ready to reauthorize it with the same short-sightedness that afflicted that naive hospital administrator. (p. 1697)

In addition, many medical experts on FDA advisory committees have personal industry ties, and there is evidence that these ties influence the decisions of those committees. For example, 'three of the eight members of the FDA's

Psychopharmacologic Advisory Committee, which recommended approval of Sarafem, reportedly had ties to Lilly' (Relman & Angell 2002, p. 39). Sarafem (a reformulation of Prozac) was approved for pre-menstrual dysphoric disorder, a new indication, and therefore it is patent protected. This occurred when the patent for Prozac was approaching its end.

As mentioned in chapter 3, the FDA is the world's most important regulator of medicinal drugs, influencing regulation in other countries, including Australia. Consequently its conflicts of interest in relation to drug regulation have international ramifications.

7.18.2 US National Institute of Mental Health

The National Institute of Mental Health (NIMH) is the leading US mental health research agency. Based in Bethesda, Maryland, it is part of the National Institutes of Health, a component of the US Department of Health and Human Services.

Like virtually all 'mental health' agencies, it focuses on mental illness, which it locates in the brains of individuals: 'We understand now that the major mental disorders are brain disorders' (Insel 2006). According to the Director, Thomas Insel (2005), the mission of the NIMH is 'to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior'. There is no suggestion there that research into social or environmental factors might also be useful. Furthermore, increasingly, the emphasis is on *genetic* causes of brain disorders:

> Since mental disorders are brain disorders, the path forward is to exploit the power of genomics and neuroscience to solve these mysteries of the mind. Genetics can now help us to understand how one person is susceptible to an illness and another is resilient. (NIMH 2006)

However, the NIMH pays lip-service to the role of environmental factors in mental illness, sometimes almost laughably. This statement equates the environment with behaviour, an extremely narrow interpretation:

> we recognize that progress in mental disorders requires an understanding of environmental as well as genetic factors. NIMH is uniquely positioned to advance the understanding of gene-environment interactions, given our long history of support for the behavioral sciences. (Insel 2005)

A more recent statement (NIMH 2006) uses a slightly broader interpretation of the environment, but makes it clear that the environment is considered important only when there are predisposing genes to trigger or activate:

> Of course, environmental factors — such as loss of a loved one, traumatic events, or physical attributes of the fetal environment — exert a powerful influence on the development of mental disorders, possibly triggering the leap from genetic predisposition to illness. Researchers are now asking how environmental factors during critical phases of development exert long-term effects on how and when genes are activated.

NIMH publications stress the similarities between mental illnesses and physical illnesses. For example, according to a 'Director's Update' by Insel (2006), 'Neuroscience now allows us to study the brain in children and adults with mental disorders just as we study the heart in those with cardiac disease'. The final paragraph in that same publication, which provides a useful summary of the NIMH perspective, and has also been posted on several National Alliance for the Mentally Ill (NAMI) websites, is:

> One of the most elusive elements of improving mental health, however, will be the integration of psychiatry with the rest of medicine. Stress and depression, for example, are among the risk factors for heart disease and other serious medical conditions. The mechanisms underlying these relationships aren't yet clear, but integration will be a significant step toward improved care of the whole person by an effective treatment team, while also reducing the stigma felt by those with these devastating diseases.

The argument that psychiatry should be integrated with the rest of medicine is particularly significant in the US, where many health insurance plans discriminate against people with mental illnesses by imposing expenditure caps and increasing co-payments (patient contributions). For over a decade, industry-funded organisations like NIMH and NAMI and the American Psychiatric Association and the American Psychological Association have advocated for 'mental health parity' – for health insurers to give people with mental illness the same rights in relation to health services as those with physical illness. Although such parity should be supported on human rights grounds, pharmaceutical companies would benefit significantly from increased sales of psychiatric drugs.

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Mental health parity is not directly relevant to Australia, where there is universal coverage of both mental and physical illnesses by Medicare and the Pharmaceutical Benefits Scheme. However, trends in the US mental health field influence the Australian mental health field, and the rhetoric of parity is also used here in the mental health reform debate:

> 90 per cent of people with physical illness gain ready access to quality care, while only 35 per cent of those with mental ill-health do. (McGorry 2010)
>
> the Minister would never suggest that people with cancer should choose between access to specialist cancer treatment or access to their general practitioner. She would rightly say that people with cancer deserve and need both. This is not the case with mental illness apparently. Only one in three people with a mental illness receive any care for that illness and this compares very poorly with other chronic illnesses where people enjoy much higher rates of access to treatment. (Rosenberg, in Sweet et al. 2010)

The argument that depression is a risk factor for physical illnesses strengthens the case for mental health parity, and more generally it is used to bolster arguments that it is crucial for depression to be treated.

The claim that integration would reduce stigma is part of a broader argument that if people believed mental illnesses were biological brain disorders, there would be less stigma associated with both mental illnesses and sufferers. However, this is a questionable argument for which there is significant counter-evidence (Read et al. 2006).

NIMH relationship with pharmaceutical industry

As mentioned in section 7.14, the NIMH helped to redefine panic attacks as a legitimate psychiatric disorder. More generally, and not surprisingly, given its position that mental illnesses are biological brain disorders, the NIMH embraces the pharmaceutical industry as a partner. According to an NIMH (2004) press release, 'The NIMH approach is built on the assumption that progress in developing new treatments will require collaboration between the best academic, government, and industry scientists'.

More tellingly, an NIMH (2002) budget request positioned the NIMH and the pharmaceutical industry in partnership to influence the FDA:

> The Food and Drug Administration (FDA) currently approves most drugs for psychiatric disorders only for diagnoses categorically defined in the Diagnostic and Statistical Manual (DSM) of Mental Disorders (4th Edition). Research that

> leads to an appreciation of psychiatric diagnoses as "multi-dimensional" will position NIMH to partner with FDA and industry to achieve consensus on appropriate methods and clinical endpoints other than DSM diagnoses. If symptom complexes such as cognitive impairment in schizophrenia were to be recognized by the FDA as legitimate targets for new drug registration, the pharmaceutical industry would be provided with powerful incentives to develop treatments targeting these specific disabilities and great benefits in health might accrue.

This makes it clear that NIMH supports the industry agenda of increasing the number of approved therapeutic targets and getting around the limitations of the DSM (*Diagnostic and Statistical Manual of Mental Disorders*) system (but not abandoning the system altogether). Currently, there is little incentive for drug companies to develop drugs that address a limited range of symptoms. However, if specific symptoms as well as diagnoses were the basis of drug registration, this would increase opportunities for patents and profits. Use of multiple psychotropic drugs is already increasingly common, but would be likely to dramatically escalate, as would costs and profits.

Significantly, on at least one occasion, NIMH has intervened publicly to the potential benefit of the pharmaceutical industry. In September 2005, the results of a major NIMH-funded trial (CATIE – Clinical Antipsychotic Trials of Intervention Effectiveness) were published (Lieberman et al. 2005), revealing that newer ('second-generation', 'atypical') antipsychotic drugs were no better than an older 'first-generation' drug, perphenazine, which costs approximately one-tenth as much as the newer ones, which account for US$10 billion in annual sales and ninety percent of the US antipsychotic market (Carey 2005). The NIMH (2005) swiftly released a statement, 'NIMH perspective on antipsychotic reimbursement: Using results from CATIE', which stated:

> Understandably, these results appear to invite a "fail-first" policy with perphenazine as the treatment of choice or possibly a restriction to reduce access and use of the atypical antipsychotics. NIMH believes that such a change in reimbursement policy is premature

The NIMH gave four reasons for this stance: Lieberman et al. only reported phase I of the three-phase study; other outcomes, particularly cost-effectiveness, are more

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relevant to reimbursement; individual patients may have responded far better to particular drugs; and CATIE only included people with moderately treatment-resistant schizophrenia.

These are valid comments about the limitations of the study and the Lieberman et al. paper. However, they contrast strikingly with the NIMH's uncritical reporting of other findings more in line with the NIMH agenda and the pharmaceutical industry's interests. Some examples related to depression are discussed below.

NIMH perspective on depression

The NIMH has had a major focus on depression for a number of years. In 2003, it published *Breaking ground, breaking through: The strategic plan for mood disorders research* (NIMH 2003). This publication 'reflects the best collective thinking of some 200 experts about how we can fill in the gaps in our knowledge' yet it has no references. It is full of the rhetoric that characterises many NIMH publications:

> We fully intend that this plan will serve the Nation and the world as a tool not only to break new scientific ground, but also, by assigning highly visible priority to scientific excellence in the conquest of mental disorders, to break through the hurtful and damaging stigma that should never again be unjustly borne by those who live with mood disorders. (p. vi)

The strategic plan includes one variant of the incorrect statistic that fifteen per cent of people with depression will die by suicide (discussed in chapter 5): 'Left untreated, or inappropriately treated, mood disorders are potentially fatal; nearly one in six persons with severe, untreated depression will die by suicide' (NIMH 2003, pp. 1, 15). This appropriately specifies *severe* depression, but erroneously claims that Guze and Robins' (1970) study, the ultimate source of this statistic, focused on people who were not treated. Instead, they were *hospitalised*, receiving more intensive treatment than most people with depression.

Insel and Charney (2003) summarised the priority areas identified in the NIMH (2003) strategic plan as follows:

- Identify the vulnerability genes for depression
- Describe the neural basis for mood regulation and dysregulation
- Define the developmental risk factors for depression

- Develop new treatments
- Reduce suicide
- Decrease the impact of depression on comorbid illnesses
- Address the disturbing gap between what is known and what is applied in clinical practice (pp. 3167-3168)

These priorities demonstrate the belief that depression is a genetically influenced brain disorder. Not surprisingly, the discussion about treatments focused primarily on drugs, with non-pharmacological treatments mentioned only at the end. Furthermore, the word 'new' implies drugs rather than psychological interventions.

In relation to the seventh priority, Insel and Charney contended that 'only 25% of patients with depression receive appropriate psychopharmacological or psychosocial treatment' (p. 3168), citing Young et al. (2001). Such claims of undertreatment are common but flawed, as discussed in chapter 4.

The strategic plan discusses prevention as well as treatment, but very narrowly. Under the heading 'Opportunities for the Prevention of Mood Disorders' (p. 12) is one dot-point only: 'Determine what interventions are needed during various phases of an illness to help prevent the recurrence and relapse of mood disorders'. This is a very limited conception of prevention, which unfortunately is common in the psychiatric arena. Because it focuses on patients rather than the population, it is secondary prevention (early diagnosis and treatment) or more likely tertiary prevention (late stage treatment and rehabilitation). There is no mention of primary prevention (controlling specific causal factors) and primordial prevention (tackling underlying conditions leading to causation), which have the greatest potential to improve health at a population level (Beaglehole et al. 2000, p. 85).

Elsewhere a somewhat broader perspective on prevention is presented:

> Prevention—Though genetic factors may play some role in predisposing individuals to developing depression, it is clear that the triggers for depression are largely environmental. As a result, studies aimed at identifying and understanding the environmental risk factors for depression should provide insights for developing novel behavioral, educational, and pharmacological methods for preventing depressive symptoms from occurring or reducing their duration and severity when they do recur. (p. 3)

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However, many environmental factors such unemployment and racial discrimination are not amenable to behavioural, educational, and particularly pharmacological interventions; furthermore, the focus on depressive *symptoms* reveals a very individualistic non-structural focus. Although the strategic plan mentions in passing that 'low socioeconomic status and poverty increase the risk for mood disorders' (p. 96), there is no suggestion that poverty might be an appropriate target for prevention.

Another issue is entwinement of the NIMH with pharmaceutical companies (Insel 2010b). In 2006, a scientist employee pleaded guilty to failing to declare to the NIMH a conflict of interest involving a payment of approximately US$300,000 from Pfizer (Lenzer 2006). More recently, Insel was accused of a personal conflict of interest related to disgraced KOL Charles Nemeroff (Insel 2010a).

There is no NIMH equivalent in Australia. However, the Australian pharmaceutical industry benefits from the international influence of the NIMH.

7.18.3 Australian industry-government links

In Australia, industry representation on government committees has been problematic. In 2001, the appointment to the Pharmaceutical Benefits Advisory Committee of Pat Clear, former CEO of Glaxo-Wellcome Australia and former Chief Executive of the Australian Pharmaceutical Manufacturers Association, attracted widespread criticism (Loff & Cordner 2001; Zinn 2001). Also controversial was the appointment of Dr Rachel David as a director of the National Institute of Clinical Studies. David, a senior pharmaceutical industry employee, was an adviser to the ex-Federal Health Minister Michael Wooldridge during some of the events leading up to the controversial disbanding of the Pharmaceutical Benefits Advisory Committee in 2001 (Dow 2001).

According to Professor Gordon Parker, 'the pharmaceutical companies' influence "has grown so strong I believe they are now driving the agenda in mental health"' (Macken 2006). Much of this agenda-setting is achieved by sophisticated public relations techniques that enable drug companies to influence the government via the public and the media (Beder et al. 2003, p. 7).

The Pfizer-funded SPHERE program, which won a pharmaceutical industry marketing award, has been extensively promoted by *beyondblue: the national depression initiative*. SPHERE was developed by Ian Hickie, the inaugural CEO of

beyondblue, who was also the Co-Chair of the Committee for Incentives for Mental Health, which oversaw the development of Better Outcomes in Mental Health Care (Hickie et al. 2004, p. S19).

7.19 RELATIONSHIPS WITH CONSUMER AND COMMUNITY ADVOCACY ORGANISATIONS

Like key opinion leaders, consumer and community advocacy organisations play an important role in disease awareness campaigns. It is commonplace for drug companies to fund consumer organisations (Lofgren 2004).

Consumer/community organisations are commonly used as partners in disease awareness campaigns:

> Within many disease categories informal alliances have emerged, comprising drug company staff, doctors, and consumer groups. Ostensibly engaged in raising public awareness about underdiagnosed and undertreated problems, these alliances tend to promote a view of their particular condition as widespread, serious, and treatable. Because these "disease awareness" campaigns are commonly linked to companies' marketing strategies, they operate to expand markets for new pharmaceutical products. (Moynihan et al. 2002, p. 886)

According to Weinstein (2004, pp. 136-138), working with advocacy groups (including consumer organisations) can be much a more effective marketing strategy than direct-to-consumer advertising:

> working with advocacy groups is one of the most accomplished means of raising disease awareness and enhancing the industry's image as deliverer of new and tangible value to patients. Often this advocacy work is unbranded, stimulating consumers to ask doctors about their symptoms.

In the US in 2006, a public education campaign called 'Depression is Real' was launched by a coalition of consumer/community organisations, including the Depression and Bipolar Support Alliance, NAMI, the National Mental Health Association, and the American Psychiatric Foundation (a philanthropic and educational subsidiary of the American Psychiatric Association). Funded by Wyeth, it aimed to 'counter misconceptions about depression' and 'educate Americans that

depression is a serious, debilitating disease that can be fatal if left untreated' (NAMI 2006).

Consumer/community organisations are also used to lobby governments in the interests of pharmaceutical companies (Raven 2008). As mentioned earlier, a detailed Australian example of industry use of other players to influence government mental health policy is given in chapter 9. A detailed example of an influential US consumer organisation – the National Alliance for Research on Schizophrenia and Depression – is given below, because US consumer organisations have an international influence.

Also in the US, Silverstein (1999) documented how 'An influential mental health nonprofit [NAMI] finds its 'grassroots' watered by pharmaceutical millions'. NAMI has received substantial funding from Eli Lilly, the manufacturer of Prozac, as well as other pharmaceutical companies. NAMI is an influential campaigner against discrimination against people with mental illnesses. In particular, it advocates for mental health parity legislation that would mandate that mental illnesses be covered by health insurers on the same basis as physical illnesses.

Behney et al. (1997) estimated that there were 'hundreds, perhaps thousands' of local mental health consumer groups in the USA, as well as several prominent national groups. They noted that:

> Differences among these groups are real, and sometimes acrimonious. However, as they coalesce around shared goals, they also have much in common (n.p.)

Some of the differences among consumer/community organisations are of course related to focus (e.g. schizophrenia versus depression) and niche (e.g. state versus national). There is also competition for funding and publicity. Some groups are very skilled at marketing and promotion.

An extension of this is that consumer/community organisations present a smorgasbord of strategic potential interactions to the pharmaceutical industry. Companies seeking organisations to fund can pick and choose among different mental disorders, different organisational functions (e.g. advocacy, education, counselling). Similarly, although consumer/community organisations are sometimes critical of pharmaceutical companies, there is a considerable overlap and compatibility of interests. In particular, both benefit from the conceptualisation of mental disorders as brain diseases.

Consumer/community groups vary in their willingness to accept pharmaceutical industry funding. However, those that do not accept such funding are often affiliated with other groups that do accept funding. This can be a win/win/win situation

Sometimes so-called consumer groups are nothing more than front groups set up by drug companies. This strategy is referred to as 'Astroturf lobbying': the use of fake 'grassroots' organisations to lobby governments. For example, in the United States, the Pharmaceutical Research and Manufacturers of America (PhRMA) hired a PR firm to telephone people and organisations to support 'The Consumer Alliance' in its opposition to proposed legislation that would lower the cost of prescription drugs purchased through the Medicaid system (Anonymous 2002). This also happens in other industries such as the chemical industry (Beder 1998).

However, many, probably most, single-issue health consumer groups are genuine, composed of well meaning but often rather naïve people who believe that they are immune to conflict of interest. This is illustrated by Australian web-based group depressioNet's (2002) justification for accepting pharmaceutical industry funding:

> **Sponsorship and Independence**
>
> A number of people have asked recently how depressioNet can remain truly independent when we accept sponsorship from commercial organisations. This is an important issue as we work very hard to maintain our independence so that our first priority and focus will always be the people we exist to serve – Australians living with depression and related conditions.
>
> We will only accept financial support from those individuals and organisations that support the depressioNet philosophy and integrity, and at no time will we compromise these either in practice or perception. All of our Sponsors and Partners share and respect this philosophy and work with us to reduce the impact of depression on the lives of Australians. The value we bring to them is in helping them in any activity that may be of interest and / or benefit to Australians living with depression, and related conditions.
>
> Wyeth have recently provided major sponsorship to depressioNet for a second year. Their support has been a lifeline for depressioNet and we are deeply grateful. Our assistance with the Martin Keller tour is an example of how we work with Wyeth to add value to the work they are doing in helping doctors understand the needs and issues for people with depression. A win(depressioNet)-win(Wyeth)-win(doctors)-win(all Australians living with depression) situation. This is the perfect example of depressioNet partnerships.

Common acronyms in this chapter: ACCC Australian Competition and Consumer Commission; APA American Psychiatric Association; CGP clinical practice guideline; DSM Diagnostic and Statistical Manual (of Mental Disorders); DTCA direct-to-consumer-advertising; FDA Food and Drug Administration; KOL key opinion leader; NAMI National Alliance for the Mentally Ill; NARSAD National Alliance for Research on Schizophrenia and Depression; NIMH National Institute of Mental Health; PhRMA Pharmaceutical Research and Manufacturers of America; ROI return on investment; SSRI selective serotonin reuptake inhibitor; SNRI serotonin and noradrenalin reuptake inhibitor; TCA tricyclic antidepressant; TGA Therapeutic Goods Administration

Keller is the US psychiatrist about whom Angell (2000), then Editor of the *New England Journal of Medicine*, wrote:

> The article by Keller et al. . . . provides a striking example. The authors' ties with companies that make antidepressant drugs were so extensive that it would have used too much space to disclose them fully in the Journal. We decided merely to summarize them and to provide the details on our Web site.

Industry representation on decision-making structures of community groups is another tactic. In the US, Silverstein (1999) documented the 'loan' of an Eli Lilly executive to NAMI to undertake 'strategic planning' for NAMI, making a mockery of NAMI's supposed independence.

More subtly, the pharmaceutical industry influences community groups and other organisations indirectly via researchers and clinicians with financial links to industry. It is very common for medical experts to have financial ties with the pharmaceutical industry. Angell (2000), discussing the extent to which academic medicine has become intertwined with the pharmaceutical industry, reported: 'as we spoke with research psychiatrists about writing an editorial on the treatment of depression, we found very few who did not have financial ties to drug companies that make antidepressants'.

7.19.1 National Alliance for Research on Schizophrenia and Depression

The New York based National Alliance for Research on Schizophrenia and Depression (NARSAD) is 'the largest donor-supported organization in the world devoted exclusively to supporting scientific research on brain and behavior disorders' (NARSAD 2005). From 1987 to 2006, it awarded approximately US$200 million in nearly 3000 research grants. It is 'the major non-governmental source of grants for psychiatric research at major American universities' (NARSAD 2006, inside cover).

NARSAD was formed in 1986 by the National Alliance for the Mentally Ill, the National Mental Health Association, the National Depressive and Manic Depressive Association, and the American Schizophrenia Foundation. In around 2006, NARSAD adopted the business name NARSAD: The Mental Health Research Association, to reflect its broader funding focus, which includes 'schizophrenia, depression, anxiety and many other psychiatric diseases' (http://www.narsad.org/about). A number of other mental health consumer organisations, including SANE Australia, have similarly broadened their focus.

NARSAD's 2005 annual report (p. 49) disclosed substantial donations from pharmaceutical companies:

- US$50,000-plus: AstraZeneca, Forest, Wyeth-Ayerst
- US$30,000-plus: Janssen, Pfizer, Solvay
- US$10,000-plus: Amgen, Aventis, Eli Lilly

NARSAD does not seek or receive government funding. However, according to its 2005 annual report, 'NARSAD-funded research very often leads to major grants from the government [most likely NIMH] and other sources because our emphasis on innovative research has led the field in advancements, including the recognition of two Nobel Prizes to NARSAD-funded researchers'. The 2005 annual report includes a ringing endorsement of NARSAD research funding by Thomas Insel, the current NIMH Director:

> NARSAD is unique because it funds only breakthrough, cutting-edge, innovative research. NARSAD grants enable up-and-coming scientists to gather pilot data which can then be parlayed into significantly larger grants, and allow more senior investigators to branch out into new and exciting areas … and that's really extraordinary. (p. 48)

This shows the compatibility of the NARSAD and NIMH research agendas, and suggests the potential for research funded by industry via NARSAD to influence NIMH research directions. Furthermore, nine members of NARSAD's Scientific Council, which assesses all NARSAD research funding applications, are senior NIMH staff. Five current or previous members have been NIMH Director.

Many members of the Scientific Council have strong pharmaceutical industry links. In some cases, these have been very controversial. This is particularly the case for Charles Nemeroff (Harris 2008; Warner 2008), and Martin Keller (Angell 2000; Hughes & Minchin 2003; Jureidini et al. 2008) (mentioned above in relation to depressioNet).

Like NIMH, NARSAD has an international influence. It funds research in many countries. In Australia, it has funded Orygen Youth Health (n.d.). Its international influence is likely to have increased since its 2005 joint launch of the International Partnership for Mental Health Research (NARSAD 2006, p. 4).

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NARSAD's President, Constance E. Lieber, has a relatively high public profile. Her involvement was spurred by her daughter's schizophrenia (Bender 2002). She is also President of the Essel Foundation, which she founded in 1963 with her husband. The Essel Foundation has contributed millions of dollars to mental health research via NARSAD.

Many of the other contributors to NARSAD, some of whom contribute over $100,000 in a year, would also be people with relatives with a mental illness, and would regard explanations rooted in neuroscience as the only alternative to parent-blaming, particularly mother-blaming. They would also be seduced by rhetoric of progress in neuroscience, For example, in relation to depression, according to a NARSAD/NIMH funded research paper (Nestler et al. 2002, p. 13):

> Current treatments for depression are inadequate for many individuals, and progress in understanding the neurobiology of depression is slow. Several promising hypotheses of depression and antidepressant action have been formulated recently. These hypotheses are based largely on dysregulation of the hypothalamic-pituitary-adrenal axis and hippocampus and implicate corticotropin-releasing factor, glucocorticoids, brain-derived neurotrophic factor, and CREB. Recent work has looked beyond hippocampus to other brain areas that are also likely involved. For example, nucleus accumbens, amygdala, and certain hypothalamic nuclei are critical in regulating motivation, eating, sleeping, energy level, circadian rhythm, and responses to rewarding and aversive stimuli, which are all abnormal in depressed patients. A neurobiologic understanding of depression also requires identification of the genes that make individuals vulnerable or resistant to the syndrome. These advances will fundamentally improve the treatment and prevention of depression.

Most people concerned about a family member suffering from depression would have little comprehension of the scientific terminology, but would be impressed by it. The final sentence would make sense to them and would give them hope, as would this statement by Lieber in the 2005 annual report: 'We see the achievements of 2005 as part of an exciting period of acceleration, as scientific inquiry reveals more, new and better ways to provide care for people struggling to live with mental illness' (p. 4).

NARSAD also skilfully taps into altruism and compassion:

> Everyone who is helping to support NARSAD should take enormous pride and satisfaction in knowing that they are sustaining critical research in an area of human illness more devastating than any other. (NARSAD 2006?, p. 5)

According to Steven B. Hyman, Provost of Harvard University, former NIMH Director, and current NARSAD Scientific Council member: 'There is no organization

in the United States doing a better job of dealing with the gap between our nation's real and profound public health needs and our ability to fund research than NARSAD' (NARSAD 2006?, inside cover). This statement is striking for its uncritical acceptance of the ideology that it is appropriate for the US government to delegate responsibility for much research funding to private philanthropy and the pharmaceutical industry.

NARSAD's dual primary focus on schizophrenia and depression is problematic, given that schizophrenia, unlike depression, is a low-prevalence, high impact disorder. More generally, it is supports the claims of antidepressant manufacturers that depression is a serious mental illness that requires pharmacological treatment.

There is no equivalent of NARSAD in Australia but, as discussed, NARSAD has an increasing international influence.

7.20 CHEMICAL REFORMULATION

Several antidepressants have had their patent life effectively extended by the development and marketing of similar antidepressants that are slightly different chemically from the established ones. This is a common 'evergreening' strategy used by pharmaceutical companies to extend patent life, often without significant advantages (Kubler 2006). Many drugs are a mixture of both left-and right-handed molecules that are mirror images of each other (enantiomers), with pharmacological properties that differ to varying degrees. Pharmaceutical companies are increasingly marketing single-enantiomer versions of their existing drugs that are mixtures of the two enantiomers (racemates). This is referred to as 'chiral switching' (Somogyi et al. 2004; Svensson & Mansfield 2004).

A similar approach is to identify the active metabolite of an existing product, and develop that metabolite as a drug in its own right. Sometimes there is a good reason for doing this, such as in the case of the antihistamine, terfenadine, which caused significant adverse effects that its metabolite, fexofenadine, did not (Pratt et al. 1999).

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This strategy was used by Wyeth with its SNRI antidepressant Pristiq® (desvenlafaxine) when its established racemate Effexor® (venlafaxine) was approaching the end of its patent life in several countries (Healthy Skepticism 2010). However, according to Australia's National Prescribing Service (2009), there is 'no evidence that desvenlafaxine is more effective, safer or better tolerated than venlafaxine or other antidepressants'. Furthermore, although desvenlafaxine was approved in the United States and in Australia, Wyeth withdrew its application in Europe because the European Medicines Agency (EMEA) was critical of the evidence, particularly the dosages used and the lack of statistically significant results in several trials. The EMEA also questioned the clinical relevance of the results, and was concerned that very few elderly people were included in the trials.

The single-isomer strategy was also used by Forest when it developed a new SSRI, Lexapro® (escitalopram), to replace its older SSRI, Celexa® (citalopram), a few years before Celexa's patent expired. This is discussed in the Lexapro case study below.

7.21 CASE STUDY: LEXAPRO

In the US in September 2002, Forest Pharmaceuticals launched a new SSRI, Lexapro® (escitalopram), to replace their older SSRI, Celexa® (citalopram), which was due to run out of patent in 2005. In Australia, Lexapro was listed on the PBS on 1 February 2004 (Stokes 2004).

Lexapro is a single (active) isomer version of Celexa (Svensson & Mansfield 2004), which contains both the active isomer and its mirror image isomer. Both antidepressants were developed by the Danish pharmaceutical company Lundbeck, which markets them in Europe as Cipramil® (citalopram) and Cipralex® (escitalopram). Forest is licensed by Lundbeck to market them in the US.

Samples played a key role in establishing Lexapro in the US market, encouraging doctors to make a 'natural transition' to Lexapro. In an industry news-sheet (ImpactRx 2002), the President, Kenneth Goodman, discussed the launch strategy:

> "We are not promoting switching between Celexa and Lexapro," Goodman said. "We are promoting this product to new patients, recurrent patients who come back in, or patients who were having problems with either efficacy or side effects."

Goodman reported (on 21 October 2002, shortly after the launch):

> "Most physicians would have given their patients a couple of weeks of samples," he said. "Almost half of the patients who left doctors' offices to begin with didn't receive anything but samples. Even those who received an initial prescription would have received probably two weeks of samples and a 30-day prescription."
>
> Forest also gave 30,000 physicians 10 one-month Lexapro samples to help them gain experience with the drug; at least three-quarters have been used. "Those patients who were started on those products would be in need of prescriptions probably in November at the latest," Goodman noted. (ImpactRx 2002)

The following year, a senior ImpactRx employee reported on the success of the campaign: 'Forest also quickly established a strong Lexapro sample usage with Primary Care physicians … as well as Psychiatrists' (Glogowski 2003). Samples were also a component of the marketing strategy in Australia: a 'Dear Doctor' (Stokes 2004) encouraged GPs to fax back a request form for starter packs.

A unique element of the Lexapro marketing campaign was the involvement of Andrew Solomon, son of Forest CEO Howard Solomon, and author of *The noonday demon: An atlas of depression* (2001), which won the won the National Book Award for nonfiction in 2001. In the book, which functioned as a form of literary de facto DTCA for antidepressants in general, Solomon defended antidepressants against: 'an industry of Prozac detractors who misrepresent the drug as a grave peril that is being foisted on an innocent public' (p. 81).

A notable aspect of the Lexapro launch, related to Andrew Solomon, was the portrayal of Forest as altruistic for deciding to launch Lexapro several years before its existing antidepressant, Celexa, lost its patent protection:

> Celexa's patent does not run out until late 2005. However, the company decided to seek FDA approval for Lexapro and market it as soon as possible.
>
> "Forest is taking a successful $1.4 billion dollar-a-year drug, Celexa, out of active marketing three years before the patent expires," says Andrew Farah, a psychiatrist and medical director of High Point Regional Hospital in High Point, N.C. "They are replacing it with a drug that is costing them more to make, but for which they plan to charge less."
>
> "**Lexapro is stronger, starts working faster and appears to have a lower side-effect profile.** They could have held off on Lexapro, and made their

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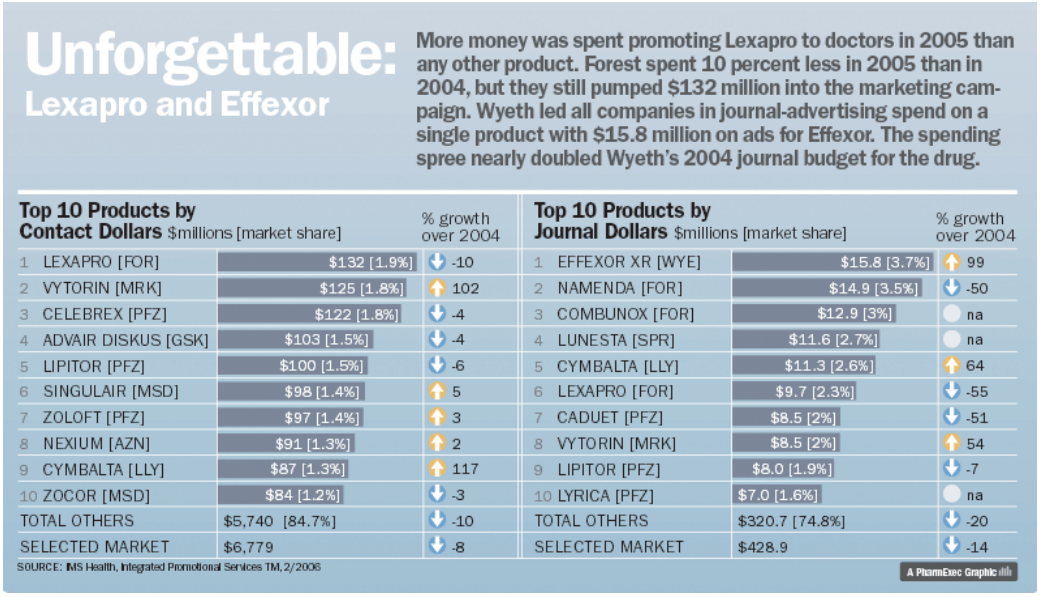
billions off of Celexa first. But that isn't happening here, and the implications, especially in terms of potency, side effects and costs, could be huge for patients," he adds.

Farah notes the decision was driven by Howard Soloman [sic], chief executive officer of Forest, whose son, Andrew, suffered from debilitating depression. The Solomans [sic] have publicly discussed the impact of the disease on their family life and on their business priorities, mot [sic] notably in a Business Week cover story in May. (Sylvester 2002)

Lexapro has been very heavily and expensively promoted, as this table from West (2006) reveals:



Unforgettable:
Lexapro and Effexor

More money was spent promoting Lexapro to doctors in 2005 than any other product. Forest spent 10 percent less in 2005 than in 2004, but they still pumped $132 million into the marketing campaign. Wyeth led all companies in journal-advertising spend on a single product with $15.8 million on ads for Effexor. The spending spree nearly doubled Wyeth's 2004 journal budget for the drug.

	Top 10 Products by Contact Dollars $millions [market share]		% growth over 2004		**Top 10 Products by Journal Dollars** $millions [market share]		% growth over 2004
1	LEXAPRO [FOR]	$132 [1.9%]	-10	1	EFFEXOR XR [WYE]	$15.8 [3.7%]	99
2	VYTORIN [MRK]	$125 [1.8%]	102	2	NAMENDA [FOR]	$14.9 [3.5%]	-50
3	CELEBREX [PFZ]	$122 [1.8%]	-4	3	COMBUNOX [FOR]	$12.9 [3%]	na
4	ADVAIR DISKUS [GSK]	$103 [1.5%]	-4	4	LUNESTA [SPR]	$11.6 [2.7%]	na
5	LIPITOR [PFZ]	$100 [1.5%]	-6	5	CYMBALTA [LLY]	$11.3 [2.6%]	64
6	SINGULAIR [MSD]	$98 [1.4%]	5	6	LEXAPRO [FOR]	$9.7 [2.3%]	-55
7	ZOLOFT [PFZ]	$97 [1.4%]	3	7	CADUET [PFZ]	$8.5 [2%]	-51
8	NEXIUM [AZN]	$91 [1.3%]	2	8	VYTORIN [MRK]	$8.5 [2%]	54
9	CYMBALTA [LLY]	$87 [1.3%]	117	9	LIPITOR [PFZ]	$8.0 [1.9%]	-7
10	ZOCOR [MSD]	$84 [1.2%]	-3	10	LYRICA [PFZ]	$7.0 [1.6%]	na
TOTAL OTHERS		$5,740 [84.7%]	-10	TOTAL OTHERS		$320.7 [74.8%]	-20
SELECTED MARKET		$6,779	-8	SELECTED MARKET		$428.9	-14

SOURCE: IMS Health, Integrated Promotional Services TM, 2/2006

A PharmExec Graphic

More recently, social media have played an important role in the promotion of Lexapro to consumers and potential consumers:

> According to a study conducted by Envision Solutions, 5 percent of U.S. Internet users looking for information about the antidepressant Lexapro visited the popular blog crazymeds.org between mid-December 2006 and mid-January 2007. They are relying on this Weblog because it provides straight talk about the safety and efficacy of many commonly used psychiatric medications. (Johnmar 2007)

However, Forest's central claim – that Lexapro is more effective than Celexa because of its single isomer composition – has been vigorously challenged. According to Svensson and Mansfield (2004), the evidence supporting Lexapro's superiority to Celexa is weak:

> The advertising claims are not justified because they are based on secondary outcomes, non-intention-to-treat analyses and arbitrarily defined subgroups…. Methodological flaws in the trials could account for the differences found…. On the evidence available to us the manufacturer's claims of superiority for

> escitalopram over citalopram are unwarranted. The Swedish and Danish drug regulatory authorities reached similar conclusions. (p. 10).

In the UK, Lundbeck was found to have breached the Prescription Medicines Code of Practice by claiming in medical journal advertisements that "Cipralex is significantly more effective than Cipramil in treating depression" (Boseley 2003). The claim was based on a favourable meta-analysis of three comparative trials, none of which individually demonstrated that Cipralex was superior.

In September 2010, Forest pleaded guilty to multiple charges, including using illegal kickbacks to induce doctors to prescribe Lexapro and Celexa, illegal promotion of Celexa for unapproved prescription to children and adolescents, and illegal distribution of an unapproved drug used to treat hypothyroidism (United States Attorney's Office 2010). Forest agreed to pay more than US$313 million to resolve the matters. However, this represents a very small fraction of the profits made from these drugs. As is usually the case, Forest was well aware of the illegality of its actions, but was undeterred by the penalties.

The success of Lexapro represents the triumph of marketing – including an extraordinary use of emotive spin related to the manufacturer's family – over evidence and ineffective regulation.

7.22 INDUSTRY INFLUENCE ON DOCTORS

Despite massive expenditure, backed by research, to persuade doctors to prescribe drugs, the pharmaceutical industry strongly maintains that it does not inappropriately influence doctors. For example, Medicines Australia CEO Brendan Shaw 'described accusations that companies "brainwash doctors into over-prescribing medicines" as "not fully conversant with reality"' (Pharma in Focus 2010).

The medical profession frequently seconds the industry stance. The Australian Medical Association has a strong track record of rejecting claims that doctors are inappropriately influenced by drug companies. Two past Presidents of the Association

have been quoted to that effect in this chapter (Moynihan 2006; Hingston 2006; AAP 2008).

It is often claimed that doctors are too *intelligent* to be misled by the pharmaceutical industry. A corollary of this is that suggestions to the contrary insult the intelligence of doctors (Kaplan 1991; Bock 2010). Sometimes those who make such claims acknowledge that there may be problems with industry input. For example, according to Australian Divisions of General Practice Chairman Dr Rob Walters, 'Doctors have the intelligence to evaluate information from a clearly biased source' (Richards 2004).

Not surprisingly, pharmaceutical industry personnel sometimes vehemently argue that doctors are too intelligent to be misled. For example, the Director, Strategic Relations, of Medicines Australia, Steve Haynes, declared:

> it's the doctor, it's the psychiatrist, it's the specialist who writes the prescription. Now, I think we're doing those individuals a disservice by almost saying that they are totally gullible. And you have this image of the industry putting out propaganda, and doctors subscribing to it. Well that's just not the way it works. I mean, doctors are very, very intelligent. (Australian Broadcasting Corporation 2002)

Such claims are sometimes echoed by other players with vested interests, such as consumer organisations that accept industry funding. For example, when discussing a multimedia campaign run by Diabetes Australia and partially funded by AlphaPharm, whose drug reps distributed campaign kits, Bill Edmonds, corporate relations manager at Diabetes Australia NSW, reportedly argued that:

> he does not believe the arrangement could be misinterpreted as an endorsement by Diabetes Australia of AlphaPharm's products "because the doctors are pretty smart creatures". (Hughes & Minchin 2003)

As mentioned in relation to medical journal advertisements, Keizer (1996) has argued that pharmaceutical promotion exerts its effect at a subcortical level, bypassing doctors' critical faculties:

> It's a kind of science in 'drag' and it is this exactly this 'science' which far below the cortex, runs along its brief spinal trajectories (not one cortical neurone even shimmering briefly in this darkness) and which is taken seriously by doctors and patients.
>
> Now, the pharmaceutical industry has, after a training period lasting several centuries, developed an incredible finesse in adopting a cortical manner while selling spinal reflexes. They love to speak in a pseudo-scientific way about the effects of their pills. What they say is often demonstrably wrong. (pp. 67-68)

It is also claimed that doctors' integrity ensures that they are not inappropriately influenced by the pharmaceutical industry and that any suggestions to the contrary are insulting (Spilker 2002, p. 243; Black 2004, p. 1656). According to Medicines Australia (2002, p. 1):

> Those that criticise the relationship between prescription medicine companies and the medical profession as simply a means of inducing inappropriate prescribing are insulting the integrity of our highly skilled, dedicated and hard working medical practitioners. Speaking earlier this year on Australian Agenda, Dr John Gullota of the Australian Medical Association said that prescription medicine companies educate doctors not pressure them, "there is no obligation to prescribe anything, it's a doctor's decision."
>
> It is unreasonable to think that providing doctors with vital information about medicines, will somehow compromise their high ethical standards.

Another argument used is that doctors can avoid conflict of interest by having links to *multiple* drug companies because these links cancel each other out. This was suggested by PhRMA spokesperson Jeff Trewhitt in relation to gifts (Black 2004, p. 1656), who disingenuously ignored class effects in promotion when he commented: 'It is entirely possible that a physician is going to have a pen and a pad from one company and then a pen and a pad from that company's main competitor'. Similarly, a UK consultant psychiatrist flippantly commented:

> I have received sponsorship and hospitality from several companies. I minimise my own bias by having as many different mugs as possible!' (Moliver 2005, p. 231)

More significant links are also rationalised using this argument. For example, Associate Professor Philip Mitchell (now one of Australia's most prominent psychiatrists) argued:

> I avoid conflict of interest because I don't align myself to any particular company. I have been on the advisory committees for most of the new drugs; Prozac, Aropax, Aurorix, Efexor. (Moynihan 1998, pp. 145)

In the US, prominent US psychiatrist and radio host Frederick Goodwin, a former director of the National Institute of Mental Health, whose links to pharmaceutical companies were exposed by Senator Charles Grassley argued:

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> He defended the views he expressed in many of his radio programs and said that, because he consulted for so many drugmakers at once, he had no particular bias.
>
> "These companies compete with each other and cancel each other out," he said. Harris (2008)

However, as Harris reported, 'Industry critics dismiss that view, saying that experts who consult for drugmakers tend to minimize the value of nondrug or older drug treatments'.

Similarly, in Australia, Singh et al. (2004) claimed that the fact that psychiatric researchers continue 'to enjoy strong professional relationships with a number of pharmaceutical companies' (p. 222) protects them from bias. Together with colleagues, I countered:

> This optimistic view fails to consider that it is in the interests of all pharmaceutical companies to increase overall drug usage. An individual company is better off with a 20% share of a $2bn market than a 30% share of a $1bn market. Therefore, the more that academics do to support the use of drugs rather than non-drug alternatives, the better it will be for all pharmaceutical companies. (Raven et al. 2005, p. 83)

As discussed in relation to drug reps (Steinman et al. 2001, p. 554) and gifts (Halperin et al. 2004), there is a tendency for doctors to believe that they personally are immune to industry influence, but *other* doctors are susceptible. Similarly, according to Rutledge et al. (2003, p. 663), although many doctors recognise the possibility that industry funding to attend conferences might influence prescribing habits, few recognise that they themselves are susceptible.

Despite the frequent denials, some doctors are willing to admit their susceptibility to industry influence. Prominent among them is Australian GP Peter Mansfield, the founder of the organisation Healthy Skepticism, which aims to improve health by reducing harm from misleading drug promotion and misleading health information more generally (http://www.healthyskepticism.org/).[12] According to Mansfield (2007), the belief that to suggest that doctors are susceptible to industry influence is insulting is one the most important barriers to healthy skepticism about drug promotion. Mansfield used an analogy to nineteenth century understandings of

[12] As noted in chapter 3, I am a member of Healthy Skepticism, and I have previously been a member of its Management Group.

hygiene, addressing claims that doctors' intelligence and integrity renders them invulnerable to influence:

> In the 1840s doctors did not understand the risk of invisible microbes so were offended by the suggestion they should wash their hands. Nowadays the existence of invisible microbes is well accepted so the idea that we should wash our hands is not regarded as a personal insult. We are now going through a similar paradigm shift towards understanding the risk of invisible unintended bias from exposure to industry influence techniques. Just as professionalism, integrity, intelligence and education provide little protection against invisible microbes they also provide little protection from invisible bias.

Arguably the definitive analysis of the influence of the pharmaceutical industry on doctors is Wazana's (2000) review of the studies of the effects of interactions between physicians and industry. He concluded (p. 378) that the overall impact was negative:

> most studies found negative outcomes associated with the interaction. These included an impact on knowledge (inability to identify wrong claims about medication), attitude (positive attitude toward pharmaceutical representatives; awareness, preference, and rapid prescription of a new drug), and behavior (making formulary requests for medications that rarely held important advantages over existing ones; nonrational prescribing behavior; increasing prescription rate; prescribing fewer generic but more expensive, newer medications at no demonstrated advantage.)

As mentioned earlier, the pharmaceutical industry often highlights the existence of rules and guidelines about industry practices, implying that they are effective. In Australia recently, Edwards (2010) argued:

> the Medicines Australia Code of Conduct is an example of a rigorous, enforceable framework for promoting ethical relationships between industry and healthcare professionals in an open and transparent way. The 16th edition of the Medicines Australia Code was authorised by the Australian Competition and Consumer Commission in December 2009. Enhancements to the Code should deliver public benefits through provisions such as protecting the public from exposure to inappropriate advertising and specifically regulating disease education and awareness campaigns. There are specific provisions and principles dealing with relationships between industry and health consumer organisations and there are specific enforcement mechanisms to deal with false and misleading conduct.

As is usually the case, Edwards provided no evidence that the code of conduct is actually effective.

Common acronyms in this chapter: ACCC Australian Competition and Consumer Commission; APA American Psychiatric Association; CGP clinical practice guideline; DSM Diagnostic and Statistical Manual (of Mental Disorders); DTCA direct-to-consumer-advertising; FDA Food and Drug Administration; KOL key opinion leader; NAMI National Alliance for the Mentally Ill; NARSAD National Alliance for Research on Schizophrenia and Depression; NIMH National Institute of Mental Health; PhRMA Pharmaceutical Research and Manufacturers of America; ROI return on investment; SSRI selective serotonin reuptake inhibitor; SNRI serotonin and noradrenalin reuptake inhibitor; TCA tricyclic antidepressant; TGA Therapeutic Goods Administration

There is often support within the medical profession for industry self-regulation. For example, President of the Australian Medical Association, Rosanna Capolingua, endorsed the Medicines Australia Code of conduct:

> Dr Capolingua said the AMA supported the Medicines Australia code of conduct as the best way to prevent pharmaceutical companies engaging in inappropriate marketing. (AAP 2008)

Notably she did not allude to the possibility of inappropriate behaviour on the part of doctors. This is not surprising, given her claim that drug promotion does not affect doctors' prescribing choices (Hingston 2006).

Sometimes it is acknowledged that there are occasionally breaches of rules, but it is claimed that they are uncommon and are effectively punished:

> Medicines Australia's code of conduct sets the high standard for the industry. It is one of the toughest, if not the toughest Australian industry code. The code complements the tough legislative requirements from government….
>
> Claims that inappropriate behaviour by the pharmaceutical industry is widespread or on the rise are simply untrue. Inappropriate hospitality in association with education events is a rare occurrence. Where it is found, the code is strictly enforced and tough sanctions are applied. (Chalmers 2007)

In Australia, however, there have been repeated breaches of the Medicines Australia Code of Conduct (Harvey 2006). In 2006, the Australian Competition and Consumer Commission (ACCC) incurred the wrath of the industry by imposing a strict condition on the re-authorisation of the Code: 'The ACCC has required as a condition of authorisation of the code significantly greater level of disclosure and transparency, requiring MA to publish details of all functions sponsored by pharmaceutical companies' and 'The information will also be available to the public, via a website, in a timely manner' (ACCC 2006). Medicines Australia and the Australian Medical Association both objected to this condition, reinforcing perceptions of complicity between industry and doctors.

Furthermore, the ACCC (2006) questioned the effectiveness of self-regulation: 'this is a self regulatory code and thus it is unclear how effective it is in actually regulating drug companies' conduct'. Clearly, the ACCC did not share the industry's and the AMA's faith in Medicines Australia's Code.

7.23 CONCLUSION

This chapter has analysed key practices and issues related to the pharmaceutical industry, focusing primarily on practices most relevant to the promotion of antidepressants. Pharmaceutical companies skilfully utilise sophisticated marketing strategies that profoundly influence doctors' prescribing practices. However, both the industry and the medical profession are at pains to downplay the extent of influence, as do other players, including consumer organisations.

The industry invests many millions of dollars annually on drug representative ('drug rep') promotion of antidepressants, the most heavily detailed category of prescribed drug (Forest 2003, p. FCA0017722), and there is evidence of a high return on investment (Neslin 2001). Although many doctors deny being influenced by drug reps, the Deputy Director of the Royal College of Psychiatrists research unit testified to the UK House of Commons (2005b, p. Ev 117) that psychiatrists' antidepressant prescribing is 'obviously influenced' by relationships with reps. Furthermore, the drug samples that reps distribute have been shown to distort prescribing (Patounas & McGuire 2007).

Key opinion leaders have also been demonstrated to influence doctors' prescribing (Robertson et al. 2003). They provide a valuable blend of status and credibility derived from their perceived independence. They participate in multiple promotional strategies, including continuing medical education, guideline development, disease awareness campaigns, and publication of ghost-written journal articles.

Medical journals are another crucial traditional conduit of information from drug companies to doctors, via both advertisements and journal article content in regular issues, supplements, and reprints. Journals' financial dependence on industry creates conflicts of interest and potential bias in favour of drug companies.

Disease awareness campaigns, in which disorders are sold in order to sell drugs, play a very important role in expanding markets, and have been skilfully used by antidepressant manufacturers since at least 1961. Such campaigns often involve health professional organisations such as the American Psychiatric Association and consumer organisations such as NAMI and NARSAD.

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The pharmaceutical industry also skilfully subverts evidence-based medicine in several inter-related ways. It funds the majority of clinical trials, manipulating their design. It strongly influences reporting of clinical trials, using selective reporting, suppression of unfavourable findings, and biased interpretation. Key opinion leaders and ghost-writers are often involved in this. It also commissions and distorts clinical guidelines

Pharmaceutical companies also have significant relationships with health professional organisations, consumer organisations, and government entities. Often there are synergistic triads involving industry, government, and consumer organisations, based on economic factors and a shared agenda to medicalise social problems. One notable example is NARSAD's close and synergistic yet hands-off relationship with the internationally influential US National Institute of Mental Health, which provides a conduit for industry influence on the NIMH. All three parties espouse neuroscientific explanations not only of psychiatric disorders, but also of distress.

Internationally, antidepressants have featured in several high-profile controversies, some of which have culminated in litigation, including the retraction of David Healy's job offer at a teaching hospital affiliated with Toronto University (Healy 2002), and the illegal promotion of Lexapro (United States Attorney's Office 2010).

In response to criticism, the pharmaceutical industry has invested considerable resources in challenging and even discrediting critics. It continues to dogmatically promote its role as the benevolent developer of life-saving and life-changing medicines, playing down its responsibility to maximise profits for shareholders. It has established itself as a self-regulator in Australia, among other countries, helping drug companies (and doctors) to deflect criticism. It has also strategically consolidated its role as a 'partner' in the healthcare arena, including participation in policy-making processes in many countries, including Australia.

The Lexapro case study illustrates not only many problematic promotional practices but also the cooperation of many other players in the promotion of antidepressants and depression. None of this is unique to Lexapro; many other antidepressants could have been used as case studies.

The pharmaceutical industry undoubtedly has an enormous and profitable influence on prescribing of many drugs, including antidepressants, through massive investment

in a range of marketing and promotional strategies that target a range of people and entities. This chapter has analysed how many key strategies are used by pharmaceutical companies to promote prescribed drugs in general (with some examples of antidepressant promotion). The next chapter narrows the focus to depression awareness campaigns, a key promotional strategy for depression and antidepressants .

Common acronyms in this chapter: ACCC Australian Competition and Consumer Commission; APA American Psychiatric Association; CGP clinical practice guideline; DSM Diagnostic and Statistical Manual (of Mental Disorders); DTCA direct-to-consumer-advertising; FDA Food and Drug Administration; KOL key opinion leader; NAMI National Alliance for the Mentally Ill; NARSAD National Alliance for Research on Schizophrenia and Depression; NIMH National Institute of Mental Health; PhRMA Pharmaceutical Research and Manufacturers of America; ROI return on investment; SSRI selective serotonin reuptake inhibitor; SNRI serotonin and noradrenalin reuptake inhibitor; TCA tricyclic antidepressant; TGA Therapeutic Goods Administration

Chapter 8

Depression awareness campaigns: Selling depression and antidepressants

8.1 INTRODUCTION

As briefly discussed in chapter 7, disease awareness campaigns are an important marketing strategy used by pharmaceutical companies to 'sell' diseases or disorders in order to sell drugs. Sometimes disease awareness campaigns sell diseases as social problems, not merely as medical problems. This is the case with depression, which has been sold not only to the public and the medical profession but also to governments. Wiener's (1981) analysis of agenda-building is clearly relevant to this, particularly her discussion of strategies for 'legitimizing the problem' and 'demonstrating the problem'.

This chapter analyses in detail three important disease awareness campaigns focusing on depression in the US and the UK in the 1980s and the 1990s. These campaigns clearly influenced the development of the Australian depression awareness campaign, the Mental Health Foundation of Australia's *National Depression Awareness Campaign*, which is discussed in chapter 9. That campaign in turn, along with the US and UK campaigns, significantly influenced *beyondblue: the national depression initiative*, the pre-eminent mental health entity in Australia.

Other depression awareness campaigns have been launched subsequently, and several of these are briefly discussed at the end of this chapter. However, it is the three campaigns discussed in detail in this chapter that seem to have particularly influenced the Australian campaigns, which in turn have profoundly influenced Australian mental health policy and practice.

Key themes in depression awareness campaigns include Regier et al.'s (1988, p. 1351) triple claim that depressive disorders are 'common, serious, and treatable' and claims that depression has a biological/chemical basis (all of which were analysed in some detail in chapter 4). Claims that depression is caused by a chemical imbalance are often accompanied by claims that antidepressants can fix this imbalance. Furthermore,

antidepressants are sometimes portrayed as not merely curing depression but enabling a return to true selfhood.

Also prominent are visual depictions of misery. Both graphics and photos are used for this purpose. Misery is often strikingly contrasted with happiness using dual visual images, conveying the purported effects of antidepressants.

Two other very important, and inter-related themes, are stigma/destigmatisation and 'mental health (il)literacy'. These are discussed in some detail the next section, because they have been mentioned only in passing elsewhere in this thesis.

8.2 DESTIGMATISATION AND MENTAL HEALTH LITERACY

Destigmatisation and mental health literacy are key concepts in the mental health arena. As noted in chapter 2, two reasons frequently given for undertreatment of depression are stigma and low 'mental health literacy', both of which discourage people from seeking treatment. Furthermore, stigma is seen as a result of lack of understanding about depression (low depression literacy). Consequently it is often taken for granted that destigmatisation of depression is necessary and that education about the nature of depression (depression literacy raising) is particularly necessary to combat stigma. This was emphatically stated in the World Health Organization's widely cited *World Health Report 2001: Mental health: New understanding, new hope*:

> The single most important barrier to overcome in the community is the stigma and associated discrimination towards persons suffering from mental and behavioural disorders.
>
> Tackling stigma and discrimination requires a multilevel approach involving education of health professionals and workers, the closing down of psychiatric institutions which serve to maintain and reinforce stigma, the provision of mental health services in the community, and the implementation of legislation to protect the rights of the mentally ill. Fighting stigma also requires public information campaigns to educate and inform the community about the nature, extent and impact of mental disorders in order to dispel common myths and encourage more positive attitudes and behaviours. (WHO 2001, p. 98)

The World Psychiatric Association (WPA) has also identified stigma as a crucial issue. In approximately 1996, it established *Open the Doors: The WPA Global*

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Programme to Reduce Stigma and Discrimination because of Schizophrenia (Rosen et al. 2000, p. 19). The program is funded by Eli Lilly (p. 25). Pharmaceutical industry funding for destigmatisation campaigns is relatively common, and several other examples are discussed in this chapter.

In Australia, stigma has been identified as a major issue and destigmatisation has been advocated in many key mental health policy documents, including the *Second National Mental Health Plan* (AHM 1998) and the *National Action Plan for Depression* (Commonwealth Department of Health and Aged Care 2000/2001). Not surprisingly, 'Community awareness and destigmatisation' is one of *beyondblue's* five key priority areas (beyondblue 2010, p. 5).

As mentioned in chapter 7, it is commonly argued that if people believed mental illnesses were biological brain disorders, there would be less stigma associated with both the disorders and the sufferers. Although there has been more investigation of stigma related to more serious mental illnesses (particularly schizophrenia) (Kelly & Jorm 2007, p. 13), depression has been at the forefront of this agenda in the public arena, with frequent claims that it is a 'chemical disorder'. This is a key destigmatisation theme.[1]

This is a good example of challenging a supposed myth about depression. Using Wiener's (1981) arena-building terminology, it is an example of 'legitimizing the problem' (p. 21) by redefining its scope, analogous to the promotion of the disease model of 'alcoholism' as an alternative to the moral model).

In fact, there is significant evidence that biological beliefs about mental disorders do not reduce stigma (Read et al. 2006; Jorm & Griffiths 2008; Pescosolido et al. 2010). Furthermore, the belief that biological explanations reduce stigma is based on the false dichotomy (discussed in chapter 4) that if depression is not an illness it must be a weakness of character.

The evidence about mental health literacy (a key concept in mental health promotion) is also less sanguine than it is generally assumed (Kelly & Jorm 2007; Goldney et al. 2005, pp. 136-137). However, analysis of this evidence is beyond the scope of this

[1] It could be referred to as a sub-theme rather than a theme, because it is part of the destigmatisation theme, However, this distinction is not important for this discussion.

thesis. Instead the focus here is on how biological explanations and depression literacy concepts and strategies are used.

Other themes in depression awareness campaigns are also linked to stigma. For example, it is sometimes argued that public education that depression is common will help to destigmatise it (beyondblue 2004; Pethick 2005).

8.3 DEPRESSION AWARENESS, RECOGNITION, AND TREATMENT PROGRAM (D/ART)

In 1988, the US National Institute of Mental Health (NIMH) launched a high-profile public education campaign as a key part of its *Depression Awareness, Recognition, and Treatment Program* (D/ART) (Regier et al. 1988). The broader D/ART program was announced in March the previous year (p. 1352). It had three audiences: primary health care providers (including doctors and nurses), mental health specialists (including psychiatrists and psychologists), and the general public (p. 1352).

D/ART is described in detail in Regier et al.'s (1988) highly cited article, 'The NIMH Depression Awareness, Recognition, and Treatment Program: Structure, aims, and scientific basis'. Published in the American Psychiatric Association's (APA's) flagship journal the *American Journal of Psychiatry*, and emanating from the NIMH, that article had almost unassailable authority.

As discussed in chapter 7, the NIMH has strong links to the pharmaceutical industry, embracing it as a partner. Not surprisingly, therefore, pharmaceutical companies played an integral role in D/ART, not just as financial supporters but also as campaign consultants:

> Campaign consultants include representatives from all the major mental health associations; health and mental health organizations; businesses, including pharmaceutical companies; labor, religious, and educational groups; and mental health advocacy groups. (Regier et al. 1988, p. 1353)

The catchcry of D/ART was that depressive disorders are 'common, serious, and treatable' (Regier et al. 1988, p. 1351). This mantra, which was included in the abstract as well as the body of the article, has been extremely influential both in the

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US and elsewhere, including Australia, where it was incorporated into Royal Australian and New Zealand College of Psychiatrists (RANZCP) clinical practice guidelines for the treatment of depression (Ellis, Hickie, & Smith 2003, p. 34; RANZCP 2004b, p. 389).

Prior to the launch of D/ART, a group of clinical investigators convened by NIMH met to review the evidence, and 'identify major areas of scientific agreement regarding diagnoses and treatments for depressive disorders', and advise NIMH about how to develop the program. The group formulated a three-part message:

1. Clinical depression is a common disorder that usually is unrecognized. When identified, it can be treated.
2. There are effective pharmacological and psychological treatments that often are used in combination.
3. The large majority of clinical depressions, including the most serious, improve with treatment, usually in a matter of weeks. (Regier et al. 1988, p. 1352)

This message characterised depression as common and treatable, but did not emphasise its seriousness. However, that was stressed earlier in the article:

> For some of those who go untreated, depression may be a fatal disease, as demonstrated by the very close association between clinical depression and suicide. (p. 1351)

Economic costs were also emotively emphasised in addition to 'tragic human costs':

> Research on the economics of mental illness has underscored the urgency – and the potential benefits – of undertaking an aggressive effort to ensure the availability of appropriate, high-quality care for depressive disorders.
>
> …. The Depression Awareness, Recognition, and Treatment Program is premised on the conviction that creating the opportunity for an enlightened positive investment in effective treatment will relieve society not only of the tragic human costs but also of a substantial economic burden. (p. 1356)

Regier et al. painted a very positive view of the benefits of treatment:

> Today, 80% to 90% of persons with a major depressive disorder can be treated successfully. (Regier et al. 1988, p. 1351)
>
> Most persons who remain untreated suffer needlessly, given the array of effective psychological and pharmacological treatments that exist. (p. 1351)
>
> Recent decades have witnessed as extraordinary expansion and refinement of an array of treatment modalities for the depressive disorders. The availability of

> effective pharmacological, other somatic, and psychosocial interventions greatly enhances the benefits of early identification and treatment. (p. 1354)

The claim about the benefits of early identification supports screening, promotion of which has been a major component of industry-funded depression awareness campaigns since then, including National Depression Awareness Day (Horwitz & Wakefield 2007, p. 187).

Regier et al.'s discussion of treatment was biased towards pharmacological treatment. The article emphasised the 'solid base of research evidence documenting the effectiveness of psychopharmacological treatments for bipolar and major depression' (p. 1354), and the 'pathophysiology of depressive disorders' (pp. 1355, 1356), which implies that treatment would need to have physiological effects.

In addition, Regier et al. effectively damned psychotherapy with faint praise. They managed to pay lip service to it but subtly discount it as impractical in this description (pp. 1354-1355):

> Research on psychotherapeutic approaches also has been productive, yielding a number of new, short-term (usually in the range of 16 to 20 sessions) therapies that are focused on symptom reduction and are highly interactive between therapist and patient.

Few people would regard 16 to 20 sessions as short-term – or as affordable. Furthermore, describing it as 'focused on symptom reduction' suggests that it does not address the root causes of depression, and that it is at best an adjunct to real (pharmacological) treatment.

The first phase of D/ART, in 1987, focused on the first two identified audiences, primary care and specialist health professionals (p. 1352). Universities and medical schools were funded to provide short-term training on 'the diagnosis and treatment of depression'. NIMH also sponsored professional organisations to provide continuing education programs. Pharmaceutical companies were also involved in this training phase, which not surprisingly was biased towards pharmacological treatment.

> With pharmaceutical company support, APA also has sponsored a series of training sessions for primary care physicians. Particular emphases for nonmedical mental health providers have been on biological and

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> pharmacological treatments; for medical specialists, diagnoses and a full range of treatment techniques have been emphasized. (p. 1352)

Then the public education campaign was launched in May 1988 (p. 1351). Its objectives were:

1. To increase public knowledge of the symptoms of depressive disorders and the availability of effective treatment.
2. To change public attitudes about depression so that there is a greater acceptance of depression as a disorder rather than a weakness.
3. To motivate changes in behavior among the public and treatment professionals. (p. 1352)

The second objective invokes the false dichotomy that if depression is not a disease, it must be a character flaw.

D/ART was multi-faceted and multi-modal:

> The program has provided printed materials, radio and television spots, a toll-free telephone number, special events, and consultation. The community and professional partnership program has instituted model collaborations with states and local entities. D/ART also organizes special events, such as health fairs. (Hirschfeld et al. 1997, p. 336)

The printed materials included millions of brochures. Healy (2004, p. 9) cited a D/ART update that reported that Eli Lilly funded eight million copies of a brochures titled *Depression: What You Need to Know*, and two hundred thousand posters. Another brochure was *Depression: What Every Woman Should Know* (NIMH n.d.).

It was planned that D/ART would be evaluated. According to Regier et al. (p. 1352):

> Information on public attitudes towards depression will provide baseline data against which change can be assessed. Service utilization data will be employed to determine changes in rates of treatment for depression.

However, D/ART has not been formally evaluated (Parslow & Jorm 2002, p. S118), apart from an evaluation of a health professional training program in Iowa (O'Hara et al. 1996). Despite this, it has generally been rated a success. This is reflected in comments such as these:

> The D/ART program appears to have been successful in addressing its goals. It has not, however, been subjected to formal evaluation which would indicate the quantitative impact of its initiatives. (Hirschfeld et al. 1997, p. 336)

> D/ART has been highly successful in de-stigmatizing and creating general public awareness regarding etiology, intervention, and treatment of depressive

> disorders. According to Isabel Davidoff, one of the founders of D/ART… D/ART was a major catalyst in the explosion of information and materials on depression in the general media. (Gabriel 2000, p. 29)

Healy (2004, p. 9) suggested that in fact the beginnings of the media explosion *preceded* D/ART:

> DART and other national campaigns were launched on the waves of an incoming tide. The 1980s saw a dramatic increase in articles about depression in both medical journals and general-readership magazines.

No doubt it was a chicken-and-egg situation, with mutual encouragement by campaign organisers and the media.

Not surprisingly, D/ART's perceived success, along with its authoritative pedigree, has led to it being used as a model for subsequent campaigns, including the UK Defeat Depression Campaign (Rix et al. 1999, p. 99).

Several years in, D/ART shifted much of its focus to the workplace, developing its National Worksite Program in conjunction with the Washington Business Group on Health (Gabriel 2000, p. 29). That program 'established a structure for mental health awareness and training through contact with business and corporate organizations' (Hirschfeld et al. 1997, p. 336).

According to Gabriel (2000, p. 29), D/ART had already achieved substantial influence in the workplace arena prior to the launch of the National Worksite Program:

> It also spurred the increased receptiveness of employers to recognizing the impact of depression on costs and performance. By the late 1990s, at least among larger employers, a substantial change had occurred in the understanding of depression and other mental health disorders. In 1997, D/ART was reconfigured as the National Worksite Program, which works almost exclusively with employers and organizations handling employment issues.

In 1995, the National Institute of Mental Health published a guide for supervisors about how to deal with depressed employees. It did not use the phrase 'common, serious, and treatable', but it got those three elements of D/ART's catchcry across:

> These individuals may be suffering from a very common illness called **clinical depression**….
>
> - Each year, depression affects more than 19 million American adults ….

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- Untreated clinical depression may become a chronic condition that disrupts work, family, and personal life.
- Depression results in more days in bed than many other ailments (such as ulcers, diabetes, high blood pressure, and arthritis)

….

More than 80% of depressed people can be treated quickly and effectively. (NIMH 1995, p. 1)

It also promoted the idea that poor work performance was attributable to depression, listed among the symptoms of which were:

- Decreased productivity
- Morale problems
- Lack of cooperation
- Safety risks, accidents
- Absenteeism (p. 2)

The guide emphasised the economic costs of depression as well as the health costs:

- Estimates of the cost of depression to the nation in 1990 range from $30-$44 billion. Of the $44 billion, depression accounts for close to $12 billion in lost work days and an estimated $11 billion in other costs associated with decreased productivity. (p. 1)

Those estimates are drawn from Greenberg et al.'s (1993) much-cited analysis of the economic burden of depression, which is briefly discussed in section 8.4.

Despite generally favourable opinions, D/ART has attracted some criticism. Most vociferous among the critics has been Fred Gardner, a journalist who has published more than one article criticising D/ART and the NIMH, and depression awareness campaigns more generally, in relation to pharmaceutical industry involvement. According to Gardner (2004), D/ART was effectively a marketing strategy for Eli Lilly:

> The NIMH has played a "handmaiden" role at every key juncture in the peddling of Prozac. In 1987, as Lilly was gearing up to market it, NIMH launched its Depression Awareness, Recognition and Treatment (D/ART) Program to convince the American people that they suffered from "clinical depression" en masse and could get help from a prescription drug.

Prozac® (fluoxetine) was approved by the Food and Drug Administration on 29 December 1987 (Food and Drug Administration 2008). Notably, Regier et al.'s article, which was published in November 1988, did not mention Prozac (or selective

serotonin reuptake inhibitors), and it stated that 'Tricyclic antidepressants and related heterocyclic drugs currently are the pharmacologic treatments of choice for major depressive episodes' (p. 1354). This would not have mattered much to Lilly, because they were able to unleash multi-million-dollar marketing strategies emphasising Prozac's novelty and supposed superiority over these older drugs. It could even be interpreted as beneficial to Lilly in the sense that D/ART was not overtly associated with Prozac, the launch of which could (naively) be interpreted as coincidental.

Gardner (2008), in an article provocatively titled 'Dr. Goodwin and the infinite con: Still shilling after all these years', singled out psychiatrist Frederick Goodwin, one of Regier's co-authors, for particularly vituperative condemnation:

> He's never been anything but a drug-company shill. As Scientific Director of the National Institute of Mental Health (NIMH) in the 1980s Goodwin played a key role in the marketing of Prozac. That sales campaign, brilliantly orchestrated by Eli Lilly, created the template by which Big PhRMA pushes its pills to this day.

Goodwin, who was later the Director of the NIMH, also played a role in the Australian National Depression Awareness Campaign, which is discussed in chapter 9. Sponsored by Roche Australia, he performed the official launch of the campaign in October 1994 (Balshaw 2007, p. 80).

Gardner (2008) elaborated on the role of government in facilitating industry objectives:

> The D/ART Program not only put the governmental stamp of approval on the corporate-funded depression research, it created a mechanism whereby corporate money and personnel could be employed to stimulate demand for antidepressants. NIMH arranged for pharamaceutical [sic] company representatives to draft promotional materials that the nonprofit National Mental Health Association (NMHA) then disseminated.

According to Gardner (2004), it was Eli Lilly staff who drafted the promotional materials, and the NIMH also paid for the distribution:

> D/ART produced "depression awareness" materials – drafted by private sector "campaign consultants" on the Eli Lilly payroll – that were *distributed at government expense*. [italics added]

Hirschfeld et al. (1997) lauded D/ART as 'a model of government participation in provision of support for public health needs' (p. 336). An industry perspective on

using governments is given in section 8.4, providing a rather different slant on government-industry partnership.

D/ART illustrates a remarkable synergy between the agendas of the pharmaceutical industry (particularly Eli Lilly), the National Institute of Mental Health, psychiatrists (particularly the APA and the psychiatrists within the NIMH), and mental health advocacy/consumer organisations (particularly the National Mental Health Association). And it served not only as a model of government participation but also as a model for subsequent depression awareness campaigns, with or without overt government involvement.

8.4 NATIONAL PUBLIC EDUCATION CAMPAIGN ON CLINICAL DEPRESSION

The National Public Education Campaign on Clinical Depression (NPECCD) was launched in the US in 1993 (Hirschfeld et al. 1997, p. 336). The lead player this time was the National Mental Health Association (NMHA), which subsequently became Mental Health America. There was considerable continuity of players from D/ART. Co-sponsors included the APA, D/ART, the National Depressive and Manic Depressive Association (NDMDA), the National Alliance for the Mentally Ill (NAMI), and more than 100 other organisations (Hirschfeld et al. 1997, p. 336). The National Institute of Mental Health (NIMH) was also involved, via the co-sponsorship by D/ART, but did not play a lead role. Additional organisations including the American Academy of Child and Adolescent Psychiatry and the American Public Health Association subsequently became involved (Gabriel 2000, p. 37).

The NPECCD aimed to educate Americans en masse about depression and its treatment. Its campaign message was:

> to deliver a message of hope and recovery to millions of Americans suffering from clinical depression by educating them that clinical depression is a medical illness which can be successfully treated; by helping them to recognize the symptoms of the illness; and by encouraging them to seek help and treatment. (Mental Health America Alaska 1996)

The NPECCD was a very intensive campaign, and it generated impressive statistics in terms of dissemination and population reach:

> The NPECCD was launched in 1993 with paid public service advertising about depression. Ninety-three percent of the US population was reached an average of 11 times each. Over 300000 people responded to the ads over a 3-week period. In the intervening years many activities have been conducted by NPECCD, including the distribution of over 2.5 million brochures. In addition, 40 local campaigns have provided extensive programs around the country. (Hirschfeld et al. 1997, p. 336)

The NPECCD also promoted and facilitated screening for depression, running a National Depression Screening Day with the assistance of organisations such as the American Society on Aging and operating a toll-free, year-round phone-line providing information about screening locations (Cavanaugh 1998).

Pharmaceutical funding was more significant and more overt than in D/ART. The NPECCD received massive funding from Eli Lilly – a $4-million-a-year 'educational grant', according to Gardner (2008). Much of this was spent on public service advertising. Some was spent on videos, which Lilly not only funded, but also actively developed and produced. These included:

> **Depression and Women: Dispelling the Myths** (1995; Adult; 16 min.) Features the inspiring profiles of five women, ranging in age from 18 to 80, who share their stories of their successful battles with depression. Produced by Eli Lilly & Co. for the NMHA's public education campaign on clinical depression.
>
> ….
>
> **Moving Back Into the Light** (1993; Teen/Adult; 15 min.) Developed by Eli Lilly & Co. for the NMHA's national public education campaign on clinical depression. This video exposes the myths and corrects misconceptions about the illness and its treatment. (Mental Health Association of Franklin County 2001)

The upbeat and emotive nature of these titles and descriptions – 'successful battles with depression', and 'Moving Back Into the Light' – is not surprising, nor is the emphasis in both videos on challenging myths about depression.

Lilly also funded depression screening. This included funding for the American Society on Aging to provide grants for 'innovative approaches to screening large numbers of older adults; working with high-risk populations, such as older adults with diabetes; or making depression screening an ongoing part of client intake and assessment' (Cavanaugh 1998).

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Like D/ART, the NPECCD had a partial focus on depression in the workplace, 'specifically describing the economic impact of depression, employees' attitudes towards depression, recognizing the symptoms, and where to go for help' (Gabriel 2000, p. 37). This was assisted by the strategic publication of an analysis of the economic burden of depression (Greenberg et al. 1993), published the year the NPECCD was launched. Like the NPECCD, with which it was not explicitly linked, the study was funded by Eli Lilly. Greenberg et al. concluded that depression cost the US economy $44 billion in 1990, of which 55% was the cost of absenteeism and reductions in productive capacity in the workplace. This widely cited study has been very influential, representing a very effective investment for Lilly. Using Wiener's (1981) arena-building terminology, this is an example of 'demonstrating the problem' by selecting supportive data (p. 22). However, it involved not merely *selecting* supportive economic data but actively commissioning it. Furthermore, as briefly discussed in chapter 4, Greenberg's study is sometimes misrepresented as quantifying the cost of *untreated* depression, making it even more supportive for Lilly.

Another significant article strategically published during the NPECCD, but not explicitly linked to it, is 'The National Depressive and Manic-Depressive Association Consensus Statement on the Undertreatment of Depression' (Hirschfeld et al. 1997). This was the outcome of a consensus conference sponsored by Bristol-Myers Squibb, co-chaired by Professor Martin Keller of Brown University (briefly discussed in chapter 7 in relation to his high-profile key opinion leader activity, including a Wyeth-funded tour of Australia) and Susan Panico, Executive Director of the NDMDA, which was one of the co-sponsors of the NPECCD.

The consensus statement began by emphasising how common and serious and debilitating depression is:

> DEPRESSION is one of the most frequent of all medical illnesses. Depression is a pernicious illness, associated with episodes of long duration, high rates of chronicity, relapse, and recurrence, psychosocial and physical impairment, and mortality and morbidity (p. 333)

It ignored the fact that evidence of the *frequency* of depression comes primarily from surveys of the population and surveys of primary care patients, but evidence of the *perniciousness* of depression comes primarily from studies of patients in secondary or tertiary treatment settings, whose depression is unrepresentative (much more severe

on average) of that of primary care patients and, even more so, depressed people who have not sought treatment. It thus conflates common, relatively mild depression with much less common and much more severe depression, and greatly inflates the supposed burden of depression.

Not surprisingly, given the title of the consensus statement, it concluded:

> There is overwhelming evidence that individuals with depression are being seriously undertreated. Safe, effective, and economical treatments are available. The cost to individuals and society of this undertreatment is substantial. Long suffering, suicide, occupational impairment, and impairment in interpersonal and family relationships exist. (p. 333)

The abstract of the consensus statement lists 'failure to consider psychotherapeutic approaches' as a factor in undertreatment, yet Hirschfeld et al. paid lip service to psychotherapies in the body of the paper. Most notably, in a 1600-word section in response to the questions 'Is depression undertreated in the community and in the clinic? How extensive is the gap between current available knowledge and actual treatment?', psychotherapy was mentioned only twice. Once was in passing: 'In most instances the medical specialty or graduate degree of the person who treated the patient (perhaps in psychotherapy or in a general medical office setting) and the person who prescribed the treatment is not known' (p. 334). The second instance was in the final paragraph, which was appended like a postscript to the conclusion in the paragraph preceding it, and subtly disparaged psychotherapy by implying that it needs to be delivered for a long period of time:

> In conclusion, it is unfortunate that the vast majority of those treated with antidepressant medication are not prescribed an adequate dose for a long enough time. It is not yet clear if use of the newer antidepressants will lessen this problem because of their generally more favorable adverse effects profiles.
>
> Effective structured psychotherapies for depression also exist. Unfortunately, few patients with depression actually receive these psychotherapies. When they do, they may not receive them for a long enough period of time. (p. 335)

As discussed in chapter 6 it is very common for treatment to be equated with antidepressants, particularly in publications with industry links.

Not surprisingly, given its status as lead player (as the National Mental Health Association), Mental Health America has described the NPECCD very positively.

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This includes listing it as number 7 in the list of the 'Top 10 Victories of the Past 100 Years':

> 7. Mental Health America and its affiliates launched the Campaign for Clinical Depression which began a process that has dramatically changed public attitudes toward mental health conditions. (Mental Health America 2009b)

Mental Health America (2007a), promoting its more recent Campaign for America's Mental Health, which focuses on mental disorders more broadly (and is sponsored by multiple pharmaceutical companies), also lauded the NPECCD:

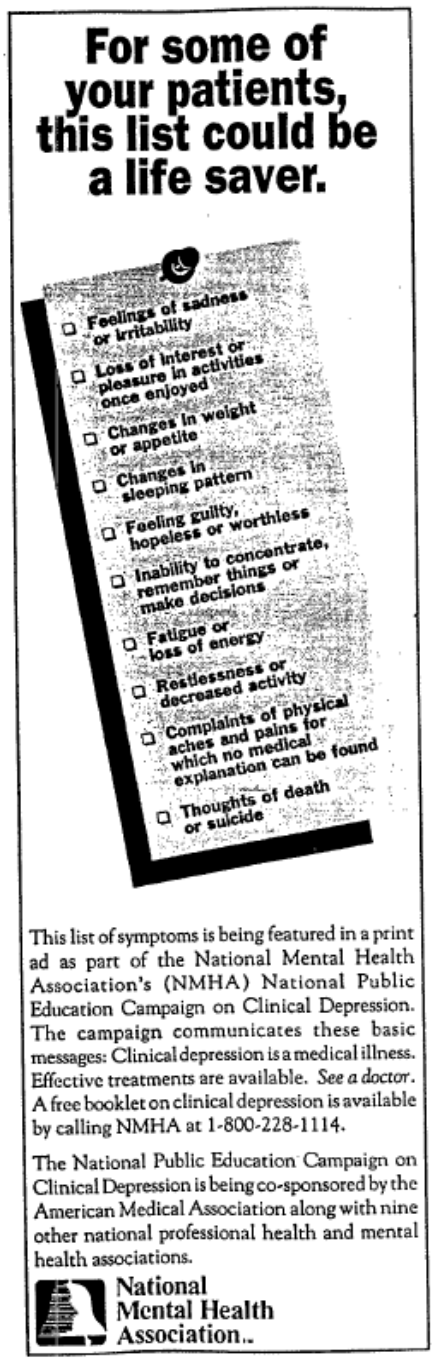
> The Campaign for America's Mental Health is a broad-based public education program that builds upon the success of a long-standing outreach initiative, the Campaign on Clinical Depression. Over the past decade, the Campaign on Clinical Depression has educated millions of Americans about depression and has helped hundreds of thousands seek treatment and resume productive, fulfilling lives.

Both these quotes allude to the fact that the focus on depression in the NPECCD facilitated a subsequent broader focus on mental disorders more generally. This is also a feature of other depression awareness campaigns, including the Australian campaign discussed in chapter 9.

Not surprisingly, given his attitude towards D/ART, journalist Fred Gardner has also been a strong critic of the NPECCD. According to Gardner (2008), there was a marked lack of transparency, among other problems, including over-inclusive screening instruments (questionnaires):

> The people on the receiving end of the info barrage – articles in Parade Magazine, segments on TV news shows, etc. – did not know its ultimate source. For example, on December 1, 1993, "Dear Abby" ran a letter asserting that millions of Americans suffer from clinical depression without realizing it. The letter was signed by a member of an NMHA affiliate in White Plains, New York. Abby urged her readers to call the NMHA's toll-free number to get the free booklet entitled "Answers to Your Questions About Clinical Depression." The booklet included a handy nine-question test for depression. Very few grown-ups who answered it honestly could escape a diagnosis of depression.

Advertisements in medicals journals also failed to disclose the Lilly funding, but invoked the legitimacy and authority of credible co-sponsors that would be likely to be viewed as objective and impartial. For example, this advertisement in *JAMA* (NMHA 1995) informed the reader that the campaign was 'co-sponsored by the American Medical Association along with nine other national professional health and mental health associations':



Notably the ninth item on the checklist, 'Complaints of physical aches and pains for which no medical explanation can be found' is not a DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) (APA 1994) criterion for major depression, unlike the other items. It taps into the theme of somatisation masking depression.

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The NPECCD was managed by Josh Weinstein, then executive vice president and managing director at public relations behemoth Burson-Marsteller (Weinstein 2002a). Weinstein has enthusiastically discussed the NPECCD on the website of jwEinstein Strategic Messaging, the public relations and marketing company he subsequently founded:

> Our principals have managed the largest and most successful advocacy and public education campaign in US history – the National Public Education Campaign for Clinical Depression – which de-stigmatized the name of the disease, identified the symptoms, and then brought millions of patients into needed treatment. (Weinstein 2002b)

According to Weinstein (2004, pp. 1-2), working with advocacy groups can be much a more effective marketing strategy than direct-to-consumer advertising. This long quote, which again discusses the NPECCD, gives an illuminating industry perspective on the rationale for and benefits of collaboration with advocacy groups:

> working with advocacy groups is one of the most accomplished means of raising disease awareness and enhancing the industry's image as deliverer of new and tangible value to patients. Often this advocacy work is unbranded, stimulating consumers to ask doctors about their symptoms. Then, companies can compete by promoting their brands to physicians….
>
> consumers need to know they have a treatable problem and must be motivated to seek that treatment. Then the individual product teams can use professional promotion to battle for brand share of the newly diagnosed patients in the doctor's office.
>
> Over the years, the industry has worked through existing or specially convened advocacy panels or government-industry collaborative groups to raise awareness of disease states such as hypertension, high cholesterol, and clinical depression. Certainly, sending controlled messages through DTC ads was important to category expansion by helping patients rapidly identify themselves as candidates for treatment. But *these disease categories' success would have been lessened without the strong PR messages from doctors, advocacy groups, and the government*….
>
> [One] example is the National Public Education Campaign for Clinical Depression, which was rolled out by a coalition of more than 150 advocacy groups (many of which were supported by pharma companies) to increase awareness of the chemical nature of the illness, its rapid treatability, and the need for aggressive screening.
>
> *Education and destigmatizing disease greatly expanded the market for drugs*. Then, salesforces battled for market share—appropriately—in doctor's offices.
>
> ….
>
> The reason advocacy-based public education builds longer-term support than brand-name DTC promotion is founded on a fundamental PR principle: *a*

> *message's credibility is greater when delivered by impartial third parties than by entities seeking to profit from it*.
>
> Unlike DTC, advocacy-based promotion brings with it a *cadre of allies who've bonded with their industry colleagues in pursuit of a common cause*. This factor grows in importance as the pharma industry becomes more of a political target. *Advocacy groups who know a company and its values can be counted on to speak out for it and relevant issues in times of need*, and *the media will view them as more objective sources than industry spokespeople*. [italics added]

Weinstein's confidence that advocacy groups are *allies* who can be counted on to support the pharmaceutical industry is striking, as is his confidence that doctors will also willingly participate, not only by diagnosing depression and prescribing antidepressants, but also by providing 'strong PR messages'. His confidence in the effectiveness of such alliances is supported by Beder et al.'s (2003) analysis:

> Front groups enable corporations, such as pharmaceutical companies, to take part in public debates and government hearings behind a cover of community concern. Corporations could do this openly and in their own names but it is far more effective to have a group of citizens or a group of experts—preferably a coalition of such groups—which can publicly promote the outcomes desired by the corporation whilst claiming to represent the public interest.

Another key point in Weinstein's approach is the use of *unbranded* disease awareness raising – of which the NMHA (1995) *JAMA* advertisement shown above is a good example – as a driver of *branded* pharmaceutical sales. This shows that prohibitions on branded advertising often have limited effect.

One important 'common cause' in advocacy-based promotion is the desire shared by advocacy groups and pharmaceutical companies to destigmatise conditions such as depression. Destigmatisation is a key pharmaceutical marketing strategy precisely because of this association, not only because of its potential to greatly expand the market for drugs by encouraging people to seek diagnosis and treatment but also because it is an ideal focus of bonding and partnership, which bolsters legitimacy.

It is notable that Weinstein has used the US campaign as an example of a successful *marketing* strategy in two different publications for which the primary audience is people in the pharmaceutical industry. The tenor of his comments about it there are very different from the content of the NMHA advertisement, even though Weinstein might have personally written the copy for the advertisement. As discussed in chapter

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7, pharmaceutical industry and marketing personnel are adept at crafting different messages for specific audiences.

Weinstein's (2004) mention of harnessing *government* public relations messages is highly significant. It supports Gardner's (2004) accusation that the NIMH has played a 'handmaiden' role in relation to the pharmaceutical industry, particularly Eli Lilly. Industry use of government PR messages in Australia is also discussed in the case-study in chapter 9 of the MHFA's National Depression Awareness Campaign.

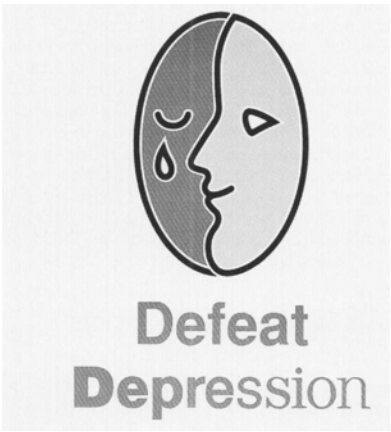
8.5 DEFEAT DEPRESSION CAMPAIGN

The Defeat Depression Campaign (DDC) was launched in the UK in 1992 by the Royal College of Psychiatrists (RCPsych) and the Royal College of General Practitioners (RCGP). It ran for five years. According to Rix et al. (1999, p. 99), DDC was influenced partly by the US Depression Awareness, Recognition, and Treatment Program (D/ART) and by an important depression education campaign for GPs in Götland, Sweden (Rutz et al. 1992), which is briefly discussed in section 8.6.

The aims of the DDC were:

- to educate health professionals, particularly general practitioners, about recognition and management of depression
- to educate the general public about depression and the availability of treatment, in order to encourage people to seek help earlier
- to reduce the stigma associated with depression (Paykel et al.1997, p. 60)

The DDC had a yin/yang-style logo of a face crying on one side and smiling on the other:



(copied from Paykel et al. 1997, p. 61)

This dual image vividly represents sadness and happiness. Juxtaposed with the Defeat Depression slogan, it is almost certain to be interpreted specifically as depression and its resolution. Another dual image, in a Prozac® advertisement, is shown in section 8.6.

Like D/ART, the DDC was multi-faceted (Paykel et al. 1997, p. 61), including leaflets, fact sheets, audiocassettes, newspaper and magazine articles, and television and radio interviews. In addition, several books were published (Rix et al.1999, pp. 99-100). One was Wright's (1993) *Depression: Recognition and management in general practice*, which was distributed to RCGP members. Two others were written for lay readers (and published by the RCPsych's own imprint, Gaskell): Pitt & Calman's (1993) *Down with gloom!*, and Graham & Hughes' (1995) *So young, so sad, so listen*, which focused on depression in children and adolescents and was pitched primarily to parents and teachers. A revised version of Graham & Hughes (2005) includes this alarmist statement by acclaimed children's author Philip Pullman:

> There's nothing mild or gentle about what we call depression. In fact, at its worst it's a savage and merciless disease. Those of us who have felt its power dread it and shun it, and know the way it can ravage and torment the mind, and pursue us unrelentingly while shutting off every avenue of escape, until there seems to be only one way out of the dark labyrinth we're trapped in: and that way is suicide….
>
> …. Whatever the cause and wherever it comes from, if depression strikes you when you're young, it strikes very hard indeed. (p. vii)

The DDC began early in 1992 with a press conference at the RCPsych premises. According to Paykel et al. (1997, p. 61), this launch had considerable impact: 'for about a week there seemed to be no national newspaper, radio program, or television channel that did not feature something on depression'. Media interest continued and coverage was not difficult to obtain: Paykel et al. (1998, p. 522) commented:

> There was a considerable increase in media coverage, including newspaper and magazine articles, television and radio programmes and interviews on depression and acknowledgement by media figures of their own depression. These were often generated specifically by the Campaign to influence public attitudes, but in some cases appeared to be a consequence of the media climate being set by the Campaign.

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According to Priest et al. (1995, p. 493) over 4 million leaflets – *Depression*, *Depression in the Elderly*, *Depression in the Workplace*, and *Postnatal Depression* – had already been distributed.

The DDC was preceded by two consensus meetings in 1991, focusing on recognition and management of depression in general practice. These meetings were attended by representatives of the two colleges and 'other experts' (Paykel & Priest 1992, p. 1198). There was no disclosure of industry funding. However, many of the participants (p. 1202) were industry-funded key opinion leaders, including psychiatrist Stuart Montgomery (briefly discussed in chapter 7) and academic GP Greg Wilkinson, author of a short easily readable book, *Depression: Recognition and treatment in general practice* (Wilkinson 1989), which was distributed free by Boots Pharmaceuticals (inside front cover).

The views of these experts were published as a consensus statement in the *British Medical Journal* (Paykel & Priest 1992). Key points in the consensus statement included: depression is very common in the general population and among general practice patients (p. 1198); GPs frequently fail to detect depression, and they require training to address this (p. 1199); antidepressants are effective in treatment of major depressive disorders; they should not be withheld even if depression seems to be caused by stressful life events; and they should be continued for four to six months after the initial treatment phase, to prevent relapse (p. 1200). Psychotherapies were discussed more positively than in Hirschfeld et al.'s (1997) consensus statement, but support for them was nevertheless more qualified than 'Antidepressants are effective in treatment of major depressive disorders' (p. 1201):

> cognitive and behavioural techniques are effective for *symptom remission* in *milder* clinical depressions….
>
> Disadvantages of cognitive therapy are that *a typical course takes 15 hours* and is not readily available in all areas. *Some patients require preliminary treatment with antidepressants* before they can function well enough (coping, decision making) to make use of psychological measures. (p. 1201) [italics added]

The consensus statement was rewritten as a booklet of guidelines (Management and Scientific Advisory Committee of the Defeat Depression Campaign 1993). These guidelines were distributed to all GPs in England, Scotland, and Wales (Rix et al. 1999, p. 99).

A postal survey of GPs was undertaken after the end of the DDC, to evaluate its impact on awareness of and attitudes towards the campaign and on awareness and use of campaign materials (Rix et al. 1999). Two-thirds of GPs reported being aware of the campaign (p. 99). The consensus statement and guidelines had had the greatest impact, having been read in detail by a quarter of respondents. Forty per cent of respondents said they had definitely or possibly made changes in practice as a result of the campaign. These are impressive results for an education campaign. Clearly the DDC had significant success in terms of educating general practitioners about recognition and management of depression.

The DDC seems to have also been effective in terms of increasing antidepressant prescription. Donoghue et al. (1996, p. 861) reported that overall antidepressant prescribing increased nearly 33% between June 1993 and June 1995, and SSRI prescribing increased 134%. Subsequently, Donoghue (1998) found that there was a five-fold increase in SSRI prescriptions in the five years of the DDC (1992-1996), and a four-fold increase in the number of patients receiving them, indicating that average duration of use increased somewhat.

A public survey in 1991 also preceded the 1992 launch of the DDC, and it was repeated in 1995 and 1997 to evaluate changes in attitudes (Paykel et al. 1998). Funded by the DDC Charity Fund, Priest et al. (1996) investigated lay attitudes to depression and its treatment, in a relatively rigorous stratified door-to-door survey run by the Market and Opinion Research Institute (MORI) in 1991. The key messages of their report were:

- The Defeat Depression campaign encourages depressed people to seek medical treatment and also helps doctors to recognise depression
- Before beginning its five year task the campaign sought opinions from 2003 members of the public
- Most of the sample (78%) thought that antidepressants were addictive, and only 16% thought that they should be given to depressed people
- Most patients treated with antidepressants in primary care abandon taking them prematurely; fear of dependence is one likely explanation
- Patients should be informed clearly when antidepressants are first prescribed that discontinuing treatment in due course will not be a problem (p. 859)

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It is striking that three of these points focused on addictiveness and that no treatment other than antidepressants was mentioned.

The emphasis on non-addictiveness also featured prominently in the abstract, which concluded: 'Doctors have an important role in educating the public about depression and the rationale for antidepressant treatment. In particular, patients should know that dependence is not a problem with antidepressants' (p. 858). As mentioned in chapter 6, this was a major theme of the DDC (e.g. Priest et al. 1996, p. 858). In fact, it could have been stated as a fourth aim of the campaign. The RCPsych and RCGP were clearly adamant that antidepressants were not addictive and 78% of the public were wrong. According to Medawar (1997, p. 27), they responded to the poll results with a press release headlined 'Antidepressants not addictive'.

Vize & Priest (1993) rather patronisingly suggested that the unwelcome opinion of the majority was due to ignorance: 'it seems likely that many members of the public do not know the difference between antidepressants and benzodiazepines' (p. 574). Vize & Priest seemed unaware that when benzodiazepines were introduced, it was similarly claimed that they did not cause addiction, until overwhelming evidence made this position untenable (Medawar & Hardon 2004, pp. 28-43).

In fact, the DDC's efforts to persuade the public that antidepressants were not addictive were largely futile. In the 1997 MORI survey, despite increased approval of antidepressants as a treatment strategy, the majority of respondents still regarded them as very or fairly addictive (Paykel et al. 1998, p. 520). According to UK psychiatrist David Healy, rejection of the DDC message was to be expected:

> a specter stalks the SSRIs. Most people feel that suicide on treatment is not something that could happen to them. But almost all of us believe that we could become dependent on drug treatments. This makes us skeptical of claims by the DART and Defeat Depression campaigns that antidepressants are not addictive. (Healy 2004, pp. 270)

In fact, as discussed in chapter 6, the risk of suicide has become a much more prominent spectre over antidepressants in recent years, and the dependence debate has abated markedly. Nevertheless, dependence was *the* issue in the 1990s.

As was the case with the Depression Awareness, Recognition, and Treatment Program (D/ART) and the National Public Education Campaign on Clinical Depression (NPECCD), most commentary about the DDC has been favourable, and it has

influenced other campaigns. However, there have been some critics. Most notably, UK consumer safety advocate Charles Medawar was a vociferous and persistent critic. Medawar, undoubtedly a thorn in the side of the RCPsych, ran a sustained campaign against the DDC – and antidepressant promotion more generally. This culminated in his online publication of 'The Antidepressant Web; Marketing depression and making medicines work' (Medawar 1997), a thirty-thousand-word treatise analysing the promotion of depression and antidepressants and the evidence about the safety and effectiveness of antidepressants.

In relation to safety, Medawar particularly focused on the dependence potential of antidepressants, although he also canvassed evidence that they could trigger suicidality and aggression. He argued that there was considerable evidence of withdrawal problems with selective serotonin reuptake inhibitors (SSRIs) such as Prozac®, and he criticised the consensus statement (Paykel & Priest 1992) for advocating long-term use. According to Medawar, Paykel and Priest 'addressed the abiding public concern (Priest et al., 1996) that antidepressants were drugs of dependence simply by denying it'. The denial was based on very restrictive definitions of dependence. Medawar published some excerpts from correspondence in which the two colleges relied on drug-seeking as a defining feature of dependence:

> "We have searched the literature and can find no reference to research evidence that shows that (a) drug seeking behaviour or (dependence), or (b) rebound and withdrawal occur when prescribing antidepressant medication ..." There is no street market in antidepressants. In fact it is our experience that it often difficult to get patients to take some initially, and to continue for the recommended course length." (McBride [Honorary Secretary of Council, RCGP], 1992)
>
> "The statement that antidepressants are not addictive is correct. Antidepressant drugs do not result in drug-seeking behaviour, i.e. they do not have a market value, neither do they cause dependence in a technical use of the word..." Obviously a person who is still suffering from depressive illness from whom the drug is then withdrawn would suffer a return of depressive symptoms that could have very serious consequences. This, however, is an indication of their efficacy not of dependence." (Sims [President, RCPsych], 1992) (Medawar 1997, p. 27)

More broadly, Medawar argued that the 'goalposts of dependence' had been shifted (narrowed) by the RCPsych and the RCGP and by many other players, including the American Psychiatric Association and prominent key opinion leaders. Combined with

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the greatly *broadened* 'goalposts' for depression, and aggressive promotion of SSRIs, this fostered high levels of dependence.

Another persistent critic of the DDC has been UK critical psychiatrist Joanna Moncrieff:

> In an unconscious alliance of interests, influential psychiatrists developed and popularised the view of depression as a common biologically based disorder, amenable to drug treatment and as yet frequently unrecognised. This concept had the dual benefits of vastly expanding the market for psychiatric drugs and extending the boundaries of psychiatry outside the asylum. Since this time the psychiatric profession and the drug industry have continued to try and inculcate this idea into the consciousness of both the general public and other doctors. The DDC is the latest offensive. (Moncrieff 1997)

Two years later she drily commented on the fact that DDC and the resultant increase in antidepressant use had not reduced the number of people on sickness and invalidity benefits because of depressive disorders: 'it is disappointing that the DDC and the increased prescription of antidepressants have not influenced this aspect of long-term morbidity' (Moncrieff 1999, p. 195).

Others have endorsed the DDC but expressed reservations about some aspects of it. Commenting on Donoghue et al.'s (1996) study, which found that antidepressant prescription increased so dramatically during the DDC, UK psychiatrist Simon Gilbody (1997) expressed concern about links with industry, particularly when not disclosed:

> It is important that well intentioned national initiatives (such as the Defeat Depression Campaign) designed to extend quality health care to a wider number of people are not used opportunistically by commercial interests to promote a particular product. We were surprised that the fact that Hiram Wildgust, one of Donoghue's colleagues, is an employee of Lilly Industries was not acknowledged as a conflict of interest. (p. 826)

Awareness of and disclosure of industry-related conflicts of interest were also an issue for the RCPsych. During the 2005 UK House of Commons inquiry into the influence of the pharmaceutical industry, Dr Tim Kendall, Deputy Director of the RCPsych research unit, was caught out by being unaware of industry funding of the DDC:

> Q287 Dr Naysmith: …. I just want to ask in a very snappy way whether the Royal College now regrets accepting pharmaceutical company sponsorship for its Defeat Depression campaign which was largely supported by the College.
>
> Dr Kendall: I am not convinced that they did actually receive support from the pharmaceutical industry. I can certainly find out and let the Committee know.

> ….
>
> Q290 Dr Naysmith: Would you think it a bad thing if you had?
>
> Dr Kendall: Yes, because money usually brings with it some sort of influence and in having a campaign to raise awareness about depression, we need to be really careful that is not to try to increase the use of anti-depressants just to increase profits.
>
> ….
>
> Q294 Dr Naysmith: I am sorry to embarrass Dr Kendall, but I have here a copy of a letter from the President of the Royal College of Psychiatrists to the Social Audit, published Volume 28, which says that the campaign's total income amounted to £449,800, of which only £129,530, that is 28.8%, came from pharmaceutical companies.
>
> Dr Kendall: That is terrible; I did not know that. (House of Commons 2005b, p. Ev 132)

This illustrates the fact that industry funding, even when it is not covert, is frequently unnoticed and unexamined. It also illustrates the value of persistent investigation and action on the part of critics such as Charles Medawar (the founder and principal of Social Audit).

Healy (2004), criticising both D/ART and DDC, emphasised the unintended consequences of the actions of well-meaning psychiatrists:

> In terms of professional organizational responsibility, DART of the APA and Defeat Depression of the Royal College of Psychiatrists (RCP) began as small, minimally funded campaigns, organized by a few people who really did think that increased recognition might make a difference for the better. None of those involved could have possessed any inkling that far from decreasing suicide rates, their actions might have had the opposite effect. They had almost no reason to think that the relatively small amounts of money they got from pharmaceutical companies such as Lilly compromised them. But if this is true of the small ginger groups of clinicians within APA and RCP responsible for these campaigns, it is not clear that these professional bodies can be completely exonerated, given that it is our collective duty to speak out about the hazards. (Healy 2004, p. 251)

This interpretation of D/ART, although critical, was much less cynical than that of Gardner (2004, 2008). However, both critics emphasised the considerable harms created by the two campaigns.

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8.6 OTHER DEPRESSION AND MENTAL ILLNESS AWARENESS CAMPAIGNS

There have been other depression awareness campaigns, in many countries. Among them is the *Nuremberg Alliance Against Depression* (NAD), which was launched in Germany in 2000, funded by the German Ministry for Education and Research (Hegerl et al. 2006, p. 1232). It has subsequently expanded into the European Alliance against Depression (EAAD), which was established in 2004 with funding from the European Commission, and has operated in 17 countries in Europe (Hegerl et al. 2009, p. 596).

The evaluation of the NAD found that it resulted in 'more positive attitudes towards medication treatment and antidepressants', fewer people believing that depression was caused by 'lack of self-discipline', and fewer subscribing to the notion of 'pull yourself together' as a treatment option (Dietrich et al. (2010, p. 135). However, many of the changes receded when the NAD was less intensive. Dietrich et al. concluded that there was a need for 'permanent depression awareness action'.

Like the Defeat Depression Campaign, the NAD was partly influenced (Hegerl et al. 2006, p. 1226) by the depression education program for GPs on the island of Götland, Sweden. The evaluation of that campaign found increased prescription of antidepressants and a significant decrease in suicide (Rutz et al. 1992). Consequently, the Götland study is sometimes cited as evidence that antidepressants reduce suicide. However, the effects of the program were short-lived, and Rutz et al. concluded that the program would have to be repeated approximately every 2 years to maintain the effects (p. 83).

The US *Depression Is Real* campaign, sponsored by various consumer advocacy organisations including NAMI, National Mental Health Association, and the Depression and Bipolar Support Alliance, and other organisations including the American Psychiatric Foundation (a philanthropic offshoot of the American Psychiatric Association), was funded by Wyeth (National Alliance for the Mentally Ill (NAMI) 2006). It aimed 'to counter misconceptions about depression' and:

> to educate Americans that depression is a serious, debilitating disease that can be fatal if left untreated and to provide hope for recovery to the nearly 19 million Americans who suffer from depression each year. (NAMI 2006)

Eli Lilly funded a depression awareness campaign run in Thailand by public relations giant Burson-Marsteller (Hanpongpandh 2006), which also ran the NPECCD (Weinstein 2002a). As was the case with the NPECCD and *Depression is Real*, psychiatric organisations and government were centrally involved: Burson-Marsteller was hired by the Thai Department of Mental Health, the Thai Royal College of Psychiatrists, and the Psychiatric Association of Thailand (p. 349). Extensive media coverage was obtained, using press releases, expert interviews, and a mental health seminar (pp. 350-351) as well as feature articles and advertorials.

In the US in 1995, the National Alliance for Research on Schizophrenia and Depression (NARSAD), which was established by the National Alliance for the Mentally Ill, the National Mental Health Association, the National Depressive and Manic Depressive Association, and the American Schizophrenia Foundation, and receives funding from many drug companies (NARSAD 2006?), launched an industry-funded campaign, 'Depression. A flaw in chemistry, not character.' The campaign message was famously displayed, with the phone-number for NARSAD's Infoline, in a large sign on a New York building, proclaiming:

> DEPRESSION IS A FLAW IN CHEMISTRY NOT CHARACTER
> FOR FREE INFORMATION CALL 1-800 829-8289

(http://www.pbase.com/czsz/image/41853421)

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Newspaper advertisements were placed nationwide by NARSAD (Valenstein 1998, p. 177), to challenge common perceptions about depression and educate people about its real nature. The advertising copy packed in many key themes, include the analogy that depression is a disease like diabetes (and implicitly that it similarly needs long-term drug treatment), depression is serious, the weakness/disease dichotomy, depression as chemical imbalance, the non-discriminatory nature of depression (with famous sufferers cited as proof), and progress in treatment, particularly the development of more effective new drugs:

> People with cancer aren't expected to heal themselves. People with diabetes can't will themselves out of needing insulin.
>
> And yet you probably think, like millions of people do, that you or someone you know should be able to overcome another debilitating disease, depression, through sheer will and fortitude. For untold decades, it has been thought that depression is the symptom of a weak character or underlying laziness. In reality, nothing could be further from the truth
>
> Recent medical research has taught us that depression is often biological, caused by a chemical imbalance in the brain. We've even found that depression has a genetic link.
>
> An inherited disease? You probably think that sounds pretty hopeless. But when it comes to depression, it's actually good news. Because it reclassifies depression as a physical disease instead of a mental illness. A distinction that's the difference between it being curable instead of just treatable.
>
> While these recent discoveries should help relieve the stigma associated with depression, a look at history also helps. It's a well documented fact that Abraham Lincoln was depressed for most of his adolescence and adult life. Sir Winston Churchill referred to his depression as "the black dog," starting after the failure of the 1915 Dardanelles Expedition and shadowing him his entire life. You see, depression doesn't discriminate. Anyone can get it. And today you can find books written about admitted sufferers Mike Wallace, Joan Rivers, and Dick Cavett just to name a few.
>
> The reality is, there's never been a better time to be depressed. With new therapies, drug company and academic research, and ever increasing medical interest, help is available today that only 5 years ago didn't exist. Call 1-800-717-3111 if you or someone you know needs help. With this better understanding of depression, we hope you'll see the only shame would be not calling. (NARSAD 1995, reproduced in Valenstein 1998, p. 178)

The claim that depression is curable because it is 'a physical disease instead of a mental illness', ignoring the fact that there are physical diseases that are not curable, is more unusual than claims that it is like a physical disease such as diabetes (which is not regarded as curable, and instead is generally managed as a chronic condition).

Also notable is the rather bizarrely upbeat statement that 'there's never been a better time to be depressed'.

There have also been some relevant campaigns run by drug companies without explicit involvement of other players. These have been direct-to-consumer advertising campaigns that promote depression as well as promoting antidepressants. They have included significant elements of depression awareness campaigns, rather than primarily – and overtly – promoting a specific antidepressant on the basis of its supposed benefits.

The latter is the case in the Wyeth Pristiq® (desvenlafaxine) advertisement critically analysed by Healthy Skepticism (2010), as discussed in chapter 7. The major message of that advertisement was a claim that Pristiq did not require dose titration, purportedly giving it an advantage over competitor SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin and noradrenalin reuptake inhibitors). Although the advertisement was problematic, its main audience was doctors, not the public, and it was primarily promoting a particular antidepressant, not the concept of depression.

Antidepressant advertisements that promote depression, particularly as a serious disease that requires treatment, are more insidious. There is no clear boundary between disease awareness campaigns and direct-to-consumer advertising, and there are antidepressant advertisements that clearly fit in both categories, unlike the Pristiq advertisement.

Notable among these has been Lilly's multi-million-dollar 'Depression hurts. Prozac can help.' campaign, launched in 1997 (Grinfeld 1997). That campaign featured four different two-page dual-image magazine advertisement spreads, one for each season. The spring advertisement contrasted a storm-cloud of depression with a cheerful Prozac sun:

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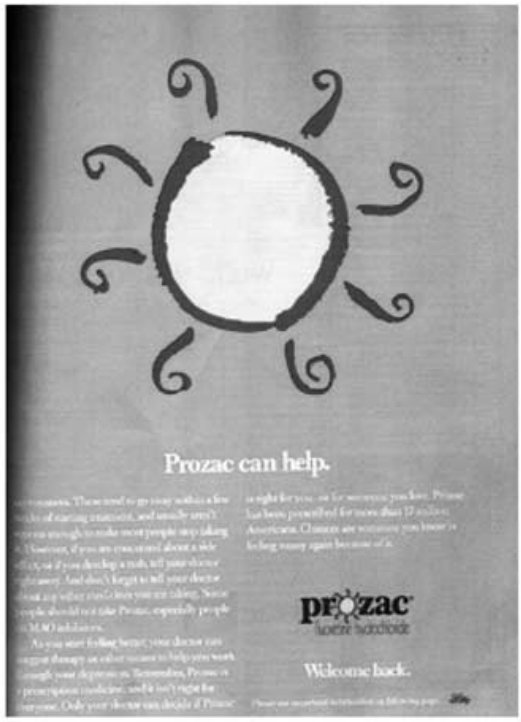

(copied from Grow et al. 2006, p. 182)

The sun image was also used as the 'o' in the drug name 'prozac', below which is the phrase 'Welcome back.', conveying the message of recovery and return to true selfhood. These advertisements ran in more than twenty major magazines, and according to Grinfeld (1997) were expected to be read by 'tens of millions of consumers'.

Like Regier et al.'s (1988) D/ART manifesto, the advertisement implies that psychotherapy is appropriate only as an adjunct to pharmacological treatment. After explaining that Prozac helps bring abnormally low serotonin levels back towards normal, it adds:

> As you start feeling better, your doctor can suggest therapy or other means to help you work through your depression.

The advertisement also strives to destigmatise antidepressant use, emphasising that it is common, and that it is likely to occur in the reader's social network:

> Prozac has been prescribed for more than 17 million Americans. Chances are someone you know is feeling sunny again because of it.

Such campaigns are often endorsed by psychiatric and mental health organisations, despite not being actively involved. For example, Grinfeld quoted the Executive

Director of the National Depressive and Manic-Depressive Association defending the 'Depression hurts' campaign by saying:

> "… what's more important than any concern over commercialism is that the message about mental illness get [sic] out to consumers.
>
> "If the Prozac ad is going to get people to see their doctor to be screened for depression, then it's a good thing," she said.

The depression awareness campaigns discussed in this chapter have paved the way for more recent campaigns about other mental disorders, although a few smaller-scale campaigns with a broader focus predate them, such as the UK *You in Mind* campaign (Barker et al. 1993). Dumesnil & Verger (2009) have provided a useful critical review of some key campaigns focusing on mental disorders (including depression) and suicide. Notably, they commented that 'No study has clearly demonstrated that such campaigns help to increase care seeking or to decrease suicidal behavior' (p. 1203). There was more evidence of success in terms of stigma reduction, which was a major theme in the campaigns they reviewed, including the New Zealand *Like Minds, Like Mine* campaign (Fearn & Wyllie 2005; Vaughan & Hansen 2004) and the Scottish *see me* campaign (Myers et al. 2009).

In the UK, the Royal College of Psychiatrists' *Changing Minds: Every Family in the Land* campaign (Crisp 2001; Crisp et al. 2005), which began in 1998, also particularly strove to reduce stigma associated with a range of mental disorders. In a trenchant sociological analysis of *Changing Minds*, Pilgrim & Rogers (2005) noted that it had had substantial drug company funding (p. 2254), but they concentrated primarily on the role the campaign played in relation to the status and credibility of psychiatry as a profession. This is an example of the compatibility of the pharmaceutical industry's profit agenda with a profession's interests beyond the obvious monetary realm.

In the US, the *Campaign for the Mind of America* was launched by National Alliance for the Mentally Ill (NAMI) in 2002 'to raise awareness about mental illness and promote recovery' (Bender 2002a). As mentioned above, Mental Health America (2007) referred to it as building on the success of the National Public Education Campaign on Clinical Depression.

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As well as targeting the general public who might be 'screening themselves out of treatment because of ignorance and misunderstanding', the *Campaign for the Mind of America* also had a novel focus on high school student debaters. In addition, it included a program specifically for political candidates:

> NAMI worked on getting political candidates up to speed on a number of issues pertaining to mental health and mental illness with its "I Vote, I Count" program.
>
> The program seeks to educate candidates and voters alike on pressing mental health issues across the U.S. while clarifying candidates' positions on the issues. (Bender 2002a)

A strong political focus was also apparent in a Campaign report, 'To lift the burden: Reducing the costs of untreated mental illness in Ohio while improving care' (NAMI Ohio 2005), which declared (p. 18):

- OHIO MUST JOIN 35 OTHER STATES AND PASS A MENTAL HEALTH PARITY LAW TO END THE DISCRIMINATION IN INSURANCE COVERAGE FOR THE TREATMENT OF MENTAL ILLNESSES.
- DOCTORS MUST BE ALLOWED TO UTILIZE THE LATEST BREAKTHROUGHS IN MEDICAL SCIENCE TO TREAT THE MOST SEVERLY MENTALLY DISABLED WITHOUT BUREACRATIC [sic] RESTRICTIONS TO THE ACCESS OF LIFE-SAVING MEDICATIONS.

The report repeatedly conflated treated and untreated mental illness, implying that the burden was attributable to *untreated* cases, as suggested by the title. As discussed in chapter 4, conflation of treated and untreated depression (and other mental illnesses) is rife in the mental health arena. The title also conveyed the economic imperative for increased funding for treatment, as does this excerpt:

> What are the Positive Effects of Access to Medications?
>
> *Enhanced productivity* – With appropriate treatment, most people with serious mental illness are capable of working and contributing to the American tax base. In fact, a recent survey found that the majority of the costs of treating depression are offset by the increased productivity of the individuals who received treatment. [italics in original] (NAMI Ohio 2005, pp. 8-9)

The heading makes it clear that 'appropriate treatment' means *medications*. The emphasis in the second dot-point above on 'THE LATEST BREAKTHROUGHS IN MEDICAL SCIENCE' was part of a demand specifically for access to newer medications. The report claimed that such medications are more effective, 'LIFE-SAVING', even miraculous (p. 7):

> With effective treatment and support, recovery from mental illness is feasible for most people. For the most severely disabled, effective treatment often means access to the newest medications, such as atypical antipsychotic and anti-depressant agents. **Correctly prescribed, these miracle medications have proven to be successful tools to help the sickest citizens reclaim their lives free of the debilitating symptoms of a serious mental illness**. [bold in original]

Predictably, the *Campaign for the Mind of America* has had substantial pharmaceutical industry funding. This includes US$450,000 from Eli Lilly alone (Rothman et al. 2011), and the total is likely to be much higher. NAMI benefits enormously from drug company largesse: an investigation by Republican Senator Charles E. Grassley revealed industry donations of nearly US$23 million between 2006 and 2008 (Harris 2009). Furthermore, much industry funding has not been publicly disclosed (Rothman et al. 2011).

8.7 CONCLUSION

Depression awareness campaigns are a very public strategy for 'demonstrating the problem' (Wiener 1981, p. 22) and 'legitimizing the problem' (p. 21). An enormous amount of time and energy has been invested in such campaigns in recent decades, by health professional organisations (particularly the American Psychiatric Association and the Royal College of Psychiatrists), by mental health consumer/advocacy organisations (particularly the National Mental Health Association and its successor, Mental Health America, and the National Alliance for the Mentally Ill), and by pharmaceutical companies. The media have also been enthusiastic participants.

The key themes of depression awareness campaigns identified in the introduction have been prominent in the campaigns discussed in this chapter. Other themes have also emerged. Some themes seem to have been used only in one campaign, but many have been used repeatedly in diverse campaigns over time.

D/ART and DDC both emphasised that depression was common. The NPECCD referred to 'millions of Americans suffering from clinical depression' (Mental Health America in Alaska 1996); NAMI's Wyeth-funded *Depression Is Real* campaign more

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precisely asserted that 'nearly 19 million Americans … suffer from depression each year (NAMI 2006).

The seriousness of depression was emphasised in D/ART's catchcry and in *Depression Is Real*. There were explicit references to the risk of suicide in D/ART and DDC. Many claims about the seriousness of depression involved conflation of mild and severe depression and conflation of treated and untreated depression (as discussed in chapter 4).

The treatability of depression featured very prominently in D/ART, NPECCD, DDC, NARSAD's 'flaw in chemistry' campaign, and Eli Lilly's 'Depression hurts' campaign. The treatability of mental disorders more broadly was forcefully hammered in NAMI's *Campaign for the Mind of America*. The workplace components of D/ART and NPECCD emphasised the economic costs of depression and the benefits of treatment.

Claims that depression is common, serious, and treatable are clearly intended to educate the public and to encourage people with depression to seek treatment. They also underpin public screening activities, which not only promote diagnosis and treatment but also present opportunities to further 'educate' people about depression and antidepressants. Also, along with economic claims, they are a strategy for lobbying governments to increase funding for depression treatment (and mental health services more generally). In Australia, changes in mental health policy (discussed in chapter 9) are testament to the effectiveness of such lobbying.

The biological/chemical basis of depression was strongly promoted in D/ART, NPECCD, NARSAD's 'flaw in chemistry' campaign, and NAMI's *Campaign for the Mind of America*. The claim that the appropriate treatment is therefore biological/chemical is implicit in this theme. It was expressed more explicitly in the NARSAD campaign's use of the analogy of diabetes requiring insulin.

In addition, although psychotherapies were sometimes mentioned, this tended to be as an afterthought. Also they were often subtly dismissed or denigrated. This included stating or suggesting that: psychotherapies are only appropriate for *mild* depression (this was often stated in a context emphasising the *seriousness* of depression) or resolution of *symptoms*; they are only useful as an adjunct to pharmacotherapy; and they require many sessions to be effective.

The misery of depression was emphasised in the DDC, particularly in Graham & Hughes (2005) book *So young, so sad, so listen*. It was also verbally headlined in Eli Lilly's 'Depression hurts' campaign, and it was visually contrasted with recovery in the contrasting storm-cloud and sun images used in magazine spreads in that campaign, and in the DDC's yin/yang-style logo. Lilly's campaign explicitly attributed recovery to Prozac, and the *Campaign for the Mind of America* portrayed medications as having miraculous properties to help people 'reclaim their lives'.

The campaigns discussed in this chapter also illustrate some key characteristics of how depression awareness campaigns function and how they are used. These are strategic process issues rather than content issues.

One notable feature of some of the campaigns is the strategic publication of industry-funded journal articles that can be used for lobbying purposes (e.g. Greenberg et al.'s (1993) analysis of the economic burden of depression, and Hirschfeld et al.'s (1997) consensus statement on the undertreatment of depression). These can be viewed as extensions of depression awareness campaigns, although not explicitly linked to them.

Probably the most important characteristic of the campaigns is the fruitful synergy between pharmaceutical industry interests and the agendas of health professional organisations such as the American Psychiatric Association and the Royal College of Psychiatrists, mental health advocacy/consumer organisations, and government entities. This was particularly apparent in D/ART, NPECCD, and DDC. However, there is a marked difference in attitudes among players towards this synergy. From an industry perspective, it is something to be used in the pursuit of profit. This is explicitly acknowledged in articles published for industry-insiders that reveal calculated exploitation of common causes (e.g. Weinstein 2002a, 2002b, 2004).

In contrast, the perspectives of professional organisations and advocacy/consumer organisations tend to be naïve, accepting drug companies' and industry bodies' public statements at face value. Furthermore, if challenged about industry motives or potential conflicts of interest, they typically respond defensively, as the Royal College of Psychiatrists did when challenged by Charles Medawar in relation to the Defeat Depression Campaign (Medawar 1997).

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The contrast in perspectives is apparent in the theme of destigmatisation, which was prominent in D/ART, the NPECCD, the DDC, NARSAD's 'flaw in chemistry' campaign, and many of the campaigns reviewed by Dumesnil & Verger (2009). It was regarded as a key theme by all major players. However, their reasons differed. Weinstein (2004) promoted it as a strategy for greatly expanding the market for antidepressants. Substantial industry funding of destigmatisation campaigns suggests that many in the industry would agree with him. For the other major players, however, it was a humanitarian agenda intended both to make it easier for people with depression to seek treatment and to improve their quality of life. As mentioned in section 8.4, destigmatisation is also an ideal focus of bonding and partnership among players, and it bolsters the legitimacy of drug companies as advocates for mental health and as agents of improvement in population mental health through funding and facilitation of education, screening, diagnosis, and treatment.

Crucially for industry, the promotion of the idea that biological explanations of depression would reduce stigma (despite evidence to the contrary), as was explicitly predicted in NARSAD's 'flaw in chemistry' advertisement, also logically implies that appropriate treatment would necessarily be biological. These campaigns are part of what Beder et al. (2003, p. 5) have referred to as:

> pharmaceutical industry-funded public relations activity which has provided policy entrepreneurs and organized advocacy coalitions to promote drug treatments for what are often claimed to be imbalances in brain chemistry

So the destigmatisation agenda has had (and continues to have) multiple benefits for industry, with authoritative players promoting a key message that drug companies want promoted, in harmony with direct-to-consumer advertising, journal advertisements, and other overt marketing strategies.

From a critical perspective – which is rare in the destigmatisation literature – this seemingly humane agenda, and the broader shared agenda of encouraging people to seek diagnosis and treatment, functions not only to increase antidepressant consumption but also to normalise depression diagnosis and treatment, both to doctors who are exhorted to fulfil this role and to patients who are encouraged to seek and accept these services.

The emphasis on mental health literacy is arguably paternalistic, predicated on the assumption that the public need education by health professionals, in a one-way

transaction. At times such education has verged on indoctrination. This is evident in the determination of the Defeat Depression Campaign organisers to disabuse the public of their belief that antidepressants were addictive (a belief for which some evidence existed at the time, and considerably more has emerged since, as discussed in chapter 6). Paternalism is also evident in this quote from the Executive Director of the Depression and Bipolar Support Alliance (DBSA):

> "Education is paramount," Lewis said, to eradicate stigma surrounding mood disorders. Her statement was in response to the finding that 60 percent of Americans were not interested in learning more about mood disorders.
>
> Lewis said that this statistic will not discourage DBSA from disseminating information on mood disorders through its newsletters, speakers bureau, media projects, health fairs, and Web site. "We are proactively educating the public," she said (Bender 2002b)

Such rhetoric is remarkably similar to much of the rhetoric employed to justify the 'War on Drugs', a war that is increasingly being recognised as futile (Transform 2009).

Furthermore, claims that treatment is always necessary and that people with depression cannot heal themselves reveal the medical profession's ignorance of the evidence about so-called spontaneous remission. They also reveal lack of awareness of, and lack of interest in, the resilience and resourcefulness of people and communities.

Such claims also bolster the status of mental health professionals, particularly psychiatrists. This was noted by Pilgrim & Rogers (2005) in relation to the Royal College of Psychiatrists' *Changing Minds* campaign. The more significant a problem depression is believed to be, and the more it is accepted that psychiatric drugs are the solution, the more important psychiatrists seem. Also, like pharmaceutical companies, psychiatrists gain kudos and gratitude by promoting the seemingly humane agenda of destigmatisation. And of course the more important and caring psychiatrists seem, the more valuable they are to industry as partners who can provide legitimacy and authority.

There is ongoing strong enthusiasm for depression (and other mental illness) awareness campaigns, despite lack of clear evidence that they increase treatment-

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seeking or decrease suicidal behavior (Dumesnil & Verger 2009, p. 1203) – and often lack of evaluation of campaigns. The repetitiveness of disease awareness campaigns over decades of intensive investment of resources certainly brings into question their effectiveness in changing public attitudes. For example, eleven years after NARSAD launched its 'flaw in chemistry' campaign, and more than twenty years after D/ART commenced, NAMI (2006) and Wyeth and their allies in the *Depression Is Real* campaign were arguing that Americans needed to be educated that depression is a serious, debilitating, potentially fatal by treatable disease. Furthermore, evaluations of both the *Nuremberg Alliance Against Depression* and the Götland GP depression education program concluded that ongoing depression awareness activities were necessary.

From a pharmaceutical industry perspective, the disappointing long-term results of depression awareness campaigns are not really a problem, because antidepressant sales increase in the short term. Indeed an argument can be made that antidepressant manufacturers *benefit* from the lack of effectiveness, provided it motivates consumer organisations and health professional organisations to continue to launch new initiatives.

Furthermore, the depression awareness campaigns discussed in this chapter have served as precursors to campaigns with a focus on other mental disorders, which will pay dividends for manufacturers of other psychiatric drugs (this includes most antidepressant manufacturers). Antidepressants were blockbuster drugs in the 1990s and early 2000s, but are now much less profitable, and industry funding has already shifted away from campaigns focusing solely on depression. Notably Paykel et al. (1997, p. 60) commented that 'Depression is a good place to tackle stigma in general, compared with some other psychiatric disorders, in view of its frequency and relation to normal depressed mood'. According to Mental Health America (2009), its National Public Education Campaign on Clinical Depression 'began a process that has dramatically changed public attitudes toward mental health conditions'.

Disease awareness campaigns in the mental health arena have already shifted significantly away from print-based media towards online platforms (but this is beyond the scope of this thesis), and will continue to evolve in terms of both delivery and content. However, many of the fundamental themes and strategies that have contributed to the success of the depression awareness campaigns of the last three

decades will continue to 'sell' mental illnesses as well as drugs that are used to treat them, as long as governments and health professional organisations and consumer/advocacy organisations continue to espouse and engage in partnership with industry.

Common acronyms in this chapter: APA American Psychiatric Association; D/ART Depression Awareness, Recognition, and Treatment (Program); DDC Defeat Depression Campaign; MHA Mental Health America; NAMI National Alliance for the Mentally Ill; NARSAD National Alliance for Research on Schizophrenia and Depression; NDMDA National Depressive and Manic-Depressive Association; NIMH National Institute of Mental Health; NMHA National Mental Health Association; NPECCD National Public Education Campaign on Clinical Depression; RCGP Royal College of General Practitioners; RCPsych Royal College of Psychiatrists; SSRI selective serotonin reuptake inhibitor

Chapter 9
The Mental Health Foundation of Australia: Selling depression and antidepressants

9.1 INTRODUCTION

> The promotion of depression and related conditions has become an industry in itself in Australia in the last decade. (Moynihan 1998, p. 141)

Depression as a social problem has been vigorously promoted in Australia in recent decades. One of the key players during the 1980s and 1990s was the Mental Health Foundation of Australia (MHFA), chaired by leading psychiatrist, Professor Graham Burrows. In 1994, the MHFA launched its National Depression Awareness Campaign (NDAC), to educate the public that depression is 'serious, common and treatable' (Burrows 1997d, p. 1).

The NDAC was modelled on a United States depression awareness campaign, the National Public Education Campaign on Clinical Depression. Both campaigns were funded by pharmaceutical companies. A key tool in the Australian campaign – its flagship publication – was the *Depression Awareness Journal* (*DAJ*), a throwaway journal that was funded by two pharmaceutical companies and distributed to Australian doctors by the MHFA.

DAJ was used to aggressively promote two antidepressants. One of these, Serzone® (nefazodone), was subsequently withdrawn from the market because of potentially fatal liver toxicity. The manufacturer of the other antidepressant, Aropax® (paroxetine), has been severely criticised internationally for suppression and misrepresentation of data from clinical trials. As well as promoting these two antidepressants, *DAJ* also promoted the concept that there was a 'crisis' of depression and suicide in Australia, a key theme of the NDAC.

Several years into the NDAC, another leading psychiatrist, Professor Ian Hickie established SPHERE: A National Depression Project (Hickie 2009, p. 2), with colleagues including Burrows (Hickie et al. 1998, p. 249, figure 1), SPHERE had strong links to the MHFA and NDAC and *DAJ*, and it was also funded by the manufacturer of Serzone. It encompassed general practitioner (GP) training, a clinical

practice audit utilising the purpose-designed SPHERE (Somatic and Psychological HEalth REport) questionnaire, a 12-month disease management program, and ongoing education and practice support (p. 248). Unlike the NDAC, SPHERE did not aim to change public attitudes and did not have a public profile, but it was intensively promoted to GP. It is repeatedly mentioned in this chapter where relevant, but it is not discussed in great detail.

The industry-funded NDAC was eclipsed in 2000 by the establishment of *beyondblue: the national depression initiative*[1], which has a very high public profile and currently dominates the depression arena in Australia. Based in Melbourne, *beyondblue* is a national, independent, not-for-profit organisation working to increase awareness of depression and related disorders. Hickie was its high-profile inaugural Chief Executive Officer. *beyondblue* receives millions of dollars annually from the Federal Government and state and territory governments. It has refused to accept pharmaceutical industry funding. However, I argue in this chapter that *beyondblue* can be seen as a product of the industry-funded NDAC and SPHERE, and as an example of how collaborations between pharmaceutical companies and other key players such as psychiatrists and consumer organisations and governments can be used as very powerful marketing strategies that pay substantial long-term dividends, as advocated by Weinstein (2004).

This chapter analyses the influence of the MHFA, the NDAC, *DAJ*, and Burrows on the Australian depression arena and mental health policy and practice more broadly. The content of the 13 issues of *DAJ* is analysed in detail, supplemented by information from other sources, particularly Balshaw's (2007) *Cornerstones: History of the Mental Health Foundation of Australia 1981-2006* and an MHFA (2005) submission and presentation (Burrows & McQueenie 2005) to the Australian Government.

[1] As noted in chapter 1, the official name is all lower-case italics, i.e. *beyondblue: the national depression initiative* (beyondblue 2011). However, it is frequently written as Beyondblue or Beyond Blue.

Common acronyms in this chapter: AIHW Australian Institute of Health and Welfare; DAJ Depression Awareness Journal; CDHAC Commonwealth Department of Health and Aged Care; CDHFS Commonwealth Department of Health and Family Services; DoHA Department of Health and Ageing; GP general practitioner; D/ART Depression Awareness, Recognition, and Treatment (Program); MHFA Mental Health Foundation of Australia; NDAC National Depression Awareness Campaign; PIHP Partnerships in Health Promotion; RACGP Royal Australian College of General Practitioners; SPHERE (Somatic and Psychological HEalth Report; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant

9.2 THE MENTAL HEALTH FOUNDATION OF AUSTRALIA

In Australia, the most significant community organisation in relation to depression is the Mental Health Foundation of Australia (MHFA). It was established in 1981 by 'a group of mental health and business entrepreneurs as a response to developing awareness that governments could not permanently fund voluntary non-government organisations' (McQueenie 1998, p. 1). Throughout its existence, it has been chaired by Professor Graham Burrows, who was Professor of Psychiatry at the University of Melbourne and Director of Psychiatry at the Austin Hospital from 1983 until 2008.

The MHFA is significant for three main reasons. Firstly, its National Depression Awareness Campaign, established in 1994, served as a forerunner to *beyondblue: the national depression initiative*, which dominates the current Australian depression arena. Secondly, the flagship publication of that campaign, the *Depression Awareness Journal*, was distributed free to all Australian doctors from 1997 to 2003 and, although no evaluation of its impact has been undertaken (to my knowledge), it is likely that it significantly influenced many of its readers. Thirdly, Burrows was arguably the most influential psychiatrist in Australia in the 1980s and 1990s.

The primary functions of the MHFA have been fund-raising (Balshaw 2007, p. 21; McQueenie 1998, p. 1), awareness raising (Burrows 1997d, p. 1), and policy advocacy (Balshaw 2007, p. 22). Burrows has had a very significant media profile, which he has used strategically to lobby for increased funding for mental health. This is an example of competing for attention in order to 'demonstrate the problem', in Wiener's (1981, p. 22) parlance. He has also had strong links with senior politicians and government bureaucrats. The influence of Burrows and the MHFA and associated players on Australian mental health policy is discussed in section 9.5 of this chapter.

The MHFA has strong financial links to pharmaceutical companies, including Eli Lilly, Roche, GlaxoSmithKline (previously SmithKline Beecham), Bristol-Myers Squibb, and Pfizer (Balshaw 2007, pp. 80-82, 114). Particularly notable have been the involvements of Eli Lilly and Roche in the NDAC and the funding by GlaxoSmithKline and SmithKline Beecham of the *Depression Awareness Journal* (discussed in section 9.4).

9.3 THE NATIONAL DEPRESSION AWARENESS CAMPAIGN

The MHFA established an initial campaign, the Depression Awareness Campaign, in Victoria in 1991, then re-launched it more ambitiously as the *National* Depression Awareness Campaign (NDAC) in 1994 (Balshaw 2007, p. 43). According to Megan McQueenie, MHFA Executive Director, a major rationale for the campaign was to challenge perceptions about the seriousness of depression:

> We felt that we needed awareness of depression in the early nineties when people were talking about people experiencing depression being 'the worried well'. We were extremely concerned that that was a view held in high places. We knew that a significant population of Australia were experiencing depression but were not necessarily receiving treatment for that. So we established the national depression awareness campaign (Burrows & McQueenie 2005, p. 52)

Concern about the trivialisation of depression is a common theme in the depression arena (e.g. Hickie et al. 1999, p. 133) and in antidepressant marketing. It is discussed in chapter 4.

According to Burrows (1997d, p. 1), the mission statement of the NDAC was: 'to help all Australians understand that depression is a serious, common and treatable condition'. This is what was meant by depression awareness. The claim that depression is serious, common, and treatable is very similar to that of the US National Institute of Mental Health's Depression Awareness, Recognition, and Treatment Program (D/ART) that depressive disorders are 'common, serious, and treatable' (Regier et al. 1988, p. 1351).

The objectives of the campaign were:

- to ensure that all Australians know how to recognise major depression in themselves and others, and when and where to seek treatment
- to raise awareness amongst professionals (doctors, nurses, psychologists, etc.) of the recommended screening protocols for depressive disorders
- to facilitate a change in public attitude, so that depression is perceived not as an indication of character weakness, but as an illness, treatable by qualified professionals
- to establish and progressively expand 'the D-helpline' initial advice phone line for those needing help with depression (Burrows 1997d, p. 1)

Common acronyms in this chapter: AIHW Australian Institute of Health and Welfare; DAJ Depression Awareness Journal; CDHAC Commonwealth Department of Health and Aged Care; CDHFS Commonwealth Department of Health and Family Services; DoHA Department of Health and Ageing; GP general practitioner; D/ART Depression Awareness, Recognition, and Treatment (Program); MHFA Mental Health Foundation of Australia; NDAC National Depression Awareness Campaign; PIHP Partnerships in Health Promotion; RACGP Royal Australian College of General Practitioners; SPHERE (Somatic and Psychological HEalth Report; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant

The first three objectives of the NDAC are similar to those of D/ART:

1. To increase public knowledge of the symptoms of depressive disorders and the availability of effective treatment.
2. To change public attitudes about depression so that there is a greater acceptance of depression as a disorder rather than a weakness.
3. To motivate changes in behavior among the public and treatment professionals. (Regier et al. 1988, p. 1352)

Suicide, although not mentioned in the NDAC objectives, was prominent in the rhetoric about the campaign. According to Burrows (1997d), the campaign was launched 'in response to the increase in youth suicides in Australia over recent years' and 'to help reduce the high incidence of needless suffering, associated suicide, and cost' (p. 1). The need to reduce youth suicide was a major rationale in the establishment of *beyondblue: the national depression initiative* (Kennett 2000, p. 1). This is discussed in section 9.5.

The NDAC played a major role in the elevation of depression in Australian mental health policy and the establishment of *beyondblue: the national depression initiative*. This is discussed in section 9.5.

The NDAC received significant funding from pharmaceutical companies:

> Extensive depression awareness promotions were undertaken with brochures for which the cost was met by another of the big pharmaceuticals, SmithKline Beecham, and a special edition of the publication *Mental Health in Australia*, also financed by Eli Lilly, which was distributed to every general practitioner in Australia. (Balshaw 2007, p. 81)

> The campaign's fortunes improved somewhat in 1997 with the support of another pharmaceutical company, Bristol Myer Squibb [sic]. The company agreed to include articles about the Depression Awareness Campaign in its new magazine, *Inner Vision*, to be published quarterly and distributed to 30,000 doctors around Australia. It also offered to support reinstatement of the depression line counselling service, which had had to be suspended because of a lack of funds. (Balshaw 2007, p. 82)[2]

The involvement of pharmaceutical companies in such campaigns is a form of advocacy-based promotion, which is discussed in section 9.6.

[2] It seems likely that the proposed *Inner Vision* magazine morphed into the *Depression Awareness Journal*.

9.4 THE DEPRESSION AWARENESS JOURNAL

Central to the MHFA's National Depression Awareness Campaign was the *Depression Awareness Journal* (*DAJ*), a slender throwaway journal that was edited by Burrows and published on behalf of the MHFA. According to Burrows (2003a):

> The Mental Health Foundation of Australia launched the Depression Awareness Campaign in Victoria in 1991. It went on to launch the National Depression Awareness Campaign in 1994. This was opened by Professor Fred Goodwin, the former Director of the National Institute of Mental Health, USA, which led to the formation of the Depression Awareness Journal.

From April 1997 to September 2003, *DAJ* was distributed free to doctors – both general practitioners (GPs) and specialists – throughout Australia. On at least one occasion, it was included in the mail-out of the *Australian and New Zealand Journal of Psychiatry,* the official journal of the Royal Australian and New Zealand College of Psychiatrists, to all members of the College (Wade 1999). Pharmacists also received it (Burrows 1997a). According to Burrows (2003b) it was also read by psychologists and other health care professionals:

> The journal continues to play a role in educating medical practitioners, health care professionals and the general community. It is increasingly read by psychiatrists and psychologists.

DAJ is conspicuous for its pharmaceutical industry funding and strategically positioned antidepressant advertisements. However, it differs from many throwaway journals in that each issue was funded by a single antidepressant manufacturer, whose antidepressant was exclusively promoted. According to its first publisher, it was a 'one off medical communications piece on behalf of a sponsor company' (personal communication, Kerryn Kilkenny, Wolters Kluwer, 4 February 2009). As mentioned in chapter 7, 'medical communications' involves strategic planning and development of education programs that influence healthcare professionals, and it 'helps to build the reference and opinion framework that will form the basis of all promotional activities for a brand' (Roos 2009).

The first eight issues of *DAJ* were sponsored by Bristol-Myers Squibb, the manufacturer of Serzone® (nefazodone). The remaining five issues were funded by

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GlaxoSmithKline, the manufacturer of Aropax® (paroxetine).[3] The back cover of every issue was a full page advertisement for the respective antidepressant. There were no other advertisements for any other drugs. Ten issues included a full or partial product (prescribing) information. Six front covers included a headline about Serzone, and one included a headline about an adherence project specific to Aropax. Seven editorials mentioned the respective antidepressant by name, another two alluded to it, and another referred to an Aropax adherence project; all of these comments were positive. The back cover of every issue was a full page advertisement for the respective antidepressant.

Many of Australia's most prominent psychiatrists published papers in the journal, wielding their considerable influence as key opinion leaders. Most notably, Professor Ian Hickie, who established the SPHERE project (and subsequently became the inaugural Chief Executive Officer of *beyondblue*), published six papers, four of which were about SPHERE (Hickie 1998a, 1999b, 2003; Hickie et al. 1999).

Other prominent professors, including John Tiller ((Associate) Professor of Psychiatry, University of Melbourne), and Robert Goldney (Professor of Psychiatry, University of Adelaide), also contributed papers to *DAJ*. The participation of Gordon Parker (Professor of Psychiatry, University of New South Wales, and Research Director, Mood Disorders Unit, Prince Henry Hospital) is notable, given his objection to the 'dumbing-down' of depression (briefly noted in chapter 3). Characteristically, his article focused on distinguishing different types of depression. Along with a number of other less biased articles, it would have strengthened the credibility of the journal, without challenging the promotion of Serzone.

Issues 4 to 13 included, on the editorial page, the names of the Depression Awareness Campaign Board of Management and the MHFA's Scientific Advisory Committee, the majority of whom were professors. Whether or not they had any editorial input is unclear, but they lent considerable credibility to the journal. According to a leaked memorandum by In Vivo Communications, the publisher of *DAJ* issues 8 to 10, such boards are very effective:

> For general practitioners, In Vivo recommends a series of advertorials in leading medical magazines, featuring interviews with members of the

[3] Issue 9 was funded by SmithKline Beecham, which shortly afterwards merged with GlaxoWellcome to form GlaxoSmithKline.

> company's advisory board, because "The imprimatur of [board] members is invaluable in reassuring [general practitioners] . . . that the material they receive is clinically valid." (Moynihan et al. 2002, p. 888)

The establishment of the Depression Awareness Campaign Board of Management is an example of what Wiener (1981, p. 20) referred to as 'developing constituencies', an element of 'animating the problem'. Animating the problem is one of the three processes she identified in building an arena around the social problem of alcohol use. As discussed in chapter 1, I argue that there are some significant parallels between the construction of alcohol problems and the construction of depression as a social problem.

The high-profile psychiatrists who contributed to the *DAJ* were functioning as key opinion leaders, the use of which is a very important marketing strategy for pharmaceutical companies (Moynihan 2008), as discussed in chapter 7. The MHFA – and the pharmaceutical companies that sponsored the *DAJ* – borrowed the prestige and expertise of these psychiatrists, an element of 'legitimizing the problem' (Wiener 1981, p. 21) and the solution (antidepressants).

The influence of *DAJ* is discussed below in relation to the marketing of Serzone and Aropax. Also discussed is how it 'sold' the concept of an epidemic of depression and associated suicide.

9.4.1 Spruiking Serzone®

Serzone is nefazodone hydrochloride, a phenylpiperazine antidepressant chemically unlike selective serotonin reuptake inhibitors (SSRIs). It acts as a serotonin receptor antagonist, blocking 5-HT_2 receptors, which bind the neurotransmitter serotonin (5-hydroxytryptamine). It was marketed in Australia (and elsewhere) by Bristol-Myers Squibb. Issues 1 to 8 of the *Depression Awareness Journal* were all funded by Bristol-Myers Squibb. The first seven issues were published by Adis Press (Wolters Kluwer). Like Elsevier, the publisher of the *Australasian Journal of Bone and Joint Medicine*, the 'fake' journal published to promote the blockbuster nonsteroidal anti-inflammatory drug Vioxx (briefly discussed in chapter 7), Wolters Kluwer is a mainstream academic publisher that also produces company-sponsored journals as strategic medical education.

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Issue 8 was published by In Vivo Communications, an Australian-based 'global medical education company that has worked with many of the world's leading pharmaceutical companies and medical organisations to provide strategic medical education' (LinkedIn n.d.). What is meant by 'strategic medical education' is evident in the claim that 'our experience and independent expertise can ensure your brand's success and longevity'. In other words, strategic medical education is marketing.

All of these first eight issues have full page Serzone advertisements on the back cover. Issues 2 to 7 all have a two-page Serzone product information immediately before the back cover.

The editorial of the first issue (Burrows 1997a) thanks Bristol-Myers Squibb for funding the journal. The final article in that issue (Adis Editors 1997a) summarises the pharmacology of the classes of antidepressants available in Australia, starting with 5-HT_2 (serotonin) receptor blockers, of which Serzone is one of the few that have been developed. SSRIs and tricyclics, by far the most common classes of antidepressants prescribed in Australia in 1997 (Commonwealth Department of Health and Family Services [CDHFS] 1998, pp. 141-142), and therefore the most important competitors, were relegated to third and seventh places respectively in the body of the article and in the table of 'Antidepressants currently available in Australia'.

In 1997, many doctors would have been unfamiliar with 5-HT_2 receptor blockers, and might have been surprised to see them at the top of the list. However, few people who read this article would have been surprised by the full page Serzone advertisement on the back cover, which proclaimed:

> Soon you'll be able to block 5-HT_2 receptors to offer a brighter future to many depressed patients.
>
> The density of 5-HT_2 receptors in the brain has been shown to increase dramatically in depressed patients. As well as depression, the 5-HT_2 receptor has been strongly linked to anxiety, insomnia, and sexual dysfunction. Consequently, an agent that blocks the 5-HT_2 receptors may minimise activating effects like agitation, anxiousness, insomnia and tremor.
>
> Bristol-Myers Squibb is proud to announce the imminent arrival of the first 5-HT_2 receptor blocker.

Anxiety, insomnia, and sexual dysfunction feature prominently in Serzone promotion, particularly when Serzone is compared with established antidepressants such as SSRIs.

A wide border of the front cover of this issue is purple, which features prominently in the Serzone advertisement, including the logo, which features a gold globe in a purple setting:

The Serzone logo is somewhat similar to the MHFA's logo, which features a person with outstretched arms and a round head (shown here with part of the purple border on the front cover of issue 1):

The back covers of issues 2 and 3 have a different Serzone advertisement (featuring the same purple and gold logo), which proclaims: 'SERZONE IS OFF AUTHORITY! August 1 1997' and 'Now it's even easier to treat patients who suffer an anxious kind

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of depression'. Being off authority meant that doctors could prescribe it without telephoning for approval from the Health Insurance Commission (Liaw et al. 2003). It claims that Serzone is not only as effective as established antidepressants in relieving depression, but also superior in relation to onset of action, sleep, and sexual function:

> Serzone (nefazodone) is a new class of antidepressant that's just as effective as SSRIs and TCAs in alleviating depression. But because it potently blocks the 5-HT_2 receptor sites, it also has some important clinical advantages.
>
> For a start, Serzone relieves anxiety and agitation symptoms – with results as early as one week. What's more, Serzone improves the quality of sleep and sexual function when compared to other treatments.

Issue 2 is more blatantly promotional than issue 1. Burrows' (1997b) editorial mentions Serzone by name, and again praises Bristol-Myers Squibb. On the front cover is a headline, 'Serzone® – for the anxious depressed patient'. The article it refers to begins: 'Long-awaited relief for depression with anxiety is now at hand with the recent release of Serzone®' (Adis Editors 1997b). The description of the drug is very positive, and including the claim that its side-effect profile is 'preferable to many other antidepressants'. The two sidebars proclaim:

> Nefazodone has an early onset of action with lowering of anxiety and improvement in the quality of sleep
>
> In particular, nefazodone is associated with a low incidence of unwanted psychic activation, anxiety, insomnia, sexual dysfunction, weight change and cardiotoxicity.

Such comparative claims are common in drug promotion. Discussing an advertisement for Pamelor® (nortriptyline hydrochloride, a tricyclic antidepressant), Kleinman and Cohen (1991, p. 870) commented: 'This ad disparages other antidepressants for interfering with work because of sedating side effects. The solution, of course, is a different drug'.

Notably, this issue was published about a month after an article in the influential *Australian Prescriber* (1997, p. 78) argued that 'On currently available short-term data, it appears that nefazodone has no obvious advantages over SSRIs and is unlikely to be a first-line drug for depression'. This made it crucial for the *DAJ* to emphasise Serzone's supposedly better side-effect profile and onset of action than established antidepressants.

Issue 3 also has a Serzone cover story: 'Serzone® relief from depression, improved sleep patterns' (Adis Editors 1997c), emphasising its superiority over tricyclic antidepressants and SSRIs, the market leaders at the time. Burrows' (1997c) editorial also promotes it: 'We continue our review of the antidepressant Serzone® (nefazadone [sic]) and highlight the minimal impact of this agent on patients' sexual function'.

The lead article, 'Management of depression in the elderly' (Burrows & Norman 1997), focuses almost entirely on antidepressants, mentioning psychotherapy in only two sentences. One sentence acknowledges that 'social factors frequently result in dysphoric symptoms, which respond to psychosocial rather than pharmacological treatment'; the implication is that the problem in such cases is not genuine depression, merely dysphoric 'symptoms'. The other sentence, in context, is subtly dismissive of psychotherapy:

> Mild depressive episodes can be treated with psychotherapy. In some cases, low dosages of tricyclic antidepressants (TCAs) may be useful for associated sleep disturbance. Moderate to severe depressive episodes are *regularly* managed with pharmacotherapy. [italics added]

The implicit message is that psychotherapy is only effective for mild cases, and even then it may need to be supplemented with tricyclics. Furthermore, the article later discusses adverse effects of tricyclics, making combined psychotherapy and tricyclics seem a less desirable option. The use of the word 'regularly' suggests appropriateness as well as frequency. Burrows and Norman mention clinical advantages but no adverse effects of SSRIs and nefazodone; adverse effects of other antidepressant classes and electroconvulsive therapy are discussed, implying that SSRIs and nefazodone are preferable. So *real* depression requires *real* treatment – antidepressants, preferably SSRIs or nefazodone, because of the side-effects of other antidepressants.

An article by Nathan et al. (1997) discusses light therapy for seasonal affective disorder. The final sentence, 'In universities throughout Australia, several Departments of Psychiatry with an interest in light therapy have specialist light boxes' (p. 4), underscores the fact that light therapy is not a feasible option for most people with depression. Inclusion of the article pays lip service to another non-

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pharmacological treatment option without challenging the dominance of antidepressants.

Issue 4 introduces a third Serzone advertisement, featuring a broken pencil and a hand-written note expressing agitation trumped by Serzone, and the admonition to doctors to 'Help rewrite your depressed patients' lives':

Like the first two advertisements, it emphasises anxiety and insomnia. It does not mention sexual dysfunction, but there is a Serzone cover story: 'Serzone® – minimising sexual dysfunction in depression' (Adis Editors 1998a), the sidebars of which proclaim:

> A depressed patient may have pre-existing sexual dysfunction that may be exacerbated by their antidepressant medication
>
> Nefazodone has minimal impact on patients' sexual function

Burrows' (1998a) editorial reinforces the message:

> We continue our review of the antidepressant Serzone® (nefazadone [sic]) and highlight the minimal impact of this agent on patients' sexual function.

In contrast, Burrows' (1998b) editorial in issue 5 does not mention Serzone, nor do any of the articles. However, there is a two-page product information followed by the same back-cover advertisement as in issue 4 (issues 6 and 7 also have that

advertisement). There is also an article by prominent KOL Professor Robert Goldney, addressing community concerns that antidepressants might be overprescribed. In its concluding paragraph it declares that antidepressants should not be feared:

> There are non-drug treatments that assist many depressed people, but if they are not effective there should be no fear of trials of antidepressants. There is nothing to lose but depression (Goldney 1998, p. 6)

It also emphasises that 'not all depression responds *without* antidepressants' [italics added] (p. 6); this is repeated in a prominent sidebar and in Burrows' editorial. Nowhere does the article state that *antidepressants* are often ineffective. Also Goldney's claim that there is nothing to lose but depression implies that antidepressant use is risk-free.

Issue 6 resumes the series of articles about Serzone: 'Serzone® (nefazodone) – clinical benefit in hospitalised patients' (Adis Editors 1998b). Like previous articles, it has a headline on the front cover, and Burrows' (1998c) editorial reinforces the message:

> The review of the antidepressant Serzone® (nefazodone) continues, with a focus on a recently published placebo-controlled trial demonstrating the efficacy of this agent in severely depressed hospitalised patients.

Similarly Burrows' (1999a) editorial in issue 7 praises Serzone:

> Serzone® (nefazodone) was first marketed in Australia in mid-1997. However, June 1998 marked five years of Serzone therapy worldwide and approximately 1.2 million patients have safely used this antidepressant agent.

The claim of safety is taken from the cover story, 'Serzone® (nefazodone) – five years of therapy' (Adis Editors 1999), which states, both in the text and in a sidebar, that 'approximately 1.2 million patients have been safely treated with nefazodone since its launch five years ago'. This claim is based on an unpublished Bristol-Myers Squibb internal report, which is also the basis of this claim (most of which is repeated in a sidebar):

> The low incidence of clinically troublesome adverse events with nefazodone has been validated: in particular, no unwanted psychic activation, no sexual dysfunction or weight change – adverse events that are often associated with other antidepressants.

Significantly, the article refers to, and attempts to dismiss the importance of, an Australian Therapeutic Goods Administration report of hepatic dysfunction associated with nefazodone use (Adverse Drug Reactions Advisory Committee 1998). According to Adis Editors:

> In most cases of hepatic dysfunction patients were receiving multiple medications. In none of the cases can any definitive causal relationship of hepatic dysfunction be established.

Issue 8, the last one funded by Bristol-Myers Squibb, also has a Serzone cover story, 'Serzone® – broadening horizons in antidepressant therapy' (1999). It also has prominent sidebars: 'Serzone – improves quality of sleep' and 'Sexual function maintained'. Again Burrows' (1999b) upbeat editorial reinforces the positive sales messages:

> Serzone® (nefazodone) is an effective antidepressant and anxiolytic agent. Unlike some other antidepressants, it does not have a negative impact on sleep during the early stages of therapy, and so may be particularly useful for patients presenting with sleep disturbance.

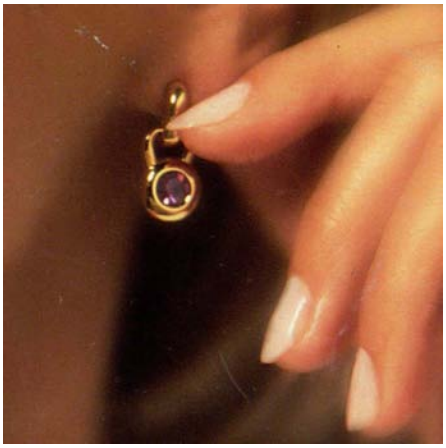
All but one of the other articles focuses on sleep disturbances. One of these articles (Givney 1999) is a case study of a woman who presents with fatigue and is successfully treated for depression with Serzone after being assessed with the SPHERE questionnaire.

Wade (1999) criticised the content of this issue, and objected to its inclusion in the mailout of the August 1999 issue of the *Australian and New Zealand Journal of Psychiatry*. In a letter to the editor, he argued that:

> the picture presented in the Depression Awareness Journal is quite misleading, and the College shouldn't be a party to such.
>
> If the College or its Journal publisher is going to give away seemingly scientific journals, it should take great care that editorial content and advertising is appropriate. If the Mental Health Foundation of Australia is being mis-used by manufacturers (such as Serzone/nefazodone's Bristol-Meyers [sic] Squibb Australia), the College should review its support for that Foundation. (p. 349)

Wade also criticised the back cover Serzone advertisement, a different one (the fourth) from previous issues. It features a photo of the mouth, chin, ear, neck, shoulders, and fingers of an apparently attractive and elegant young woman. Wade described it as an 'apparently obligatory irrelevant graphic (a smiling, well madeup person flaunting their elegant ear ring)' (p. 349). However, the woman's earring – an

expensive-looking piece with a round purple gem in a gold setting – is not irrelevant, because it is visually related to the Serzone logo's gold globe in a purple background:



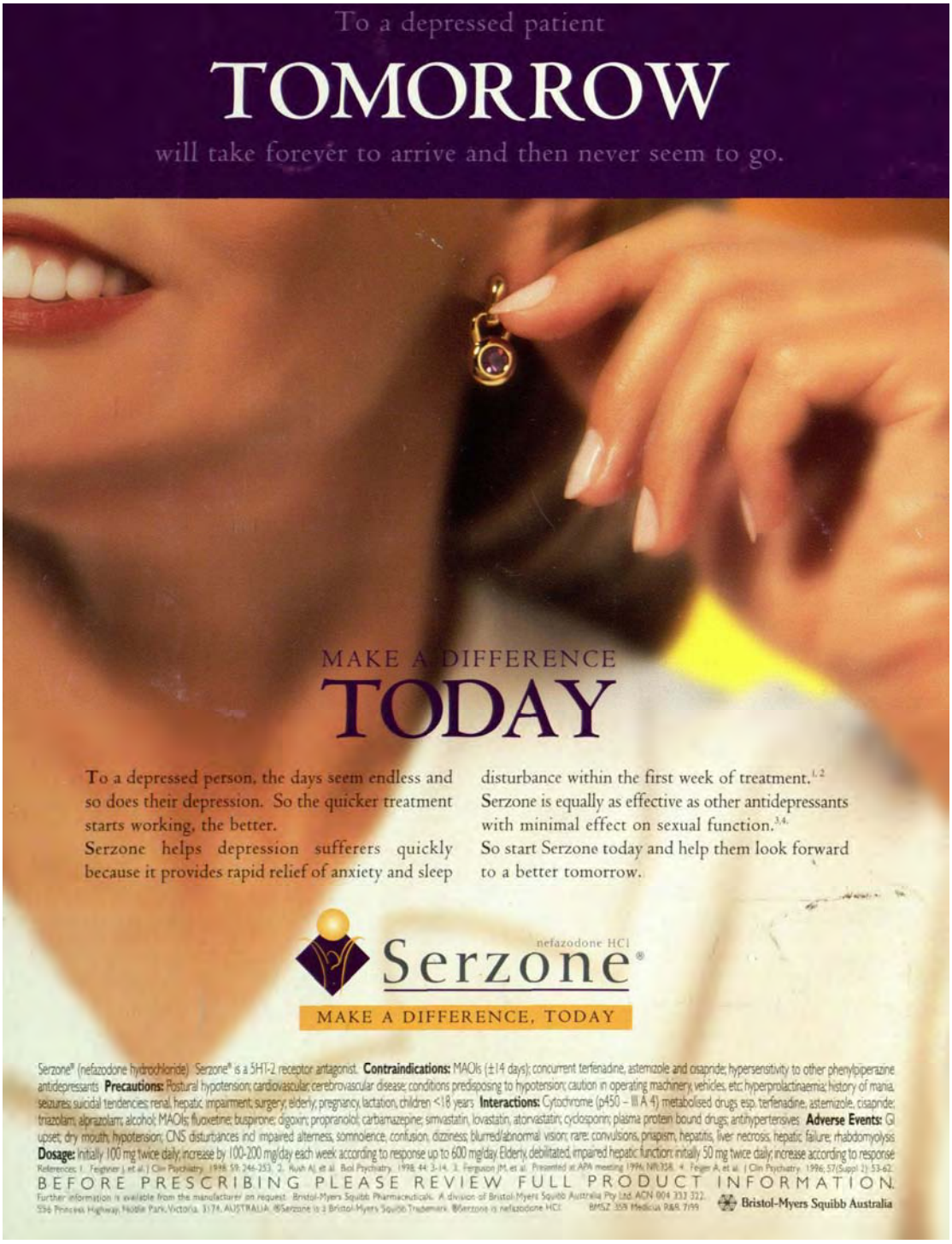
This is more apparent in the full advertisement, in which the purple gem and the gold globe are approximately the same size, and the woman's downturned fingers echo the upstretched arms of the person in the Serzone logo.

Like previous advertisements, this one emphasises relief of anxiety and insomnia, avoidance of sexual dysfunction side-effects, and rapid onset of action:

> Serzone helps depression sufferers quickly because it provides rapid relief of anxiety and sleep disturbance within the first week of treatment. Serzone is equally effective as other antidepressants with minimal effect on sexual function.

These eight issues of *DAJ* reached many Australian doctors, particularly GPs, the main prescribers of antidepressants. They were a major part of a broader marketing campaign for Serzone that also included advertisements in the influential throwaway *Australian Doctor* magazine (Moynihan 1998). At around the same time, Bristol-Myers Squibb also funded the SPHERE project (Hickie, Hadzi-Pavlovic, et al. 1999, p. 2), which encouraged GPs to be more pro-active in assessing and treating depression. SPHERE was launched in association with the MHFA in February 1998 (Hickie et al. 1998, p. 248) at Austin Hospital in Melbourne (CDHAC & AIHW 1999, p. 107), where Burrows was Director of the Mental Health Clinical Service Unit.

Common acronyms in this chapter: AIHW Australian Institute of Health and Welfare; DAJ Depression Awareness Journal; CDHAC Commonwealth Department of Health and Aged Care; CDHFS Commonwealth Department of Health and Family Services; DoHA Department of Health and Ageing; GP general practitioner; D/ART Depression Awareness, Recognition, and Treatment (Program); MHFA Mental Health Foundation of Australia; NDAC National Depression Awareness Campaign; PIHP Partnerships in Health Promotion; RACGP Royal Australian College of General Practitioners; SPHERE (Somatic and Psychological HEalth Report; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant



Hickie published four articles in *DAJ* about SPHERE (Hickie 1998a, 1999b, 2003; Hickie et al. 1999). SPHERE was also referred to in *DAJ* by two other authors. In addition, the SPHERE questionnaire was favourably mentioned in the case study by Givney (1999), and Burrows' (1998b) editorial ended with an advertisement for SPHERE:

> The SPHERE Project, developed to help GPs treat patients with psychological distress, has been launched nationally in association with the Mental Health

> Foundation of Australia and Departments of Psychiatry from Australian teaching hospitals. The programme is provided free of charge to participating GPs. For more information about the SPHERE project, phone 1300 651 344.

Serzone was also marketed vigorously in the US. In 1996, Bristol-Myers Squibb sponsored a conference that produced the much-cited National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression (Hirschfeld et al. 1997). Although that consensus statement did not mention Serzone, it emphasised, among other things, 'a compelling need to conduct research on the development and testing of new treatments for depression' (p. 340); Serzone was then a new antidepressant.

As in Australia, Serzone was defended in the US when concerns were raised about its safety. In 2002, a supplement focusing on nefazodone was published in the *Journal of Clinical Psychiatry*, funded, of course, by Bristol-Myers Squibb. Among the papers was Dunner et al.'s (2002) overview of safety issues. It mentioned hepatotoxicity (liver toxicity), but the authors were at pains to imply that the risk was no greater with Serzone than with other antidepressants:

> Rare cases of hepatic necrosis and/or failure associated with nefazodone have been identified through postmarketing surveillance …. Hepatotoxicity is not unknown with antidepressant therapy. Indeed, product labelling for many newer agents such as citalopram, sertraline, and venlafaxine contains information regarding isolated and rare cases of hepatic necrosis and/or failure. (p. 36)

Dunner et al. also referred to other possible causes:

> these reports are complicated by the presence of other confounding variables such as preexisting underlying hepatic conditions; use of concomitant illicit drugs, alcohol, other medications; or exposure to other hepatotoxic substances. (p. 36)

Eventually Bristol-Myers Squibb capitulated. Serzone was discontinued in Canada in 2003 by Bristol-Myers Squibb because of liver toxicity (Choi 2003), and it was withdrawn from the Australian market in 2004 (DoHA 2004b, p. 7).

Interestingly, however, the May 2004 *SPHERE Newsletter* (Educational Health Solutions 2004, p. 6) put a positive spin on Serzone's withdrawal from the Australian market:

> Why is Serzone being withdrawn?
>
> It is a voluntary commercial decision because of its current low and declining rate of use.

This contrasts markedly with Choi's (2003, p. 1187) explanation that 'Because of concerns of hepatotoxicity, the sale of the antidepressant nefazodone hydrochloride (Serzone) will be discontinued [in Canada] by the manufacturer effective Nov. 27, 2003', Johnson's (2005) statement that 'regulatory decisions have led to the withdrawal of nefazodone from the [Australian] market due to safety issues', and Cresswell's (2008) statement that Serzone 'was withdrawn in Australia in 2004 after being linked to liver and eye problems'. Possibly Educational Health Solutions' explanation was motivated by Bristol-Myers Squibb's funding of SPHERE in its early days.

From the introduction of Serzone to the Australian market in 1997 to its withdrawal in 2004, nearly 771 thousand Serzone prescriptions were subsidised by the Pharmaceutical Benefits Scheme or the Repatriation Pharmaceutical Benefits Scheme, at a cost of nearly $25 million (Medicare Australia 2009).[4] It is likely that significantly fewer prescriptions would have been written without the promotion in *DAJ*. Internationally, more than 4.5 million prescriptions had been written by 2003 (Edwards 2003).

9.4.2 Plugging paroxetine (Aropax®)

After a 14-month gap, *DAJ* continued, with a new focus of promotion. The new funding, for issues 9 to 13, was from GlaxoSmithKline,[5] the manufacturer of the antidepressant Aropax® (paroxetine hydrochloride), a selective serotonin reuptake inhibitor. In many countries it is sold as Paxil®; in the UK it sells as Seroxat®.

In Vivo Communications continued as publisher for issues 9 and 10. Issue 11 was published by Adrenalin Strategics, an 'accredited medical education provider for the pharmaceutical industry' (Barbagallo 2003). Issues 12 and 13 seem to have been published in-house by the MHFA.

[4] A total of seven prescriptions were processed by the Health Insurance Commission (now Medicare Australia) in 2005 and 2006, but they would have been prescribed and supplied earlier than that.
[5] Issue 9 was funded by SmithKline Beecham, which shortly afterwards merged with GlaxoWellcome to form GlaxoSmithKline.

All five issues have full page Aropax advertisements on the back cover. Issues 9 to 12 have an Aropax product information (ranging from a quarter page to two pages) immediately before the back cover. None of the front covers mentions Aropax; however, issue 11 has a headline about the Aropax a+ project (discussed below). Issues 9 to 13 all have orange front covers (ranging from burnt orange to garish tangerine), as do the back covers of issues 10 to 13. Issues 9 and 10 have wide orange borders on internal pages. Issues 11 to 14 have article titles and headings in orange, and the sidebar text in issue 11 is orange. Orange features very prominently in advertisements and promotional materials for Aropax (Robotham 2002c), functioning as a de facto logo. In the early 2000s, Australian doctors were subjected to an onslaught of orange Aropax advertisements and promotional materials. To many, these *DAJ* issues would have been recognisable as Aropax focused, simply from the colour of the front covers.

The back cover advertisements are strikingly different from the Serzone advertisements, and from most drug advertisements. There are no images, photographic or otherwise, and very little text. The issue 9 advertisement has 'Aropax®' in very large print in the middle of the page, with 'Paroxetine' below it. At the bottom of the page is a border saying 'Restores normal living' on the left and 'Aropax® Paroxetine'. Aropax® and Paroxetine are in orange text, and there is an orange dot to the left of 'Restores'. Issues 10 to 13 have nearly solid orange back covers with text reading simply 'aropax®' with 'paroxetine' below it.

Aropax was strategically positioned as pharmacotherapy for anxiety disorders, including panic disorder, as well as depression. Burrows' (2000) issue 9 editorial concludes:

> The comorbidity of depression and anxiety is supported by a number of studies. We discuss appropriate treatment that addresses both depressive and anxiety symptoms, and restores patients to normal living.

Predictably, that 'appropriate treatment' is Aropax. The last article in issue 9, 'Comorbid depression: Comorbidity – the rule rather than the exception' (2000), which is headlined on the front cover, emphasises comorbidity of depression and anxiety, and sings the praises of Aropax. However, unlike any other article in the 13 issues of

the journal, it is labelled as an advertising feature and a company commissioned article. The bottom of each page has the same border as the advertisement, featuring the slogan 'Restores normal living', which Burrows' claim 'restores patients to normal living' echoes.

The issue 10 editorial (Burrows 2001) concludes:

> We examine an integrated approach to treating depression in general practice that combines antidepressant and psychological treatments. To this end, a case study is presented in which the patient responded well to paroxetine combined with relaxation techniques. In conclusion, we discuss the factors affecting patient adherence to prescribed treatment.

The case study (Leonard 2001) was, in fact, of a woman diagnosed initially with *panic disorder* and subsequently with depression. According to Leonard:

> Antidepressant therapy was recommended and Roseann requested Aropax® (paroxetine) because one of her sisters, who suffered from panic attacks, had improved on treatment with Aropax.

The last two paragraphs of the article are worth citing in full for several reasons:

> Roseann responded well to antidepressant therapy and within 3 months of starting medication noted normal sleep and increased motivation. She described a clearing in her thinking, which enabled her to evaluate what she wanted in her marriage and her life. She noted a decrease in general anxiety as she became more adept at asserting herself.
>
> Roseann was seen frequently for about 6 months for cognitive based psychotherapy and then on an as-needed basis for a further 6 months. She continued on Aropax therapy for a total of 9 months. The specific anxiety symptoms gradually diminished with her improved self-esteem and greater sense of control over her thinking patterns. Relaxation and visualisation techniques were also very effective.

Firstly, the last sentence was the first and only mention of relaxation techniques (which were mentioned in Burrows' editorial). There was no explanation of the basis on which they were judged to have been 'very effective'. Next to the first paragraph was a sidebar in large text: 'The patient responded well to antidepressant therapy' – no mention of relaxation techniques. If relaxation techniques were commenced early, why did the first paragraph and the accompanying sidebar not mention them? If they were commenced later, after Roseann had already 'responded well' to antidepressant therapy, how was their effectiveness established? This is another classic example of paying lip service to nonpharmacological treatment but subtly dismissing it.

Secondly, the claim that 'Roseann was seen frequently for about 6 months for cognitive based psychotherapy' seems questionable. By whom was she seen frequently? It is unlikely that the GP (who may or may not have been Leonard) was able to provide *frequent* psychotherapy. This article predates the 2002 establishment of the Better Outcomes in Mental Health Care program that significantly increased access to Government-funded counselling. Few people in 2001 would have been willing and able to pay for *frequent* counselling sessions with other health professionals.

A possible explanation is that the 'cognitive based psychotherapy' referred to by Leonard was *adherence* oriented. Another article in the same issue (Hogan 2001) discusses strategies to improve treatment adherence (notably it repeatedly equates treatment with antidepressants).

Another article (Mant 2001) is critical of benzodiazepines, and emphasises the need to reduce long-term use. This is a valid claim, backed up by several appropriate references. However, Mant rather cavalierly promotes antidepressants, citing no references: 'Anecdotally, prescribing one of the newer antidepressants can be very effective in resolving depression and making it easier to discontinue the benzodiazepine' (p. 5).

Hogan's article about treatment adherence has an abbreviated Aropax product information at the end of it, and it primes the reader for a headlined article in the next issue (11), which enthusiastically promotes the Aropax a+ project[6] (Singh 2002). This project created controversy when it was revealed that the psychologists delivering the program were bound by their contracts to deliver one message – that participants should keep taking Aropax – and were otherwise not permitted to discuss drugs at all (Robotham 2002b). Robotham described the program as 'counselling with a corporate twist'. As discussed in chapter 7, pharmaceutical companies frequently emphasise the importance of adherence or compliance,[7] and there is a growing body of

[6] Singh referred to it as the 'a plus project', but in GlaxoSmithKline promotional materials it is referred to as the 'a+ project'.

[7] The terms adherence and compliance are used interchangeably in this thesis, as is common in the literature, although adherence is often advocated as being preferable because it recognises active patient involvement and agency (Lutfey & Wishner 1999).

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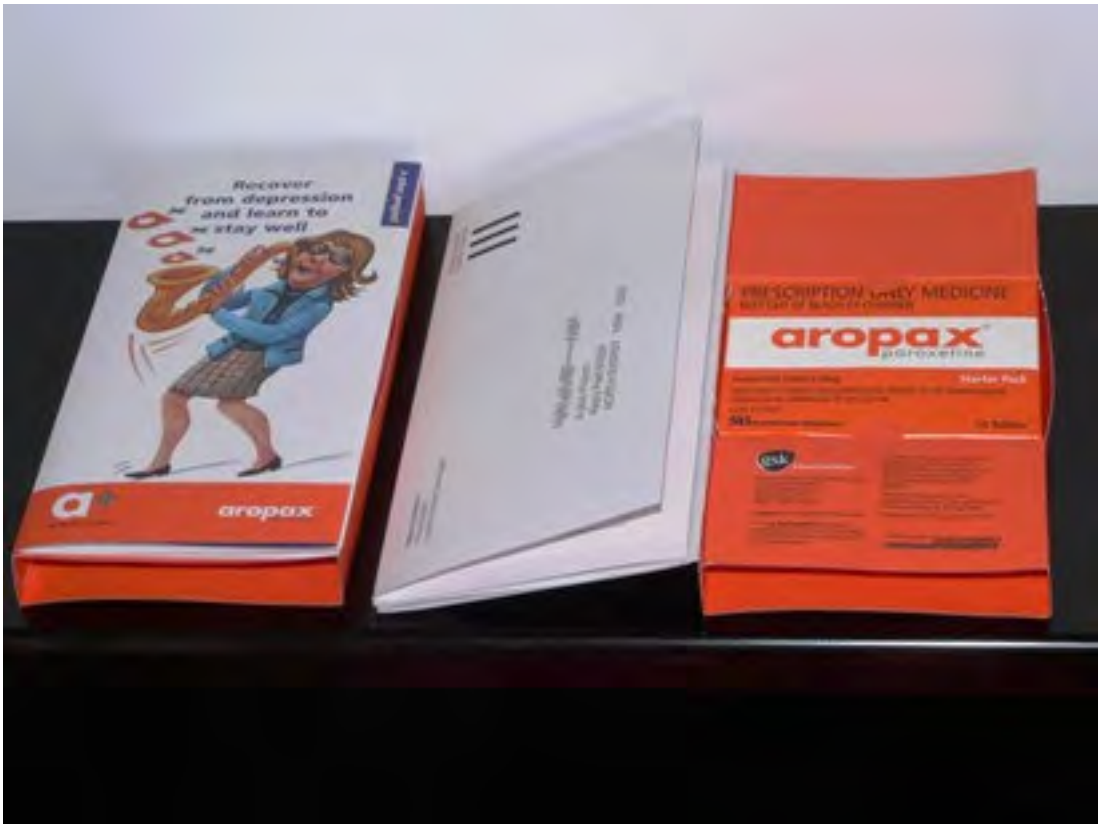
pharmaceutical marketing literature on the value of 'compliance assistance programs' and so on.

The a+ project included starter packs of Aropax in a bright orange cardboard box approximately the size and shape of a video, with a cheerful picture of a woman playing a saxophone on the cover:



Included in the box was a fold-out card providing an explanation about the project and some information about depression and Aropax, including:

> Depression is not just a 'bad mood' that you can 'snap out of' when you feel like it. It is a medical illness like asthma and diabetes, which can be successfully treated in most people by using a combination of medication and counselling.

Also included as part of the fold-out card were two pre-addressed free-post registration cards. Patients who received the starter packs could use the first of these cards to register themselves on the program, provided this was authorised by their doctor. They could also register to attend *a plus* meetings, conducted by psychologists and 'specially trained doctors', if they mailed the second card with the barcode number of a packet of Aropax dispensed by a pharmacy, as proxy proof that they were continuing to take Aropax after they finished the starter pack. Participants were also

sent 'other educational information to complement your treatment', according to the fold-out card.

Singh's article in issue 11 of *DAJ*, 'The *a plus project:* A partnership in action' is a vivid example of the deployment of positive spin in the service of pharmaceutical promotion:

> The *a plus project* is a national programme for the treatment of clinical depression which employs a multidisciplinary, cooperative approach to ensure patients achieve the maximum benefit from their treatment. The *a plus project* is an example of a healthcare partnership in action, as it adopts a cooperative mental health approach featuring GPs, pharmacists, psychiatrists, psychologists and patients. (p. 8)

A shortened version of this is repeated in large orange text in the page border. The a+ project is also endorsed in Burrows' (2002a) editorial:

> We also examine the *a plus project*, a partnership of patients, GPs, pharmacists and psychologists, working together to improve treatment outcomes in depression.

Singh paints a rosy picture of psychiatric practice, claiming that psychotherapy is routinely provided along with pharmacotherapy: 'Patients in regular contact with a psychiatrist *would* receive this kind of treatment [combined medication and psychotherapy]' [italics added] (p. 10). However, most patients with depression are treated by GPs, and do not receive psychotherapy. According to Singh, the a+ project was developed to improve the treatment received by GP patients: 'It was in response to such unmet community need that the *a plus project* was devised' (p. 10).

The trump card, however, is the strapline in bold text below the headline, which invokes the prestige and authority of *beyondblue*:

> Australia recently witnessed another first in the treatment of depression building on the major national initiative of beyondblue. (p. 8)

The theme of this whole issue is partnerships. The first article is about the MHFA's Partnerships in Health Promotion (PIHP) program (Burrows 2002b), which was funded by *beyondblue* (Hickie & Burns 2002, p. 7). The article about the a+ project is wedged between an article by the CEO and Deputy CEO of *beyondblue* (Hickie & Burns 2002), 'beyondblue – Developing community partnerships in depression' and an

article by the President of the Royal Australian College of General Practitioners (RACGP) about the PIHP program, giving it credibility by association.

The final article in this issue (Generalised anxiety disorder 2002) does not mention partnership or the a+ project, but it enthusiastically promotes paroxetine for generalised anxiety disorder, which Burrows' (2002a) editorial refers to as 'a common mental illness, second only to, and highly comorbid with, depression …. this under-diagnosed and under-treated disorder'.

Issue 12 does not mention Aropax or GlaxoSmithKline, apart from the two-page product information and the back cover advertisement. The inside front cover of issue 13 acknowledges 'Grant-in-Aid GlaxoSmithKline'. The only mention of Aropax is in the back cover advertisement. Both of these issues have a different, less sophisticated, format from previous issues. No publisher is stated; the issues were presumably prepared in-house by the MHFA. The articles in these issues are also different from those in previous issues. Some are significantly longer and more academic in tone, with multiple references. There is much less emphasis on antidepressants and none are mentioned by proprietary name. Notably absent are the publisher-supplied articles about antidepressants in most previous issues. Despite the acknowledgment in issue 13 of GlaxoSmithKline's 'Grant-in-Aid', it seems likely that the funding had more or less run out by then. The fact that issue 13 was the last issue supports this; it would probably have been prohibitively expensive for MHFA to fund the distribution of subsequent issues.

Issue 12 begins with an article about the Depression Stress and Anxiety Education and Training Project, run by the MHFA's PIHP consortium. The formation of this consortium is an example of what Wiener (1981, p. 22) referred to as 'combining for strength (e.g. forming alliances)', an element of 'demonstrating the problem'.

Next is an article about the SPHERE project (Hickie 2003), briefly summarising the results of the GlaxoSmithKline-funded clinical practice audit. Possibly this article would not have been published if this issue had been funded by GlaxoSmithKline, because SPHERE was by then funded by rival antidepressant manufacturer Pfizer (Lifeblood 2007). However, it promotes messages favourable to all antidepressant manufacturers, arguing that common mental disorders such as depression are

underdiagnosed and undertreated by general practitioners, and psychotropic drugs are under-prescribed:

- 'Unmet need' for basic assessment of mental disorders in general practice is unacceptably high – only 44% of patients with current mental disorders (and 54% of those with the more severe disorders) attract psychological diagnoses….
- Treatments provided in general practice are largely non-pharmacological, and most consist simply of non-specific advice and support which are unlikely to have significant effects on the outcome of more severe depressive or anxiety disorders….
- Pharmacological treatments are not widely used for common mental disorders (only 12% of all patients, 39% of patients in whom a doctor makes a diagnosis, and 27% of patients with the most severe disorders). (p. 6)

Next in issue 12 is an article about diagnosis of depression in the medically ill, another about depression in anorexia nervosa, and another about how pharmacogenomics may generate individually tailored antidepressants.

Issue 13 begins with an article about the national charity The Smith Family, a member of the PIHP consortium. Next is an article about early detection of postnatal depression, then a second article about diagnosis of depression in the medically ill, another about family therapy in general practice, and another about electroconvulsive therapy. There is no Aropax product information, just the back cover advertisement.

Since paroxetine was introduced to the Australian market in 1994 (Australian Prescriber 1994), over 16 million paroxetine prescriptions have been subsidised by the Pharmaceutical Benefits Scheme or the Repatriation Pharmaceutical Benefits Scheme, at a cost of over $460 million (Medicare Australia 2012). Aropax had patent exclusivity until 2002, when a generic competitor was approved by the TGA (Terry White Chemists 2011, p. 18).

Internationally, GlaxoSmithKline has been severely criticised in relation to paroxetine, particularly for withholding clinical trial data demonstrating that it was ineffective for childhood depression and increased the risk of suicidal behaviours in children (Kondro & Sibbald 2004; McGoey & Jackson 2009). The use of antidepressants in children and the risk of suicide for both children and adults are discussed in detail in chapter 6. GlaxoSmithKline has also had the dubious distinction

of having a book published about its unethical marketing of Paxil®, the US brand of paroxetine (Bass 2008); this book has received positive reviews in medical journals (Friedman 2008; Eth 2009). In addition, high rates of adverse reactions to Seroxat®, the UK brand, were published in a BBC Panorama documentary (discussed in Medawar et al. 2002), the first of several Panorama documentaries, including one focusing on the withholding of clinical trial data (BBC 2007).

9.4.3 Selling depression and suicide

DAJ not only promoted Serzone and Aropax but also promoted depression as a social problem. This began on the front covers, which quite powerfully conveyed images of suffering. The cover of issue 1 is a photograph of part of an attractive young woman's face with a web of cracks, rather like barbed wire, superimposed. Slivers of this image also occur on the borders of several internal pages, reinforcing the theme of pain. Similar images, predominantly female, were used for issues 2 to 7, with variations in the colour of the wide border on the right hand side where an abbreviated table of contents was given.

Issue 8 has a different front cover design: a grid of nine small photos of an apparently anguished man. The cover of issue 9 has nine photos of an anguished woman's face; issue 10's cover is a combination of her photos and those of the man from issue 8. Issues 11 to 13 also combine photos of predominantly troubled looking men and women.

Most issues follow a problem/resolution pattern: photographic representations of anguish on the cover, textual descriptions of depression and associated disorders and/or suicide in several articles, then an article about Serzone or Aropax and/or its product information, capped off by an up-beat advertisement for Serzone or an orange advertisement for Aropax.

Several key themes of the current orthodoxy about depression and suicide are apparent in *DAJ* and other MHFA publications. Some illustrative examples are given here.

Theme: An epidemic of depression and associated suicide

The MHFA promoted the concept of an *epidemic* of depression and associated suicide in Australia (and elsewhere). Burrows' (1997a) editorial in *DAJ* issue 1 refers to 'depressive illness – Australia's quiet crisis' and 'the worsening crisis posed by

suicide'. The first article in that issue is 'The National Depression Awareness Campaign – our quiet crisis' (Burrows 1997d), according to which the National Depression Awareness Campaign was established by the MHFA in 1994 'in response to the increase in youth suicides in Australia over recent years' (p. 1).

The next article (Tiller 1997), on the facing page, focuses specifically on youth suicide, a very emotive issue, and claims that 'Youth suicide has tripled in Australia since the 1950s' (p. 3). Tiller also claims that 'suicide rates are not reported to correlate with unemployment', and discounts the importance of access to lethal means. Instead, he contends, 'The central issue appears to be the person's mental status leading to the decision to harm themselves, after which they seek an available method' (p. 3).

Burrows' (1997d) article includes the claim that 'About 70% of people who commit suicide have a known depressive illness' (p. 1), a statement repeated verbatim in Evans et al. (2000, p. 3). No reference is cited. This claim is probably based on Barraclough et al.'s (1974) widely cited psychological autopsy study which found that 70% of suicides had *post-mortem* diagnoses of depressive disorder based on psychological autopsy (using interviews of relatives, doctors, etc., and review of medical records). Only 26% were known to have been diagnosed with depression before their deaths. A *DAJ* article by Burrows and Norman (1998) also emphasises the association between depression and suicide, citing several psychological autopsy studies. It includes the claim that 'Clearly the association of suicide with dysphoric mood suggests that appropriate antidepressant treatment is essential' (p. 4). It does not mention any other form of treatment or prevention, and it challenges claims that antidepressants might trigger suicidal behaviour.

Claims about the prevalence of depression are discussed in chapter 4. Psychological autopsy studies, and more generally claims about suicide and the contribution of depression, are discussed in chapter 5. Claims about the relationship between antidepressant use and suicide are discussed in detail in chapter 6. Many of these claims, whether or not they are accurate, are examples of what Wiener (1981, p. 22) referred to as 'selecting supportive data', an element of 'demonstrating the problem'.

Common acronyms in this chapter: AIHW Australian Institute of Health and Welfare; DAJ Depression Awareness Journal; CDHAC Commonwealth Department of Health and Aged Care; CDHFS Commonwealth Department of Health and Family Services; DoHA Department of Health and Ageing; GP general practitioner; D/ART Depression Awareness, Recognition, and Treatment (Program); MHFA Mental Health Foundation of Australia; NDAC National Depression Awareness Campaign; PIHP Partnerships in Health Promotion; RACGP Royal Australian College of General Practitioners; SPHERE (Somatic and Psychological HEalth Report; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant

Theme: The burden of depression and suicide

As discussed earlier, a major part of the MHFA's rationale for the establishment Depression Awareness Campaign in 1991 was extreme concern about perceptions of depressed people as 'the worried well' (Burrows & McQueenie 2005, p. 52). Not surprisingly, therefore, *DAJ* and other MHFA publications repeatedly emphasised the prevalence, severity, and impact – the burden – of depression.

The first issue of *DAJ* strongly emphasises the high burden of depression and suicide in Australia. Burrows' (1997a) editorial refers to 'this debilitating illness' and 'the worsening crisis posed by youth suicide'. The first article (Burrows 1997d) refers to 'the high incidence of needless suffering, associated suicide, and cost' (p. 1), and claims that 'The cost of untreated depression in Australia is estimated at between 4 and 5 billion dollars annually' (p. 1). No reference is cited for that claim, nor for a similar claim in this passage in Evans et al. (2000, p. 11):

> The most recent figures for *depression alone* show that, in 1993-1994, $521 million was spent from the health budget on treatment of depressive disorders. This figure records only direct expenditure on hospitalisation and the provision of health care services – it does not take into account the hidden costs of time off work, reduced productivity , and other costs, which the Depression Awareness Campaign, run by the Mental Health Foundation of Australia, estimates to be as much as five billion dollars per year. [italics in original].

According to Burrows (2003c), the annual cost of depression in Australia was $20 billion. The $521 million claim has some credibility, because it was also made by Armstrong (1999), citing an unpublished conference paper by an authoritative Australian Institute of Health and Welfare epidemiologist (Mathers 1998). However, the 4 to 5 billion dollar claim is questionable and the $20 billion claim even more so.[8]

The second *DAJ* issue features articles on the prevalence and impact of postnatal depression (Milgrom & Burrows 1997), comorbid depression and post-traumatic stress disorder (Morris & Creamer 1997), and comorbid depression and dementia (Chiu 1997). In issue 3, Burrows and Norman (1997) focus on depression in the elderly, claiming that it is 'relatively common' and is associated with a high mortality rate (p. 1). Shea (1997) discusses depression as a potential cause of criminal

[8] These sentences do not do justice to the amount of time I spent trying to determine the provenance and validity of these claims.

behaviour, as does Shea (2000) in issue 9. Hickie (1998a, p. 7) emphasises the scale of the problem:

> Depressive and anxiety disorders are the most common forms of psychological illness in the Australian community. These disorders lead to considerable personal and family distress, including chronic disability, increased morbidity and premature death from suicide, accidental causes or associated physical illness.

Several articles cite the landmark World Health Organization's Global Burden of Disease study (Murray & Lopez 1996):

> the burden of mental illnesses such as depression has been seriously underestimated….
>
> It is predicted that, by 2020, depression will be the greatest disease burden in the developing world (Whiteford & Wells 1998, p. 1)
>
> In 1990, depression was the leading cause of DALYs [disability adjusted life years] lost worldwide in the 15-44 year age group and the leading cause of disability (in YLD [years lived with disability]) worldwide by a considerable amount. (Whiteford 2000, p. 1)

Such citations are examples of what Wiener (1981) referred to as 'selecting supportive data', an element of 'demonstrating the problem'. Claims about the burden of depression and the contribution of depression to suicide are discussed in chapters 4 and 5 respectively.

Theme: Depression as disease, not character weakness

As mentioned earlier, one of the objectives of the NDAC was: 'to facilitate a change in public attitude, so that depression is perceived not as an indication of character weakness, but as an illness, treatable by qualified professionals' (Burrows 1997d, p. 1). Evans et al. (2000, p. 14) expressed the illness-not-weakness message more emphatically:

> [myth] People with depression are weak and should develop the willpower to snap out of it.
>
> [truth] Depression is a clinically defined mental illness, sometimes with a biochemical cause in the person's brain.

Common acronyms in this chapter: AIHW Australian Institute of Health and Welfare; DAJ Depression Awareness Journal; CDHAC Commonwealth Department of Health and Aged Care; CDHFS Commonwealth Department of Health and Family Services; DoHA Department of Health and Ageing; GP general practitioner; D/ART Depression Awareness, Recognition, and Treatment (Program); MHFA Mental Health Foundation of Australia; NDAC National Depression Awareness Campaign; PIHP Partnerships in Health Promotion; RACGP Royal Australian College of General Practitioners; SPHERE (Somatic and Psychological HEalth Report; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant

According to Evans et al. (p. 13),

> Depression is stigmatised as being due to the inability of the individual to take charge of their life; they "should have" the willpower "to snap out of it;" "to stop being a wimp."

Destigmatisation of mental illness was one of three founding objectives of the 'Australian Depression Initiative' (Kennett 2000, p. 1), which became *beyondblue: the national depression initiative*.

Such claims that depression is a disease rather than a weakness are good examples of what Wiener (1981, p. 21) referred to as 'redefining the scope', an element of 'legitimizing the problem'. This redefinition strongly parallels the promotion of the disease model of 'alcoholism' that has been so influential in the alcohol arena, particularly in the US. In both arenas, there is a widely accepted false dichotomy between disease (which is considered a socially acceptable explanation) and weakness, as is discussed in chapter 4.

Theme: Depression as a chronic disorder

There are multiple claims in the *DAJ* that depression is a chronic disorder in most cases:

> Depression tends to be a chronic illness for most patients. (Singh 2002, p. 8)
>
> Most of the disorders detected by the SPHERE form are chronic rather than acute (Hickie 1998b, p. 2)

According to Hickie (1998a, p. 7), depression and anxiety disorders lead to 'chronic disability'. He reinforced this claim by comparing depression to asthma and diabetes, arguing that it is essential to:

> implement a disease management strategy for the common depressive and anxiety disorders, similar to those available for asthma and diabetes, which build on the GPs' unique skills and long-term relationship with patients.

Theme: Under-treatment of depression

Similarly, there are multiple claims in the *DAJ* that depression is undertreated:

> Only 20-25% of depressed people receive treatment. (Burrows 1997d, p. 1)
>
> Despite the increased recognition of PND [postnatal depression] in recent years, only a minority of women receive professional help. (Milgrom & Burrows 1997, p. 1)

> Although depression is treatable in most cases, it often remains unrecognised, undiagnosed and untreated (Shea 1997, p. 5)
>
> Depression is a highly prevalent, although often undertreated, disorder (Whiteford & Wells 1998, p. 1)
>
> The concern with depressive disorders in men, particularly young men, has been the lack of recognition of these disorders, and the men's lack of willingness to ask for treatment. (Buist & Stanley 1999, p. 4)

Some of the most dramatic claims about under-treatment were made by Hickie et al. (1999, p. 1), based on the results of the SPHERE clinical audit of general practice patients:

> Unfortunately, less than half of the patients who present to GPs will receive a psychiatric diagnosis and less than half of those will receive any specific form of treatment.

In a subsequent article, Hickie, Davenport, Naismith, & Scott (2001a, p. S52) reported very high rates of mental disorders among patients in the clinical audit:

> Sixty-three per cent of people attending general practice have some evidence of mental disorder (including alcohol or other substance misuse) by self-report or GP's diagnosis of psychological difficulties. (p. S52)

This claim was exaggerated in the media, in stories that reported 60% or more of GP patients had a mental illness/disorder, rather than having *some evidence* of mental disorder. Milligan (2001), in a *Weekend Australian* story titled '60pc of GPs' patients mentally ill', reported: 'MORE than 60 per cent of patients visiting GPs have a mental illness and the mental health system is failing them, a national depression audit has found'. Robotham (2001), in a story dramatically titled 'Six in 10 GP patients have mental illness: study', reported that:

> Sixty per cent of people who visit general practitioners have a mental disorder, according to a groundbreaking study of 46 000 patients. The findings, by Professor Hickie and a team of scientists at the University of NSW's School of Psychiatry, point to higher rates of mental illness than have been acknowledged to date.
>
> The research showed GPs consistently underestimated their patients' mental disorders….

Common acronyms in this chapter: AIHW Australian Institute of Health and Welfare; DAJ Depression Awareness Journal; CDHAC Commonwealth Department of Health and Aged Care; CDHFS Commonwealth Department of Health and Family Services; DoHA Department of Health and Ageing; GP general practitioner; D/ART Depression Awareness, Recognition, and Treatment (Program); MHFA Mental Health Foundation of Australia; NDAC National Depression Awareness Campaign; PIHP Partnerships in Health Promotion; RACGP Royal Australian College of General Practitioners; SPHERE (Somatic and Psychological HEalth Report; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant

Theme: The need for early intervention and treatment

The need for early intervention and treatment is repeatedly emphasised. According to Evans et al. (2000, p. 3):

> Treatment is all the more effective when the illness is diagnosed early and treatment is started as soon as possible. Seeking immediate help for any feelings of depression is very important.

The consequences of missing out on early treatment, it is claimed, can include serious crime. According to Shea (1997), 'In some cases, depression is first recognised when a person commits a crime' (p. 5). Shea concludes emotively:

> These fatal and tragic outcomes of depressive illness, rare as they may be, are reminders of the importance of recognising depression early and treating it effectively. The consequences of untreated depression are often difficult to predict, but occasionally courtroom appearances may result. If they do, then outcomes may be devastating for both depressed patients and their families. (p. 6)

Reinforcing the message is a sidebar: 'Fatal and tragic outcomes of depressive illness, rare as they may be, are reminders of the importance of recognising depression early and treating it effectively'. Tragic outcomes are also mentioned in a sidebar in Mitchell's (2001) article, claiming that 'Early intervention prevents tragic outcomes', although neither early intervention nor tragic outcomes are mentioned in the article. The same sidebar is used in Shea (2000), which presents two very short case studies in which depressed people committed crimes. Shea emphatically claims, without citing any evidence, that 'early intervention and treatment would have prevented these crimes' (p. 7).

Theme: Somatisation masking depression

As briefly mentioned in chapter 2, a significant current theme in psychiatry is somatisation – the somatic (physical) expression of psychological problems (Hickie, Davenport, Hadzi-Pavlovic et al. 2001; Sharpe 2002, p. 501). A significant number of articles claim that many cases of depression and anxiety manifest as somatic disorders:

> Between 15 and 29% of people consulting a GP are depressed. Most will present with physical symptoms, e.g. aches and pains, insomnia, fatigue. (Burrows 1997d, p. 1)

> Up to sixty percent of physical disorders have been estimated as somatised or with a significant contribution from psychological factors. (Milgrom and Burrows 2002, p. 14)
>
> Studies in primary care settings suggest that 50-95% of psychiatric patients initially present with somatic complaints' (Ellen & Burrows 2001, p. 3).
>
> Fewer than 20 per cent of patients with GAD [generalised anxiety disorder] present with complaints of anxiety symptoms. These patients are more likely to present with somatic or sleeping problems and use high levels of medical resources (Generalised anxiety disorder 2002, p. 17)
>
> Early in depression, patients may not feel or even look depressed. Instead, they may complain of the physical manifestations of depression, such as changes in appetite or sleep, fatigue, sexual problems, or various aches and pains. (Shea 1997, p. 5)
>
> **Psychological Disorders Present with Somatic Symptoms**
>
> The most common presentation of psychological distress in primary care settings is a mix of somatic, depressive and anxious symptoms. (Hickie 1998b, p. 2)

Givney's (1999) article is a case study of a woman who presents with fatigue and recurrent vaginal candidiasis, and is successfully treated for depression with Serzone. Givney commented that 'Patients usually emphasise the physical rather than psychological symptoms of their disorder'. Initially the patient in the case study does not accept depression as a likely explanation of her symptoms, but after completing the SPHERE questionnaire (which includes multiple somatic symptoms) she is 'more willing to accept a psychological interpretation of her difficulties'.

Burrows (1997d) made a related connection between somatisation and *suicide*, when he endorsed a GP workshop program developed 'to help GPs recognise depression in young people who present with somatic complaints and to screen the patients further for suicidal tendencies' (p. 2). The relevance of somatisation to suicide is reinforced emotively by quoted feedback from an unnamed workshop participant: 'I think I've saved a life'.

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9.5 GRAHAM BURROWS: POLICY ADVOCATE AND PSYCHIATRIC ENTREPRENEUR

Professor Graham D. Burrows, AO, KCSJ, BSc, MB, ChB, DPM, MD, FRANZCP, FRCPsych, MRACMA, DipMHlthSc(Clinical Hypnosis), FAChAM, DSc, has had a very distinguished career. He was Professor of Psychiatry from 1983 to 2008 at the University of Melbourne, where he is now a Professorial Fellow (Burrows 2004; International Society for Affective Disorders 2009). He was also Director of the Mental Health Clinical Service Unit at Austin Health from 1983 to 2008. He has been Chairman of the Mental Health Foundation of Australia since its inception in 1981, and President of the Mental Health Foundation of Victoria, since 1972 (Balshaw 2007, p. 44). He was also Chairman of the Australian National Association for Mental Health from 1980 to 1988 (Balshaw 2007, p. 45).

Burrows has been a key player in Australian mental health policy, particularly in the 1980s and 1990s. He has claimed credit for some of the most important policy developments during that period, and these claims have been supported by other key players.

Burrows has had a very high media profile for a psychiatrist:

> Prof. Burrows—Yes, we have the full commitment of the press. We have the Murdoch press, in particular, behind us. Here in Melbourne, the Herald and Weekly Times board and their people are completely behind it. My problem is not getting into the media; it is keeping out of the media. I would get three requests a day to do a media article. (Burrows & McQueenie 2005, p. 55)

According to a psychiatrist peer, Professor Paul Skerritt, 'Graham Burrows has quite a lot of political connections' (Tait 2006, p. 24). This is arguably an understatement. Among Burrows' political connections have been longstanding relationships with Jeff Kennett (Premier of Victoria from 1992 to 1999, and the inaugural and current Chairman of *beyondblue*), and Michael Wooldridge (Federal Health Minister from 1996 to 2001),[9] the two politicians most responsible for the establishment of *beyondblue*. Burrows also had a strong relationship with Dr Neal Blewett, Federal Health Minister from 1983 to 1990.[10]

[9] Wooldridge was Minister for Health and Family Services 1996-1998, then Minister for Health and Aged Care 1998-2001.
[10] Blewett was Minister for Health 1983-1987, then Minister for Community Services and Health 1987-1990.

Burrows' relationship with Wooldridge included official launches of mental health resources (Wooldridge 1999, 2000). Balshaw (2007) quoted fulsome praise by Wooldridge of MHFA and Burrows:

> Dr Wooldridge says he was 'in the right place at the right time' to take up the challenge in mental health. But he readily acknowledges the invaluable role of community based, non-government organisations, the Mental Health Foundation of Australia in particular…. 'without organisations like the MHFA you wouldn't have got anywhere'. Apart from the day-to-day work of the MHFA and other groups, he believes they play a crucial role in preparing the ground, the mindset of policy makers and people generally. 'We wouldn't be where we are in Australia – leading the world – without them. This partnership has been an extraordinary success.'
>
> A big factor in that success is the persona of Graham Burrows….'I've known Graham Burrows a long time – it's very hard not to know Graham Burrows. He is an immensely likable character with a large personality, and it is impossible to talk the MHFA without talking about him. He's an uncommonly good politician for a doctor. What he and the MHFA have done is make people feel good about doing things (in mental health) rather than shaming them into things by making them feel bad.' (pp. 43-44).

In his foreword to Balshaw (2007), the then Prime Minister, John Howard, also praised the MHFA:

> The Foundation can be proud of its efforts to advance this issue over the last 25 years. This history portrays a struggle for identity and an unfailing advocacy for mental health. It is a story of a committed band of people whose effort has led to the Foundation becoming a widely respected and integral partner on the national effort to combat mental illness. (Howard 2007, p. ix)

Many other prominent politicians have supported the MHFA:

> The MHFA acknowledges the ready support it has received from successive Australian Governments and Health Ministers for their leadership in promoting mental health and implementing significant reforms….
>
> Similarly the Victorian Government has been a strong supporter of the Foundation (Balshaw 2007, p. x).

According to Balshaw, Burrows 'is widely regarded as the "father" of mental health reform in Australia' (p. 44). Furthermore, the back cover blurb of Balshaw's book asserts:

> From 1981 the Mental Health Foundation of Australia has been *the* nation's champion of mental health. The people of the Foundation committed to an

> unfashionable cause that has subsequently become the western world's health pandemic.
>
> The MHFA's advocacy has been *responsible* for the major advances in mental health policy, services and awareness. [italics added]

Similarly, according to a submission to the Senate Select Committee on Mental Health (MHFA 2005, p. 3): 'The Mental Health Foundation of Australia has consistently been *the* progenitor of social action to address community mental health issues has [sic] been responsible since 1984 for successive federal governments [sic] mental health reform projects' [italics added].

Burrows' introduction to Balshaw's (2007) book claims credit for the National Mental Health Strategy:

> Our background work and advocacy led to the introduction in 1993 of the first National Mental Health Strategy, which is now in its third five-year phase, a national policy on mental health (p. xii)

This claim is supported by Terpaj's (1990, p. 1) explanation of the origins of the National Mental Health Strategy, which began:

> In 1984, the then Federal Minister for Health, Dr Neal Blewett, was advised of the need for a national policy on mental health services through reports provided by the Royal Australian and New Zealand College of Psychiatrists and the Australian National Association for Mental Health.
>
> As a result of this a consultancy was commissioned to report on mental health services in Australia. The document, A National Mental Health Services Policy (the Eisen/Wolfenden Report), was submitted to health ministers in March 1988.
>
> AHMAC subsequently established a Working Party in May 1989 to develop a Mental Health Discussion Paper as the basis for consultation around Australia.

Burrows was Chairman of both the Australian National Association for Mental Health and the Mental Health Foundation of Australia (Balshaw 2007, p. 22), when the joint report by the two organisations (*Mental health services in Australia* 1984) was submitted to Blewett.

Burrows also claims substantial credit for the establishment of the Mental Health Council of Australia, the peak Australian mental health organisation:

> Prof. Burrows—I lobbied four ministers before we started up the Mental Health Council of Australia. (Burrows & McQueenie 2005, p. 52)
>
> The Mental Health Council of Australia (MHCA) was formed in 1997 to be the peak national body for which a need was identified in the MHFA/ANAMH

> national consultation in 1984. The MHFA lobbied three successive health ministers until the Howard Government's Minister for Health, Dr Michael Wooldridge, agreed to appoint a peak national non-government organisation representing and promoting the interests of the Australian mental health sector and committing to achieving better mental health for all Australians. (Balshaw 2007, p. 38)

As mentioned in chapter 2, depression become a major focus of Australian mental health policy in the late 1990s. One key event was a ground-breaking two-day National Workshop on Depression, convened by the CDHFS in Canberra in October/November 1997 (Mental Health Branch and National Health Priority Committee Secretariat 1997). Balshaw (2007) attributed this development in part to the MHFA:

> Years of outspoken advocacy on the part of MHFA and a constant stream of information into the centres of power and the media finally paid off when the Federal Government … convened a national depression workshop for the end of October 1997. (2007, p. 82)

The workshop was attended by about 70 delegates from the mental health sector, including the MHFA (Balshaw 2007, p. 83). It developed a framework for a three-year depression action plan (Mental Health Branch and National Health Priority Committee Secretariat 1997, p. 20).

Following on from the National Workshop on Depression in 1997, the CDHAC and AIHW (1999) published the *National Health Priority Areas Report: Mental health: A report focusing on depression 1998*. That report provided a solid underpinning for the *National Action Plan for Depression* (NAPD) (CDHAC 2000/2001), which was developed as a major initiative under the Second National Mental Health Plan. The aim of the NAPD was 'to reduce both the prevalence and impact of depression in Australia' (p. ix).

Burrows also claims to have played a major role in the establishment of *beyondblue*. One of the MHFA's initiatives, according to Burrows (2005, p. 17), was: 'National Depression Initiative 1999 (beyondblue) through our National Depression Awareness Campaign launched in 1991'. In his introduction to Balshaw's (2007) book, Burrows claimed:

> The MHFA identified in its very early years the growing incidence of depression, and our pioneering work in this area – through the introduction of the National Depression Awareness Campaign in late 1984 – ultimately provided the motivation for the National Depression Initiative, today operating as beyondblue. (pp. xii-xiii) [11]

McQueenie, similarly claimed that 'we established the national depression awareness campaign, and out of that eventually grew beyondblue' (Burrows & McQueenie 2005, p. 52).

These are bold claims. Even if there is a degree of spin and self-aggrandisement to them, they are given substantial credibility by Wooldridge's and Howard's praise, and by the fact that Balshaw had been chief speechwriter for Kennett (Burrows 2007, p. xv), who is generally credited as the person most responsible for the establishment of *beyondblue*.

Burrows' political influence also extended to persuading key government personnel to contribute articles (Whiteford & Wells 1998; Casey 2000; Kennett 2000; Whiteford 2000) to *DAJ*, giving it invaluable credibility and legitimacy. Whiteford and Wells were respectively Director of Mental Health and Head, Promotion and Prevention Sector in the Mental Health Branch of the CDHFS in 1998. In November 1997, Whiteford had chaired the Department's National Workshop on Depression (Balshaw 2007, pp. 82-83). That workshop was a very significant landmark in the Australian depression arena, laying the foundation for future policy developments and initiatives including the establishment of *beyondblue*:

> The workshop outcomes, outlined in the National Workshop on Depression Report, were used to inform the development of further action to address depression including the development of the National Action Plan for Depression and the National Depression Initiative. (DoHA 2004a)

By 2000 Whiteford had left the Department but was on the recently announced Board of the National Depression Initiative, which soon became *beyondblue*. In 2000 Casey was Assistant Secretary of the Mental Health and Special Programs Branch of the CDHAC in 2000, and Kennett was the Commonwealth Government appointed Chairman of the Australian Depression Initiative.

[11] 1984 is probably a typographical mistake. Elsewhere Burrows (2003) and Balshaw (2007, p. 43) have stated that the National Depression Awareness Campaign was launched in 1994.

Burrows also persuaded the RACGP to provide legitimacy to *DAJ*, with two senior personnel contributing articles. An article by Dr Paul Hemming, then RACGP President, stated that 'The RACGP is proud to be associated with the alliance known as Partnerships in Health Promotion' (Hemming 2002, p. 12). Dr Chris Hogan, then Director of the RACGP Research and Health Promotion Unit, contributed an article (Hogan 2001) focusing on treatment adherence. As discussed earlier, it repeatedly equates treatment with antidepressants, it has a short Aropax prescribing information positioned at the end, and it primes the reader for Singh's (2002) enthusiastic promotion in the next issue of the Aropax a+ project. Dr Frank Barbagallo, Clinical Director of Adrenalin Strategics, which published issue 11 of *DAJ*, was a member of the RACGP Quality Assurance & Continuing Professional Development Subcommittee (Barbagallo 2006, p. 20). Few readers would have been aware of this link. However, it suggests that members of that subcommittee might have endorsed *DAJ* as continuing professional development.

Burrows was a consummate orchestrator of key players, including drug companies, his own profession, the RACGP, government bureaucrats and politicians. Although many people in the depression arena are unaware of his historical political influence, its effects continue today, particularly in the central position of depression in mental health policy and the ongoing funding for, and influence of, *beyondblue*.

9.6 PHARMACEUTICAL INDUSTRY LINKS

The very existence of *DAJ* is potent evidence of the MHFA's enthusiasm about working cooperatively with pharmaceutical companies. Furthermore, several *DAJ* articles in addition to Burrows' editorials endorse collaboration with pharmaceutical companies.

Four different industry-funded programs were endorsed in the journal. Most notable is Singh's (2002) glowing account of GlaxoSmithKline's a+ project. As mentioned earlier, Burrows (1997d) briefly discussed and endorsed two GP education programs funded by drug companies. Also Hickie (2003) promoted SPHERE as a suitable training program for GPs to qualify for the Australian Government's Better Outcomes

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in Mental Health Care, long after Pfizer Australia had 'joined SPHERE as an implementation partner' in 2001 (Lifeblood 2007).

According to a psychiatrist peer, Professor Jayashri Kulkarni, 'Graham Burrows is the ultimate entrepreneur in psychiatric research' (Tait 2006, p. 12). He has certainly been very popular among pharmaceutical companies, acknowledging that he 'has received travel assistance to attend Advisory Board meetings from most companies that market psychotropics in Australia' (Keks et al. 2007, p. 144).

Burrows and the MHFA already had significant links to SmithKline Beecham before Aropax became the focus of *DAJ* in 2000. Burrows chaired SmithKline Beecham's committee on panic disorder, for which it was marketing Aropax (Moynihan 1998, p. 145). SmithKine Beecham had also funded brochures for the NDAC earlier in the 1990s, and had conducted workshops for GPs on youth suicide (Balshaw 2007, p. 81).

More recently, Burrows has enthusiastically promoted Bristol-Myers Squibb's atypical antipsychotic Abilify (aripiprazole) on the girl.com.au website (Schizophrenia treatment 2004). Similarly, he promoted Organon's tetracyclic antidepressant Avanza (mirtazapine) on the femail.com.au website (Depression treatment 2003).

According to Balshaw (2007, p. 179), it was intended that MHFA's links with pharmaceutical companies would continue:

> The pharmaceutical companies who have been the major contributors to [the annual Golden Opportunity Ball] are moving toward compliance with their new funding guidelines, which require them to put sponsorship money into specific education projects rather than fundraising events. The Foundation will seek their direct support for many of its projects.

However, the MHFA and the Golden Opportunity Balls received unfavourable publicity late last year when it was alleged on 7News television that the MHFA was being investigated by Consumer Affairs for apparently operating illegally as an unregistered charity (Milligan 2011). According to the 7News story, drug company donors spend $16,000 a table to attend the 'glittering' balls, which have also been attended by politicians including Victorian Mental Health Minister Mary Wooldridge, Victorian Health Minister David Davis, and Federal Minister Simon Crean,

Burrows himself has recently suffered a substantial loss of personal reputation related to his pharmaceutical industry links. As a result of a large number of allegations of

over-medication (including prescribing high doses of antipsychotics for anorexia nervosa) and conflict of interest, he is currently being investigated by the Medical Board of Australia (Woodhead 2012). This is a dramatic fall from grace for such an influential and well connected psychiatrist.

Other players related to the MHFA and Burrows have also had pharmaceutical industry links. In Vivo Communications, the publisher of *DAJ* issues 8 to 10, also developed marketing strategies for another GlaxoSmithKline drug, Lotronex® (alosetron hydrochloride) for irritable bowel syndrome. They formulated an elaborate campaign including 'medical education', an Advisory Board of key opinion leaders, development of 'best practice guidelines', and production of 'a newsletter to "establish the market" and convince the "specialist market" that the condition is a "serious and credible disease"' (Moynihan et al. 2002, p. 888). However, the campaign was stopped because Lotronex was withdrawn from the market within months of its launch because of serious, sometimes fatal adverse reactions (Horton 2001).

As mentioned earlier, Adrenalin Strategics, an 'accredited medical education provider for the pharmaceutical industry' (Barbagallo 2003), published *DAJ* issue 11, which included Singh's (2002) article praising the a+ project. An employee, Sam Barbagallo, was involved in management of the a+ project (Barbagallo 2005). Adrenalin Strategics has also been involved in Wyeth's 'Time Efficient Mental Health – solutions for time poor GPs' program (Rural and Remote Medicine Education Online 2008), which is accredited for Level One of the Better Outcomes in Mental Health Care initiative. In 2008 that program was awarded a marketing award in the Australian Pharmaceutical Research, Innovation & Marketing Excellence Awards, reflecting industry awareness that it is an effective *marketing* strategy.

Also as mentioned above, the Clinical Director of Adrenalin Strategics, Dr Frank Barbagallo, has been a member of the RACGP Quality Assurance & Continuing Professional Development Subcommittee (Barbagallo 2006, p. 20). These links further illustrate how pharmaceutical companies have become intertwined with other players in the Australian depression arena, particularly through marketing companies such as In Vivo Communications and Adrenalin Strategics. They also illustrate the

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multiple roles – and potential conflicts of interest – that individual players such as Frank Barbagallo can have.

The funding of *DAJ* was part of a larger pattern of industry support that was very important for the NDAC overall. It is also part of a much larger pattern of industry funding of psychiatric consumer groups and advocacy groups. Such links are very common throughout medicine, but are perhaps more pronounced in psychiatry than in most medical fields (Goldberg 2009).

Although not involved in funding *DAJ*, Eli Lilly played a particularly important role in the campaign. As quoted earlier, Lilly financed a special edition of *Mental Health in Australia*, which was distributed to every Australian GP as part of the campaign (Balshaw 2007, p. 81). Lilly was also involved earlier in the establishment of the campaign:

> early [1992] Eli Lilly Australia linked up with the Foundation to establish Australia's first major Depression Awareness Campaign…. The Victorian program, which broadened to become the National Depression Awareness Campaign (DAC), was based on a similar venture in the United States. In both countries, Eli Lilly was involved actively as well as being the principal financier. (Balshaw 2007, p. 80)

The 'similar venture in the United States' was most likely to have been the National Public Education Campaign on Clinical Depression, which was discussed in detail in chapter 8.

Another commonality between the US and the Australian campaigns was the involvement of psychiatrist Fred Goodwin, former Director of the US National Institute of Mental Health. As well as being a key player in the US campaign, he also played a significant role in the Australian campaign:

> The MHFA took advantage of the timely visit to Australia of the former director of the US National Institute of Mental Health, Emeritus Professor Fred Goodwin, on sponsorship from Roche Australia, to have him perform the official launch of the campaign in October 1994. (Balshaw 2007, p. 80)

Balshaw did not elaborate about what Eli Lilly's *active* involvement in the Australian campaign entailed, but it is likely that the content of the campaign was tailored to benefit Lilly.

There is increasing recognition that it is commonplace for drug companies to use senior doctors as key opinion leaders to promote their brands (Moynihan 2008), and

to fund consumer organisations to run disease awareness campaigns and lobby on their behalf (Lofgren 2004). However, with the assistance of Burrows and the MHFA, Bristol-Myers Squibb and GlaxoSmithKline went a step further and also recruited politicians and government bureaucrats as powerful advocates for the cause. As discussed in chapter 8, the use of government as a public relations channel also occurs in the US, and its effectiveness was lauded by Weinstein (2004). However, it has received remarkably little attention here in Australia.

If Weinstein were to write about the Australian campaign, as he did about the US National Public Education Campaign on Clinical Depression, it might read something like this:

> The National Depression Awareness Campaign, one of the most successful advocacy and public education campaigns in Australian history, was rolled out by the Mental Health Foundation of Australia (a leading advocacy group supported by pharma companies) to increase awareness of the chemical nature of the illness, its rapid treatability, and the need for aggressive screening.
>
> Much of the advocacy work, particularly in the mass media, was unbranded, but some of the content of the flagship publication the *Depression Awareness Journal* was branded. Strong PR messages were elicited from doctors, advocacy groups, and the government.
>
> The campaign destigmatized the name of the disease, identified the symptoms, and then brought hundreds of thousands of patients into needed treatment. Education and destigmatizing disease greatly expanded the market for drugs. Then, salesforces battled for market share—appropriately—in doctor's offices.

Both the Australian and the US campaigns are good examples of pharmaceutical industry-funded public relations activity in the psychiatric arena as discussed by Beder et al. (2003). Such campaigns have not only promoted psychiatric diagnosis and psychotropic prescribing, but they have also significantly influenced mental health policy in both countries:

> The central thrust of agenda setting in mental health policy-making over the last 20 years in both the United States and Australia has resulted in the triumph of biological interpretations of mental disorders — together with drug-based treatment regimes — over theories and policies associated with forms of "talking therapy" like psychotherapy and family therapy. This dramatic shift of policy has largely come about as the result of pharmaceutical industry-funded public relations activity which has provided policy entrepreneurs and organized

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> advocacy coalitions to promote drug treatments for what are often claimed to be imbalances in brain chemistry. (Beder et al. 2003, p. 5)

In Australia, the MHFA and Burrows, a consummate policy entrepreneur, succeeded in profoundly influencing mental health policy, placing depression at its core. This encouraged and legitimised the increased diagnosis of depression (and related disorders such as anxiety disorders, which were also promoted in the *DAJ*). Although lip service was paid to non-pharmacological treatments, the *DAJ* relentlessly positioned antidepressants, particularly Serzone and Aropax, as the ideal treatments. This has been highly beneficial for all manufacturers of antidepressants, not merely for the pharmaceutical companies that recognised the value of Burrows and the MHFA as an allies, and provided substantial funding for the *DAJ* and the NDAC more broadly.

9.7 CONCLUSION

This chapter has analysed how both depression and antidepressants have been successfully sold in Australia by the MHFA's NDAC, its flagship publication, the *DAJ*, and the powerful influence of the MHFA Chairman, Professor Graham Burrows. It provides a detailed example of how coalitions between pharmaceutical companies and other players, particularly key opinion leaders and consumer/community organisations, can sell disorders as well as drugs.

The MHFA and Graham Burrows have been very significant players in the Australian mental health field, particularly in the depression arena. Funded by multiple drug companies, they have played a major role in the transformation of depression from an issue that few people thought about – or perhaps dismissed as an affliction of 'the worried well' – to the major focus of Australian mental health policy. Their claims to be substantially responsible for major policy developments, including the development of the National Mental Health Strategy and the establishment of *beyondblue: the national initiative*, have considerable credibility.

This chapter also provides a case study of the strategic value of a throwaway journal in two multi-faceted antidepressant marketing campaigns, confirming assertions that such journals are an important form of so-called medical education designed to boost pharmaceutical industry sales and profits. Furthermore, these antidepressant

marketing campaigns were run in tandem and in synergy with the MHFA's depression marketing campaign, illustrating the use of advocacy as a marketing tool.

More importantly, this chapter, focusing on advocacy-based promotion of both depression as a disease and antidepressants as a solution, illustrates how mental health policy can be profoundly influenced by alliances between pharmaceutical companies and other players, including key opinion leaders, consumer/community organisations, health professional organisations, government bureaucrats, and politicians, in the guise of legal and supposedly appropriate community education and medical education. This is an important issue that warrants considerably more attention than it has received.

Common acronyms in this chapter: AIHW Australian Institute of Health and Welfare; DAJ Depression Awareness Journal; CDHAC Commonwealth Department of Health and Aged Care; CDHFS Commonwealth Department of Health and Family Services; DoHA Department of Health and Ageing; GP general practitioner; D/ART Depression Awareness, Recognition, and Treatment (Program); MHFA Mental Health Foundation of Australia; NDAC National Depression Awareness Campaign; PIHP Partnerships in Health Promotion; RACGP Royal Australian College of General Practitioners; SPHERE (Somatic and Psychological HEalth Report; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant

Chapter 10
Conclusion

In Australia and most developed countries, depression has vaulted from an obscure affliction to a high-profile modern epidemic. This rise in prominence has been accompanied by a significant escalation in prescribing and use of antidepressants, which have become one of the most commonly used and most profitable classes of prescribed drugs. These developments have been underpinned by a strong orthodox story that has been promoted by many players, including doctors (particularly psychiatrists and general practitioners), pharmaceutical companies, and consumer organisations. Other players, including patients/consumers, general practitioners, health professional organisations, governments and government agencies, marketing companies, and the media, tend to support this orthodox story.

In a nutshell, according to this orthodoxy, depression is common, serious, and treatable, and the appropriate treatment is antidepressants. Among other tenets are that depression is seriously underdiagnosed and undertreated, and that antidepressants are safe and effective and should be prescribed more. Also included in the orthodox story is suicide, which is posited to be caused by depression and prevented by antidepressants. In this orthodoxy, people who are distressed have depression, are at risk of suicide, and need antidepressants to both treat the depression and ward off suicide.

However, as outlined briefly in chapter 1, there are strong public health and social grounds for questioning this orthodoxy. Vastly more people are being diagnosed with depression now than several decades ago, and antidepressant prescribing and use have escalated dramatically. Yet diagnosis of depression is subjective, and the criteria on which it is based are highly controversial. There is public disquiet with the increasing medicalisation of personal and social problems. Furthermore, the evidence that underpins the orthodoxy is strongly biased, particularly by the commercial interests of drug companies, and this is compounded by biased interpretation and reporting, particularly in relation to clinical trials of antidepressants. It is increasingly clear that the effectiveness of antidepressants has been overstated, and their safety has been

overstated. This has taken the sheen off antidepressants' reputation, but prescribing remains high.

Two analytic approaches have been used in this thesis. The first is critical analysis of the *validity of claims*, evaluating them against empirical evidence, using epidemiological analysis and critical appraisal skills from the evidence-based medicine field to challenge the orthodoxy. This has revealed numerous examples of exaggeration of the significance and severity of depression and its relationship with suicide. In relation to antidepressants, there is widespread exaggeration of effectiveness, coupled with understatement of harmful effects. Chapters 4 to 6 have critically analysed some key claims about depression (for example that depression is inherently serious), some claims about suicide (for example that 15% of depressed people kill themselves), and some claims about antidepressants (for example that increased antidepressant use improves population health). These claims have been shown to be misrepresentations of evidence and/or wishful thinking, often motivated by commercial and/or ideological agendas.

This critical analysis has included investigation of the *provenance* and *trajectories* of supposedly factual and conceptual claims. Such analysis often requires an almost forensic approach, because claims are very often made without any reference citation or mention of a source of evidence, but often can be traced back to a source, sometimes via a complicated route (for example claims may be based on secondary or tertiary sources).

Another issue necessitating painstaking analysis is citation distortion, in which sources are cited but misrepresented, sometimes resulting in 'unfounded authority' of misleading claims (Greenberg 2009). Many inaccurate claims analysed in this thesis have been found to be based, sometimes tenuously, on sound evidence that they misrepresent. When the source of such evidence is prestigious and/or authoritative (for example the US National Institute of Mental Health and the Australian National Survey of Mental Health and Wellbeing), this can give misleading claims considerable credibility.

The second approach used in this thesis is a broad analysis of strategies used by advocates of the orthodoxy. This includes an analysis of how claims have been deployed in the depression arena, focusing on *what claims have been made, by which*

players, in which contexts, for which reasons, and with what impact. Carefully selected (and often misrepresented) supportive data have been extensively used to 'demonstrate the problem' (Wiener 1980, p. 22) (and the solution). They have also been used to compete for attention (for example in the media) and to convince (or discredit) opposing ideologists. Relevant claims that support the orthodoxy have occurred in published medical literature and in a wide variety of less academic sources, including reports in the grey literature, media reports, pharmaceutical industry promotional materials, health professional organisation publications, consumer organisation publications, submissions to governments, government policy documents, and websites and blogs of various players, including depression sufferers and antidepressant users. Also analysed are pharmaceutical industry marketing strategies, many of which utilise questionable claims (for example in direct-to-consumer advertising).

Key players have strongly promoted the orthodox story, despite contrary evidence, systematically exaggerating the prevalence and severity of depression and the effectiveness and safety of antidepressants for both depression and suicide prevention. Pharmaceutical companies have played a key role in the establishment and maintenance of the orthodoxy, skilfully recruiting other players, particularly doctors and consumer organisations to their cause. Players who challenge the orthodoxy have been much less numerous, much less influential, and indeed are frequently criticised.

Key players promoting the orthodoxy have often acted in concert, based on overlapping and synergistic agendas. Often one or more pharmaceutical companies have funded and/or orchestrated such alliances. A range of strategies that have helped to develop and maintain the orthodox story have been discussed. In particular, two chapters of this thesis have focused on how pharmaceutical industry funded depression awareness campaigns, led by doctors (particularly psychiatrists), health professional organisations, and consumer organisations, have been used to promote and strengthen the orthodox story about depression and antidepressants. These campaigns, which have included many misleading claims, can strongly influence mental health policy.

An Australian case study (in chapter 9) analyses in detail how key players, including pharmaceutical companies, very successfully 'sold' both depression as a serious social and public health problem and antidepressants as the solution in the late 1990s and

early 2000s. Some very significant outcomes have occurred in the policy arena as a result. As discussed in chapter 9, depression has become central to Australian mental health policy. This has greatly contributed to the increase in antidepressant prescribing.

According to the orthodox story about depression, critically analysed in chapter 4, not only is depression common, serious, and treatable, but it is also a disease. This fourth claim, implicit in the first three claims, is very important because it legitimises medicalisation of distress.

Claims that depression is common generally overstate its prevalence. There are several reasons for this, most significant of which is increasingly broad diagnostic criteria. Another reason is inaccurate interpretation of epidemiological evidence, particularly conflation of period prevalence and point prevalence. Another key epidemiological issue is the problematic assumption that prevalence rates in population surveys are valid indicators of clinical treatment need, an assumption criticised by leading psychiatric epidemiologists but not even considered, let alone acknowledged, by most players.

Claims that depression is serious are most likely to be based on its association with suicide, which is discussed in chapter 5. The association of depression with reduced productivity and other economic costs is another important basis of claims, as is the association with physical illnesses, which has received increasing attention in recent years. The severity of depression at an individual level is routinely exaggerated, as is the aggregate burden at a population level. The most significant contributor to this exaggeration is inappropriate generalisation, firstly from clinical samples to the population, and secondly from tertiary and secondary clinical samples to primary care samples. Most of the evidence about the severity of depression comes from clinical samples consisting of treated patients. There is rarely any acknowledgement that treated patients are unrepresentative of people with depression (particularly because people with more severe depression are more likely to seek and receive treatment). This is compounded by serious misrepresentation of evidence from *treated* samples as evidence from *untreated* samples. Another contributor to the exaggerated burden of depression is research demonstrating associations of depression with physical illnesses. These associations are usually interpreted as unidirectional causal relationships, as are associations with workplace problems. Other problems such as

family breakdown and alcohol and other drug problems are also often assumed to be caused by depression rather than being interrelated in complex ways with multidirectional causal pathways.

The evidence about depression treatment does not support claims of high levels of effectiveness. Several studies have found that the long-term outcomes of treated depressed people are worse than those of untreated depressed people. Confounding by severity undoubtedly contributes to this, but it is possible that treatment may also contribute to adverse outcomes, either directly (via harmful effects of treatments, particularly antidepressants) and/or by deflecting attention away from causal factors in people's life situations that might be amenable to change (for example, couples counselling or, more radically, ending relationships might be more effective than medication of distressed partners). Furthermore, some of the arguments used by depression/antidepressant advocates, for example that long-term treatment is necessary, undermine their own claims of effectiveness. Claims about the necessity of long-term antidepressant use are discussed in chapter 6.

Critics of the orthodox story about depression are often dismissed contemptuously as ignorant, callous, and/or victim-blaming. Sometimes this is based on deliberate misrepresentation, but more often it is based on lack of understanding of their non-simplistic beliefs. In particular, many critics of the orthodoxy do not accept the influential false dichotomy that depression must be *either* a disease or a moral failing. Instead, many point to social factors that are generally ignored or dismissed as unimportant.

Many common claims about suicide are misleading. A major contributor is inappropriate generalisation. Most notably, the claim that 15% of depressed people kill themselves greatly overstates the risk, based on inappropriate generalisation from relatively severe treated cases (including people with bipolar disorder) to depressed people in general. Claims that as many as 80% or 90% of cases of suicide are associated with or even caused by depression are also problematic and misleading. The attribution of suicide to depression is very strongly established in the medical literature and the media, despite substantial evidence to the contrary. This has resulted in ongoing neglect of risk factors other than depression, and lack of investigation of prevention strategies other than detection and treatment of depression. Suicide is not

just a tragedy; it is also a powerful marketing tool for both the pharmaceutical industry and psychiatric profession.

In the 1990s, the key debate about antidepressants focused on their dependence potential. That debate has subsided since, but it is still important. Many antidepressant advocates have grudgingly admitted the possibility of withdrawal symptoms and syndromes. Claims that antidepressants are not 'addictive' continue but are less common now than they used to be.

More recently, safety concerns have focused primarily on suicide. According to orthodox beliefs, as mentioned above, antidepressants are the solution to suicide, because they supposedly cure depression, which is constructed as the sine qua non of suicide. However, there is some evidence that use of antidepressants can *increase* the risk of suicide. This is the subject of the most heated and polarised current debate about antidepressants, particularly in relation to young people. The evidence wielded by both sides of the debate is complex and ambiguous and, from an epidemiological perspective, weak. The fact that antidepressants are commonly used to treat depression makes it difficult to determine how much of the increased risk associated with antidepressant use is attributable to antidepressants as opposed to the underlying depression (confounding by indication).

Antidepressant advocates continue to push the equation that suicide prevention means antidepressants. They frequently cite ecological studies showing negative correlations between suicide rates and antidepressant prescription rates, arguing that the relationship is causal, despite the evidence not satisfying accepted criteria for causation. Ecological studies are also used to support an extension of the equation, namely that lack of antidepressants is a major risk factor for suicide. This has occurred mainly in relation to FDA warnings about the risk of suicide by children and adolescents, which has resulted in decreased prescribing rates to adults as well as children and adolescents.

In relation to effectiveness, there is mounting evidence that the apparent efficacy of antidepressants in clinical trials has been enhanced by methodological manipulations in the design of clinical trials, for example the use of placebo washout, compounded by reporting biases, including suppression of negative trials. Also a number of studies have demonstrated that increased antidepressant use has not been associated with

decreased rates of depression at the population level. The ecological nature of this evidence precludes causal interpretation, but it is notable that antidepressant advocates ignore or challenge these ecological studies and not others that support their claims about antidepressants and suicide.

As with depression and suicide, weak and sometimes manipulated empirical evidence and faulty logic are being used to support the current orthodoxy about antidepressants. Much of this is orchestrated by the pharmaceutical industry.

Not surprisingly, critics of antidepressants are themselves strongly criticised, particularly if they also question the orthodox story about depression. Ignorance, callousness, dangerousness, vested interests, and prejudice against doctors and pharmaceutical companies are among the accusations. Critics' views are often misrepresented, partly because they are oversimplified (for example opposition to antidepressants may be construed as opposition to any form of treatment).

Pharmaceutical companies skilfully utilise sophisticated marketing strategies that profoundly influence doctors' prescribing of drugs, particularly profitable drugs such as antidepressants. Drug companies spend many millions of dollars on marketing, far more than on research and development, but overall it pays off handsomely. Chapter 7 discusses key marketing strategies relevant to antidepressants. A case study towards the end of the chapter illustrates the effectiveness of a potent blend of problematic promotional practices in the marketing of one very profitable selective serotonin reuptake inhibitors, Lexapro® (escitalopram).

Expenditure on drug representatives can generate a high return on investment, and antidepressants have been heavily and effectively detailed (promoted) this way. Although many doctors deny being influenced, there is clear evidence that drug representatives significantly influence prescribing, including antidepressant prescribing.

There is also clear evidence that industry-remunerated key opinion leaders influence doctors' prescribing. They provide a valuable blend of status and credibility derived from their perceived independence. They participate in multiple promotional strategies, including continuing medical education, guideline development, disease awareness campaigns, and publication of ghost-written journal articles. Most key opinion leaders in relation to depression and antidepressants are psychiatrists, who are

among the most strongly industry-linked doctors. Several important Australian key opinion leaders are discussed in chapter 9.

Medical journal advertisements have a particularly high return on investment, clearly influencing doctors' prescribing. Furthermore, drug companies profoundly influence the academic content of the medical literature in several ways. Firstly, most journals are financially dependent on drug advertising, creating potential conflicts of interest that can influence editorial content and decisions about accepting or rejecting submitted articles. Secondly, most pharmaceutical trials are funded by drug companies, and there is substantial evidence of multiple biases, including methodological biases such as comparators and outcome measures that favour sponsors' drugs. Another very significant problem is publication bias, including selective reporting of favourable findings, and repression of unfavourable findings (including whole studies). These strategies allow the pharmaceutical industry to skilfully subvert evidence-based medicine.

Many industry-influenced journal articles profoundly affect clinical practice, particularly if their findings influence clinical practice guidelines. Such guidelines are strategically crucial targets for industry influence, and are a key channel through which evidence-based medicine can be co-opted and subverted. One particularly egregious strategy is drug company funding and coordination of the development of guidelines. Furthermore, non-industry-funded guideline development panels usually include industry-sympathetic key opinion leaders.

Pharmaceutical companies also have significant relationships with health professional organisations, consumer organisations, and government entities. Often there are synergistic alliances involving industry, doctors, consumer organisations, and governments, based on economic factors and a shared agenda to medicalise social problems and deflect attention from social and economic contributors to such problems.

Not surprisingly, both the industry and the medical profession are at pains to downplay the extent of the industry's influence, as are other players, including consumer organisations. A common argument is that doctors are too intelligent to be influenced and/or too ethical to put their own interests ahead of their responsibility to

their patients. Another strategic argument is that industry self-regulation and weak government regulation are effective.

The pharmaceutical industry has invested considerable resources in challenging and even discrediting critics, sometimes with the assistance of doctors. It continues to dogmatically promote its role as the benevolent developer of life-saving and life-changing medicines, playing down its legal responsibility to maximise profits for shareholders, and ignoring conflict between profit maximisation and the health and economic goals of the broader community. It has also strategically consolidated its role as a 'partner' in the healthcare arena, including participation in policy-making processes in many countries, including Australia.

Industry alliances and partnerships often coalesce around disease awareness campaigns, in which disorders are sold in order to sell drugs. Depression awareness campaigns, several of which are discussed in detail in chapter 8, have played a very important role in expanding markets for antidepressants, and have been skilfully used by drug companies since at least 1961.

Chapter 9 analyses in detail the National Depression Awareness Campaign (NDAC), which was coordinated in Australia in the 1990s and early 2000s by an extremely important key opinion leader, Professor Graham Burrows, Chair of the Mental Health Foundation of Australia, with funding from two antidepressant manufacturers. The NDAC was a major factor in the establishment of *beyondblue: the national depression initiative*, which has dominated the Australian mental health arena for more than a decade. This case study details how key players, including pharmaceutical companies, succeeded not only in promoting antidepressant prescribing and use, but also in making depression a central focus of Australian mental health policy, which has greatly contributed to the boom in antidepressant prescribing.

In summary, this thesis has challenged a powerful orthodox story that has dominated the mental health arena in Australia and elsewhere for more than a decade. It has critically analysed widely accepted beliefs about depression and antidepressants, including many key claims based on evidence that is non-existent, weak, and/or misrepresented. It has examined the roles of key players, particularly pharmaceutical companies, psychiatrists (particularly key opinion leaders), and consumer

organisations, in promoting the orthodoxy. This analysis makes it clear that many taken-for-granted assumptions about depression, suicide, and antidepressants, should be discarded, and much of the published literature should be regarded as untrustworthy. This has serious implications for Australian mental health policy as well as clinical practice and suicide prevention, none of which have a strong evidence base.

APPENDICES

Appendix 1

Criteria for DSM-IV Major Depressive Disorder, Major Depressive Episode, and Dysthymic Disorder

Major Depressive Episode

The essential feature of Major Depressive Disorder is a clinical course that is characterized by one or more Major Depressive Episodes (see …) without a history of Manic, Mixed, or Hypomanic Episodes

(American Psychiatric Association 1994, p. 339)[1]

[1] A text revision of the DSM-IV (APA 1994), the DSM-IV-TR (APA 2000) has been published. However, the DSM-IV-TR criteria for major depressive disorder, depressive episode, and dysthymic disorder are exactly the same as the DSM-IV criteria, and most people continue to cite the 1994 DSM-IV criteria.

Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

   Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

   (1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note**: In children and adolescents, can be irritable mood.

   (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).

   (3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note**: In children, consider failure to make expected weight gains.

   (4) insomnia or hypersomnia nearly every day.

   (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

   (6) fatigue or loss of energy nearly every day.

   (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

   (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

   (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

(American Psychiatric Association 1994, p. 327)

Diagnostic criteria for 300.4 Dysthymic Disorder

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years. **Note:** In children and adolescents, mood can be irritable and duration must be at least 1 year.

B. Presence, while depressed, of two (or more) of the following:

(1) poor appetite or overeating

(2) insomnia or hypersomnia

(3) low energy or fatigue

(4) low self-esteem

(5) poor concentration or difficulty making decisions

(6) feelings of hopelessness

C. During the 2-year period (1 year for children or adolescents) of the disturbance, the person has never been without the symptoms in Criteria A and B for more than 2 months at a time.

D. No Major Depressive Disorder (see …) has been present during the first two years of the disturbance (1 year for children and adolescents); i.e., the disturbance is not better accounted for by chronic Major Depressive Disorder, or Major Depressive Disorder, In Partial Remission.

Note: There may have been a previous Major Depressive Disorder provided there was a full remission (no significant signs or symptoms for 2 months) before development of the Dysthymic Disorder. In addition, after the initial 2 years (1 year for children and adolescents) of Dysthymic Disorder, there may be superimposed episodes of Major Depressive Disorder, in which case both diagnoses may be given when the criteria are met for a Major Depressive Disorder.

E. There has never been a Manic Episode (see …), a Mixed Episode (see …), or a Hypomaic Episode (see …), and criteria have never been met for Cyclothymic Disorder.

F. The disturbance does not occur exclusively during the course of a chronic Psychotic Disorder, such as Schizophrenia or Delusional Disorder.

G. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social occupational, or other important areas of functioning.

Specify if:

Early Onset: if onset is before age 21 years

Late Onset: if onset is at age 21 years or older

Specify (for most recent 2 years of Dysthymic Disorder):

With Atypical Features (see …)

(American Psychiatric Association 1994, p. 349)

Appendix 2

Criteria for ICD-10 Depressive Episode and Recurrent Depressive Disorder

F32 DEPRESSIVE EPISODE

G1. The depressive episode should last for at least 2 weeks.

G2. There have been no hypomanic or manic symptoms sufficient to meet the criteria for hypomanic or manic episode (F30.-) at any time in the individual's life.

G3. Most commonly used exclusion clause. The episode is not attributable to psychoactive substance use (F10-F19) or to any organic mental disorder (in the sense of F00-F09).

Somatic syndrome

Some depressive symptoms are widely regarded as having special clinical significance and are here called "somatic". (Terms such as biological, vital, melancholic, or endogenomorphic are used for this syndrome in other classification.)

A fifth character (as indicated in F31.3; F32.0 and F32.1; F33.0 and F33.1) may be used to specify the presence or absence of the somatic syndrome. To qualify for the somatic syndrome, four of the following symptoms should be present:

(1) marked loss of interest or pleasure in activities that are normally pleasurable;

(2) lack of emotional reactions to events or activities that normally produce an emotional response;

(3) waking in the morning 2 hours or more before the usual time;

(4) depression worse in the morning;

(5) objective evidence of marked psychomotor retardation or agitation (remarked on or reported by other people);

(6) marked loss of appetite;

(7) weight loss (5% or more of body weight in the past month);

(8) marked loss of libido.

In *The ICD-10 Classification of Mental and Behavioural Disorders: Clnical descriptions and diagnostic guidelines*, the presence or absence of the somatic syndrome is not specified for severe depressive episode, since it is presumed to be present in most cases. For research purposes, however, it may be advisable to allow for the coding of the absence of the somatic syndrome in severe depressive episode.

F32.0 Mild depressive episode

A. The general criteria for depressive episode (F32) must be met.

B. At least two of the following three symptoms must be present:

(1) depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks.

(2) loss of interest or pleasure in activities that are normally pleasurable;

(3) decreased energy or increased fatiguability.

C. An additional symptom or symptoms from the following list should be present, to give a total of at least four:

(1) loss of confidence and self-esteem;

(2) unreasonable feelings of self-reproach or excessive and inappropriate guilt;

(3) recurrent thoughts of death or suicide, or any suicidal behaviour;

(4) complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation;

(5) change in psychomotor activity, with agitation or retardation (either subjective or objective);

(6) sleep disturbance of any type;

(7) change in appetite (decrease or increase) with corresponding weight change).

A fifth character may be used to specify the presence or absence of the "somatic syndrome" (defined on page xx):

F32.00 Without somatic syndrome

F32.01 With somatic syndrome

F32.1 Moderate depressive episode

A. The general criteria for depressive episode (F32) must be met.

B. At least two of the three symptoms listed for F32.0, criterion B, must be present.

C. Additional symptoms from F32.0, criterion C, must be present, to give a total of at least six.

A fifth character may be used to specify the presence or absence of the "somatic syndrome" as defined on page xx:

F32.10 Without somatic syndrome

F32.11 With somatic syndrome

F32.2 Severe depressive episode without psychotic symptoms

Note: If important symptoms such as agitation or retardation are marked, the patient may be unwilling or unable to describe many symptoms in detail. An overall grading of severe episode may still be justified in such a case.

A. The general criteria for depressive episode (F32) must be met.

B. All three of the symptoms in criterion B, F32.0, must be present.

C. Additional symptoms from F32.0, criterion C, must be present, to give a total of at least eight.

D. There must be no hallucinations, delusions, or depressive stupor.

F32.3 Severe depressive episode with psychotic symptoms

A. The general criteria for depressive episode (F32) must be met.

B. The criteria for severe depressive episode without psychotic symptoms (F32.2) must be met with the exception of criterion D.

C. The criteria for schizophrenia (F20.-) or schizoaffective disorder, depressive type (F25.1) are not met.

D. Either of the following must be present:

(1) delusions or hallucinations, other than those listed as typically schizophrenic in F20, criterion G1(1)b, c, and d (i.e. delusions other than those that completely impossible or culturally inappropriate and hallucinations that are not in the third person or giving a running commentary); the commonest examples are those with depressive, guilty, hypochondriacal, nihilistic, self-referential, or persecutory content;

(2) depressive stupor.

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with mood:

F32.30 With mood-congruent psychotic symptoms (i.e. delusions of guilt, worthlessness, bodily disease, or impending disaster, derisive or condemnatory auditory hallucinations)

F32.31 With mood-incongruent psychotic symptoms (i.e. persecutory or self-referential delusions and hallucinations without an affective content)

F32.8 Other depressive episodes

Episodes should be included here which do not fit the descriptions given for depressive episodes in F32.0-F32.3, but for which the overall diagnostic impression indicates that they are depressive in nature. Examples include fluctuating mixtures of depressive symptoms (particularly those of the somatic syndrome) with nondiagnostic symptoms such as tension, worry, and distress, and mixtures of somatic depressive symptoms with persistent pain or fatigue not due to organic causes (as sometimes seen in general hospital services).

F32.9 Depressive episode, unspecified

F33 RECURRENT DEPRESSIVE DISORDER

G1. There has been at least one previous episode, mild (F32.0), moderate (F32.1), or severe (F32.2 or F32.3), lasting a minimum of 2 weeks and separated from the current episode by at least 2 months free from any significant mood symptoms.

G2. At no time in the past has there been an episode meeting the criteria for hypomanic or manic episode (F30.-).

G3. Most commonly used exclusion criteria: the episode is not attibutable [sic] to psychoactive substance use (F1) or any organic mental disorder, in the sense of F0.

It is recommended to specify the predominant type of previous episodes (mild, moderate, severe, uncertain).

F33.0 Recurrent depressive disorder, current episode mild

A. The general criteria for recurrent depressive disorder (F33) are met.

B. The current episode meets the criteria for depressive episode, mild severity (F32.0).

A fifth character may be used to specify the presence of the somatic syndrome, as defined in F32, in the current episode:

F33.00 without somatic syndrome

F33.01 with somatic syndrome

F33.1 Recurrent depressive disorder, current episode moderate

A. The general criteria for recurrent depressive disorders (F33) are met.

B. The current episode meets the criteria for depressive episode, moderate severity (F32.1).

A fifth character may be used to specify the presence of the somatic syndrome, as defined in F32, in the current episode:

F33.10 without somatic syndrome

F33.11 with somatic syndrome

F33.2 Recurrent depressive disorder, current episode severe without psychotic symptoms

A. The general criteria for recurrent depressive disorders (F33) are met.

B. The current episode meets the criteria for severe depressive episode without psychotic symptoms (F32.2).

F33.3 Recurrent depressive disorder, current episode severe with psychotic symptoms

A. The general criteria for recurrent depressive disorders (F33) are met.

B. The current episode meets the criteria for severe depressive episode with psychotic symptoms (F32.3).

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with the mood:

F33.30 with mood congruent psychotic symptoms

F33.31 with mood incongruent psychotic symptoms

F33.4 Recurrent depressive disorder, currently in remission

A. The general criteria for recurrent depressive disorder (F33) have been met in the past.

B. The current state does not meet the criteria for a depressive episode (F32.-) of any severity, or for any other disorder in F3 (the patient may receive treatment to reduce the risk of further episodes).

F33.8 Other recurrent depressive disorders

F33.9 Recurrent depressive disorder, unspecified

(World Health Organization 1993)

World Health Organization. (1993). *The ICD-10 Classification of mental and behavioural disorders: Diagnostic criteria for research*. Geneva: World Health Organization. http://www.who.int/classifications/icd/en/GRNBOOK.pdf (6 March 2006).

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