Collateral Damage:
A Mixed Methods Study to Investigate the Use and Withdrawal of Antidepressants Within a Naturalistic Population

By Susan Thrasher

A thesis submitted to Victoria University of Wellington in partial fulfilment of the requirements for the degree of Masters of Science Psychology
2010

Abstract

The use of modern antidepressants has flourished over the past few decades with the modern attribution of affective disorders such as depression to biomedical causation. However, recent re-examination of clinical trials has raised questions regarding antidepressant drug efficacy, and issues around side effects and dependency are prevalent. In spite of this, as many as 10% of us may be taking these medications (Szabo, 2009). This study examines responses to an anonymous online survey about antidepressant use and withdrawal. Participants included 176 current users, 181 currently withdrawing, 108 ex-users, and a control group of 44 participants who had never used antidepressants. Participant groups were compared quantitatively regarding attitude towards antidepressants use and perceived value, effect on well-being and mood, symptoms and side effects, and their perceived changes in themselves on and off the drugs. Participants were also given the opportunity to include spontaneous comments at the end of the survey which were analysed thematically. Key findings include: 1) Antidepressant users have a more positive estimation of the value of the drugs than those who have discontinued the drugs or who have never used them; 2) Scores on the WHO-5 well-being survey for all three groups with antidepressant experience (users, those withdrawing, and ex-users) showed poor levels of well-being, suggesting that neither antidepressant therapy nor cessation of antidepressant therapy were adequate interventions to create positive well-being; 3) Multivariate analysis of participant responses revealed a significant difference between the four groups on 35 of 37 physical and emotional symptoms associated with antidepressant use or withdrawal, with the never-used group

scored the lowest in all cases except one, and the withdrawing group scoring the highest for 27 of the symptoms; 4) Concern over antidepressant dependency and withdrawal was the most prevalent topic reported by all user groups in spontaneous comments; other key themes included frustration with side effects and lack of information and support from the medical profession; 5) study results suggest that antidepressant withdrawal may take longer and be more challenging than the assumed “mild”, “self-limiting” and “resolving spontaneously…three weeks after onset” (Haddad & Anderson, 2007); and 6) 30% of ex-users spontaneously reported what they believed were adverse drug reactions, or withdrawal reactions, months or years after antidepressant use had ceased, a long-term iatrogenic disablement that has yet to be addressed in the literature. Overall, the study reveals that antidepressants are not an adequate intervention to create positive well-being in patients and their use comes with a substantial risk of unpleasant side effects, dependency, and the potential for residual post-drug health complications.

Acknowledgements

This project—and indeed my passion for the topic—would not exist were it not for the impetus and inspiration of two very special people. One is my de facto partner, Graham Stuart[1], whose personal antidepressant and withdrawal experience led me to question the value and safety of these drugs in the first place. The other is Rachel Liebert who inspired me with her master's research project, her passion, and her desire to increase public awareness of potential antidepressant risks.

Special thanks must also go, of course, to my two supervisors, John McDowall and Marc Wilson, who provided invaluable suggestions and guidance for this research and preparation of the manuscript.

Lastly, a huge thank you must go to the hundreds of survey participants who freely gave their time and wisdom to share information about their own antidepressant experiences for this project.

[1] Graham, incidentally, chose not participate in this research or survey.

Table of Contents

List of Tables

Chapter 1

Antidepressants in Modern Society

> *The pharmaceutical industry is undoubtedly the most influential actor in the health and mental health systems today.*
>
> David Cohen, 2008

Modern antidepressant use is not an event that occurs in isolation, nor is it simply the result of increasing incidence or awareness of depression in modern society. It is the product of an historical, scientific, cultural, social, and economic amalgam. To understand the prevalence and standing of antidepressants in our society, it is essential to look at the bigger picture.

The pharmaceutical industry today is enormous, with worldwide sales in excess of $600 billion in 2006 (Britten, 2008). Pharmaceuticals were ranked third in 2009 by *Fortune 500,* after communications and internet services, with a profit margin of over 19% (Fortune 500, 2009). A significant amount of this profit came from the sale of antidepressants, the most commonly-prescribed class of medication in the U.S. (Olfson & Marcus, 2009), which accounts for 15% of the total annual cost of medication there (Kirsch, 2010b).

Approximately 10% of Americans reported taking antidepressants in 2005, twice as many as in 1996, with 80% of those prescriptions written by general practitioners (Szabo, 2009). This includes approximately 2.5% of U.S. children aged 6-17 who were prescribed antidepressants in 2005 (Olfson & Marcus, 2009) in spite of the U.S. Food and Drug Administration's (FDA's) black box warning against paediatric use. In Britain, antidepressant prescription rates, also around

10% (Petty, House, Knapp, Raynor & Zermansky, 2006), increased by 36% between 2000 and 2005, reflecting not only new prescriptions, but also long-term use of the drugs by many patients (Moore et al., 2009). In New Zealand, the number of antidepressant prescriptions nearly doubled from 1.1 million in 1997 to 2.1 million in 2005 (Ministry of Health, 2007) with the Pharmaceutical Management Agency of New Zealand (PHARMAC) reporting approximately 10% of the population being treated, including adolescents, children and toddlers (Sabin, 2010).

Yet depression is today's fastest-rising diagnosis and third most common reason for consultation with a general practitioner (GP) (Currie, 2005; Mitchell & Coyne, 2007), and it is identified by the World Health Organisation (WHO) as the leading cause of poor health worldwide (Daly, 2009). According to the National Institute of Mental Health (NIMH, 2010), anxiety disorders frequently co-occur with depressive disorders, affecting over 18% of the U.S. population aged 18 and over. These include panic disorder, obsessive compulsive disorder (OCD), post traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), and a variety of phobias (NIMH, 2010). Antidepressants are U.S. FDA approved treatments for all of these disorders, and more (see Table 1, p. 16).

Concurrent with the rise in antidepressant use is the rise in the number of individuals disabled by mental illness, reflected in a four-fold per capita increase of patient care episodes and a sixfold increase in people on social security disability insurance for mental illness in the U.S. since 1955 (Whitaker, 2005). In New Zealand, a 2003/2004 nationwide representative sample survey of 12,992 reported an alarming national mental disorder prevalence, based on survey

responses, of 46.4% (extrapolated lifetime likelihood of mental illness diagnosis), with 20.7% reporting diagnosis of a mental disorder within the past 12 months (Oakley Browne, Wells & Scott, 2006). In the survey, mental illness was defined as suffering from a mood disorder such as depression, anxiety disorder, eating disorder, and/or substance abuse disorder.

It wasn't always this way. Less than a hundred years ago, Sigmund Freud observed that melancholy—depression—generally resolved of itself, even without treatment, and suggested it plays an important role in ego development (Freud, 1917). He argued that melancholia could be best understood and treated through conversation or "talk therapy". Nearly fifty years ago, Nathan Kline[2] observed "most depressions terminate in spontaneous remissions…regardless of what one does" (1964, as reported in Whitaker, 2010, p. 153). Thirty-six years ago, NIMH depression section head Dean Schuyler described depression as a self-limiting condition with complete recovery rates exceeding 50% without any intervention (Schuyler, 1974 as reported in Whitaker, 2010, p. 153). Yet today, with all the trappings of scientific study, and modern antidepressant drugs mooted as standard first-line treatment for depression and anxiety, the incidence of these afflictions has risen to unprecedented levels, prompting the American Psychiatric Association (APA) to now define depression as "a highly recurrent and pernicious disorder," with only 15% of patients expected to experience full remission (quoted in Whitaker, 2010, p. 161-162).

It is a paradox. As antidepressant treatment rates go up, recovery rates go down, and chronic mental health disability increases. Correlation does not imply causation, of course, but is it possible that antidepressant treatment may actually

[2] Kline and his colleagues were the first to recognize the antidepressant properties of the MAOI iproniazid, and developed the TCA amitriptyline which remains the world's most popular tricyclic antidepressant. See Chapter 2.

worsen the course of depression? In the 1960s and 1970s, some European physicians observed that antidepressant use appeared to shorten remission intervals between depressive episodes and often lead to chronic impairment (Whitaker, 2010, pp. 157-158). When drug-treated vs. non-treated depressive patients in fifteen countries were compared in a major WHO study, those who had not been exposed to antidepressants had significantly better outcomes at the one year point, prompting researchers to conclude—contrary to expectations—that failure to recognize or treat depression did not appear to have adverse consequences (Goldberg, Privett, Ustun, Simon & Linden, 1998). A Canadian study of employees found those on short-term disability due to depression were significantly more likely to become long-term disability clients if treated with antidepressants, a situation that was further exacerbated if the antidepressants were switched or augmented (Dewa, Hoch, Lin, Paterson & Goering, 2003). In another Canadian study, analysis of longitudinal data from two large (n = 130,880 and n = 17,262) Canadian health surveys found that, contrary to expectation, patients prescribed antidepressants following a depression diagnosis reported more weeks of depression and a higher risk of relapse following drug treatment than those not prescribed antidepressants (Patten, 2004). Yet prescribing rates continued to climb.

Short-term use of antidepressants appears to produce positive outcomes, at least in published clinical trials, most of which averaged 6 to 8 weeks duration. There are, however, problems with the apparently positive antidepressant clinical trial results: Firstly, although trials with positive results are generally published, trials with negative results rarely are. In a meta-analysis of 74 antidepressant trials lodged with the FDA, Turner, Matthews, Linardatos, Tell and Rosenthal (2008)

found just 38 with positive drug efficacy results; 37 of those were published in journals, 11 of the trials with negative results were published in such a way as to convey a positive outcome, and only 3 published trials showed no drug efficacy. Furthermore, the FDA only requires two clinical trials with positive efficacy results compared to placebo for drug approval, no evidence is required that a new drug is superior to any existing drugs, and data from unsuccessful trials need not be lodged with the FDA (Medawar, Hardon, & Herzheimer, 2004). The overall impression conveyed to researchers, physicians, and patients, based on published reports, is one of positive drug efficacy.

How positive are those short-term results? In another meta-analysis of FDA-lodged antidepressant trial studies, this one focussing just on the six SSRI antidepressants, Kirsch et al. (2008) found an "exceptionally large" placebo response of over 80% and concluded that the small difference between drug and placebo response was only clinically significant for severely depressed patients, a result that was echoed more recently by Fourier et al. (2010). Kirsch also found no difference in drug response between drugs types—it did not matter, all drugs produced the same degree of improvement (Kirsch, 2010a, p. 12), echoing the findings of Anderson (2000) and anticipating those of Hagen, Wong-Wylie, and Piji-Zieber (2010). If the placebo used in a trial was active—meaning it produced one or more side effects—no significant difference was found between drug and placebo; indeed, the strongest correlation Kirsch found in the meta-analysis was between reported drug side effects and depression improvement (.92 for fluoxetine, but all extremely high) (Kirsch, 2010a, pp. 18-20).

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush et al, 2004), which followed 4000 depressed patients treated with a

variety of antidepressants, 25-30% achieved remission within 12 weeks of treatment, about the same as the remission rate on placebo found in other studies (STAR*D did not have a placebo arm), but only 3% of participants showed a sustained remission rate following a year of continuous drug treatment (Leventhal & Antonuccio, 2009), suggesting that long-term efficacy results are poor, and echoing Fava's 2003 literature review that revealed a "very unfavourable long-term outcome of major depression [when] treated by pharmacologic means."

Chapter 2

A (Relatively) Brief History of Antidepressants

Ancient times

The use of a variety of ingested substances to ameliorate depression and its first cousin anxiety goes back to ancient times. Alcohol, a relatively simple-to-make anxiolytic, was a very early de-stressor. The brewing of beer and fermenting of grapes or other fruit for wine was recorded by Egyptian and other Middle Eastern cultures as early as 6000 B.C, and production quickly spread throughout the ancient world (McGovern, 1996, p. ix; Nunn, 1996, pp. 10-13). Opium poppies, called "the plant of joy" by the ancient Sumerians in the 3rd millennium BC, yielded opium, which was a widely-traded narcotic throughout Asia, the Middle East and Europe in ancient times (Payk, 1994). Atropa belladona, extracted from deadly nightshade, and hashish were both identified in a 3rd millennium BC Assyrian herbal text as remediation for a variety of nervous disorders (Payk, 1994), and a circa 1600 BC Egyptian papyrus recommends extracts from henbane and thorn apple (containing the psychotropic alkaloids hyoscyamine and scopolamine respectively), sometimes mixed with alcohol, as a remedy for melancholy (Payk, 1994).

The word *melancholia* derives from the ancient Greek words *melas*, meaning black, and *kholé*, meaning bile[3]. Although the ancient Greek doctor Hippocates (460-377 BC) attributed the development of melancholia, or excessive

[3] Bile is a fluid made by the liver and stored in the gall bladder. It helps the body digest fat. An imbalance of its primary components cholesterol, salts, and the pigment bilirubin causes gall stones. Bile is usually a yellow-green colour (MedTerms, 1998a).

black bile, to the psychological issues of lingering shame, grief, or fear (Bennett, 1992; Wong & Licinio, 2001), popular pharmaceutical treatments of the time—*pharmacon* is the Greek word for drug—included opium, mandrake, ass's milk, and barley gruel, prescribed along with a vegetarian diet, abstinence from sex, massage, baths, physical exercise and dance, and distraction (Payk, 1994; Thompson, 2007, p. 7, Wong & Licinio, 2001).

The advent of psychiatry

The term *psychiatry* was created in 1808 by the German physician Johann Christian Reil by uniting the Greek words *psyche* (soul) and *iatry* (physician, from the greek *iatros*) (Marneros, 2008). Reil argued that mental illness could be treated, initially and in the most severe cases, by medical interventions including alcohol, drugs, pain, blistering agents, and baths (Hansen, 1998). These physical remedies, he believed, should be combined with sensory treatments involving music, art, and massage—also appropriate first-line treatments for less-disabled patients—and, when the patient was ready, "talk therapy" to positively influence ideas, imagination and judgement and enable patients to achieve a level of "full consciousness" (Hansen, 1998).

A century later, another German medical doctor and psychiatrist, Sigmund Freud, taught that mental disease (dis-ease) was the result of unconscious impulses and repressions which he felt could be addressed through a process he called psychoanalysis. However, with the advent of psychochemistry in the second half of the 20th century, depression, anxiety and their derivatives were identified not so much as the product of responses to difficult situations, painful emotions, conscience-pricking behaviours, or general dissatisfaction about life in

general which could be treated with talk therapy, but as chemically-induced abnormal brain states that could be treated with a range of pharmaceuticals (Breggin, 1991, p 11-12; Cohen, 2008). In spite of this, there are today no biological tests for depression, and there is no scientific evidence to support a biochemical explanation for this disorder (Levanthal & Antonuccio, 2009; Whitaker, 2010a, pp. 78-79).

Early chemical treatments for depression and anxiety

A variety of chemical substances deemed useful for the treatment of melancholia and anxiety appeared in the 19th century. Potassium bromide, a psychotropic sedative and hypnotic, was introduced in 1826 initially as a treatment for epilepsy and to lessen sexual urges; problems with dependence became apparent by the mid-1800's, and it is rarely used today (Lader, 1991). Codeine, a derivative of opium, appeared in 1832, followed by chloral hydrate in 1869 and paraldehyde in 1882 (Payk, 1994).

The first trade-marketed anxiolytic from a chemistry lab was the barbiturate Barbitol, synthesized by German chemists in 1903 and marketed by Bayer in 1904 under the trade name "Veronal". This was followed by phenobarbital ("Luminal") in 1912 and amobarbital in 1923 (Lader, 1991). Well over a thousand barbiturate compounds were synthesized, and about 50 were brought to the market, but significant issues with toxicity and dependence made the need for safer sedative formulations apparent (Lader, 1991).

In 1929, Gordon Alles, a biochemist working on decongestants, developed a new compound, beta-phenyl-isopropylamine, which came to be known as amphetamine. A base form of the compound was patented by the pharmaceutical

firm Smith, Kline and French (SKF) in 1933 and the inhaler form was sold over-the-counter for the next 15 years[4] (Rasmussen, 2008). SKF soon found other uses for the new drug, however, and in 1937 received the American Medical Association (AMA) seal of approval for a tablet-form of amphetamine called Benzedrine Sulfate for treatment of narcolepsy, Parkinsonism, and minor depression (Rasmussen, 2008).

According to Rasmussen, SKF recruited a champion for the product in Harvard neurologist and psychiatrist Abraham Myerson, author of the then-popular book *When Life Loses Its Zest*, who reasoned that since depression is expressed by a lack of energy, enthusiasm and focus—in other words, anhedonia[5]—the adrenergic stimulation of amphetamine would be a perfect antidote and mood elevator. SKF used Myerson's reputation, medical backing and logical reasoning to launch an advertising campaign for the new drug aimed at general practitioners (GPs).

Full page SKF advertisements for Benzedrine Sulfate appeared in medical journals during the 1940's promised "a non-narcotic drug capable of alleviating depression", patients feeling "better than well" and "immediate results: favourable, in some instances spectacular." Sales of Benzedrine Sulfate tablets grew steadily (Rasmussen, 2006).

In the late 1950's, after their patent for Benzedrine Sulphate ran out, SKF introduced a new antidepressant, Dexamyl, which was composed of

[4] In 1938 the U.S. Congress initiated regulation requiring drugs be tested for safety, but it wasn't until 1951, after the passing of the Durham-Humphrey Amendment, that potentially dangerous formulations required a doctor's prescription rather than patients being allowed unrestricted access, a move which gave physicians a very privileged place in society (Whitaker, 2010, pp. 55-56)

[5] Myerson revived and reinterpreted this obscure nineteenth-century term meaning literally "lack of pleasure", rescuing it from obscurity, and broadened the previously more narrow definition of depression from the formerly used "neurasthenia", or neurotic disorder, and paving the way for increased sales to a broadening market. (Rasmussen, 2006)

dextroamphetamine and the barbiturate amobarbital. It was promoted as a product to quell anxiety without drowsiness, and also as a remedy for weight loss which would not only lessen the appetite but also treat the emotional causes of overeating. The amphetamine market continued to expand, reaching a peak in the 1960's when it was guesstimated that over 6% of the US and UK populations had used an amphetamine product within a given six month period (Rasmussen, 2008).

Meanwhile, meprobamate, developed by Frank Berger in the 1950's as a muscle relaxant for laboratory animals, became an exciting new product for anxiety, one that offered a sense of relaxation without the sedation engendered by the barbiturates. Berger coined a new term for the drug: *tranquilizer.* It was marketed under the trade names "Miltown" and "Equanil" by Carter Products, and became the first blockbuster psychotropic drug in American history (Healy 2004). In spite of its alarming dependence potential, it continues to remain popular in some countries because of cost effectiveness (Lader, 1991).

The development of the benzodiazepines, the modern tranquilizers, began with Leo Sternbach, a molecular chemist working for Hoffmann-La Roche, a chemical research company. One of the compounds he synthesized, chlordiazepoxide, was found to have clinically significant hypnotic and sedative effects. In spite of dubious safety results with initial (albeit limited) trials, it was brought to the market in 1960, and that release was followed by the still-popular diazepam (Valium) in 1963 (Lader, 1991). A bevy of other "benzos" soon flooded the market as patents for barbiturate products lapsed, launching what came to be known as the 20th century "Age of Anxiety" (Lader, 1991). Heavily promoted with direct-to-consumer advertising in popular women's magazines such as *The Ladies Home Journal* and *Cosmopolitan* and feature articles in news magazines

such as *Time*, *Newsweek*, and *Science Digest* as a panacea for the suburban frustration of modern housewifery, benzodiazepines became known as "Mother's Little Helpers"[6] (Metzl, 2003). Freudian psychoanalysis, still tremendously popular in the 1950s[7], might help identify problems, but Valium promised to fix them. Reports of "improved sleep", "frigid women…responding more readily to their husbands' advances" and "calm in frantic lives" saw sales soar, signifying the beginning of the "biological revolution" in psychiatry (Metzl, 2003).

In 1951, two new compounds, iproniazid and isoniazid, were synthesized by the pharmaceutical company Hoffman-La Roche from leftover WW II stockpiles of hydrazine, a key component in German rocket fuel, and tested on tubercular patients with gratifying results. By Easter 1952[8], headlines proclaimed iproniazid (in particular) a "TB wonder drug" (Sandler, 1990).

One unexpected side effect of iproniazid treatment was a sense of euphoria or hypomania that developed in some treated patients. Recognizing the potential of the new drug as a possible treatment for depression, psychiatrist Nathan Kline and his colleagues trialled it with 20 long-term institutionalized "probably schizophrenic" patients and found it effective (Loomer, Saunders, & Kline, 1958, as reported by Sandler, 1990). Iproniazid was the first monoamine oxidase inhibitor (MAOI). In spite of their propensity to cause liver damage and what became known as "the cheese reaction," whereby co-consumption with fermented

---

[6] The Rolling Stones song "Mother's Little Helper", written by Mick Jagger and Keith Richards, was recorded in 1965. They sang:

"*Kids are different today, I hear ev'ry mother say*
Mother needs something today to calm her down
And though she's not really ill, there's a little yellow pill
She goes running for the shelter of a mother's little helper
And it helps her on her way, gets her through her busy day"

[7] The biography *Sigmund Freud: Life and Work* by Ernest Jones made the US bestseller lists in 1955 (Metzl, 2003).

[8] This was before clinical trials were required.

foods such as cheese or wine resulted in a sudden and potentially-fatal episode of hypertension (Thase, Trivedi, & Rush, 1995), MAOIs were widely prescribed for depression during the 1950s and 1960s. Their use declined with the advent of safer drugs and more frequent outpatient care for depression, and they are rarely prescribed today (Thase, Trivedi & Rush, 1995).

Modern antidepressants

The neologism "antidepressant" first appeared in 1959 in the *New York Times* (Whitaker, 2010a, p. 60), about the same time as the first tricyclic antidepressants (TCAs) came on the market. Imipramine, a histamine-type drug with a 3-ring chemical structure (hence "tricyclic"), was developed by psychiatrist Roland Kuhn for the Swiss pharmaceutical firm Geigy; positive results from his trial with 40 depressed patients were published in 1957 (Kuhn, 1970). In retrospect, according to Moncrieff (2008), it seems possible that the "improvement", the agitation and euphoria experienced by Kuhn's patients that he identified as proof of depression remission, may have been due, at least in part, to the sudden withdrawal of the chlorpromazine they had previously been taking, but the idea that a drug such as imipramine could reverse a depressive episode leant support to the budding concept of depression as a biological disease and laid the groundwork for the development of the modern antidepressant market (Moncrieff, 2008).

Geigy, unable to recognize a significant market for an anti-depressive product at that time, saw little reason to actively promote imipramine (Healy, 2004) but a year later, the chemical company Merck approached Frank Ayd, Nathan Kline (the developer of iproniazid), and several of their colleagues and

asked them to examine amitriptyline, another chemical compound based on a tricyclic chemical structure, for possible treatment of schizophrenia or depression (Healy, 1997, pp 74-75). When the depression trials proved positive, Merck filed a patent for amitriptyline specifically as a treatment for depression in 1961 (Healy, 1997, p 75). Meanwhile, Frank Ayd wrote a book titled *Recognizing the Depressed Patient*, and Merck commissioned fifty thousand copies for distribution to psychiatrists and physicians in areas where the new drug was being actively promoted. Amitriptyline quickly became the best-selling antidepressant (Healy, 2004), and it remains the best-selling TCA today. TCAs like imipramine and amitriptyline are sometimes referred to as "first-generation antidepressants;"[9] (Julien, 2001).

To discover how to make better antidepressants, researchers needed to understand why existing ones seemed to work. What was it the pills were changing? The identification of neurotransmitters, chemicals that transmit information between brain cell synapses, prompted the amine theories of depression. In the 1960's American Joseph Schildkraut introduced the catecholamine[10] hypothesis which proposed that depression was correlated with a deficit of monoamines, most specifically norepinephrine, based on observations that drugs such as reserpine, which depletes or deactivates production of norepinephrine[11], produces sedation and depression[12], whereas drugs such as

[9] During the TCA-dominated era, the term "second generation antidepressants" referred to a second wave of TCAs (after imipramine and amitriptyline) The more modern definition of "second generation antidepressants" refers to the atypical antidepressants referred to later in this chapter, sometimes including the SSRIs in that category (Gartlehner, et al., 2008).

[10] Catecholamines function both as hormones and as neurotransmitters. The most common catecholamines in humans are epinephrine (adrenalin), norepinephrine (noradrenalin) and dopamine (Catecholamine, 2010).

[11] Both reserpine and imapramine were identified as norepinephrine reuptake inhibitors in papers at the time (e.g., Hertting, Axelrod & Whitby, 1961), but Shildkraut indicated no awareness of this.

imapramine and the MAOIs increased brain levels of norepinephrine and in doing so stimulated activity and uplifted mood (Schildkraut & Kety, 1967).

Around the same time in the UK, George Ashcroft found lowered levels of brain serotonin in the spinal fluid of depressed patients and cadavers of suicides in 1960 and hypothesized that depression might be caused by low levels of the neurotransmitter serotonin, a theory he rescinded following further studies in 1970 (Ashcroft & Healy, 2000).

Either hypothesis was a boon to the pharmaceutical industry because it suggested that depression could be approached as a medical condition or illness with a biological cause, and therefore medication could be developed to treat it. If depression was caused by low levels of key amines such as norepinephrine or serotonin, and new antidepressants could be shown to target this low level, the prospects for marketing would be enormous. Forty years on, the chemical imbalance theory of depression, and the suggestion that depression results from deficiencies of any monoamine neurotransmitters remains widely reported but unsupported by any scientific evidence (Leventhal & Antonuccio, 2009; Watters, 2010, pp. 234-235).

The TCAs dominated the antidepressant drug market until the mid-1980s when the first Selective Serotonin Reuptake Inhibitors (SSRIs) were developed. Table 1 shows the most commonly prescribed antidepressants in the US in 2007.

[12] Interestingly, in 1955, in the first modern clinical drug trial, Michael Shepherd compared reserpine to placebo in a group of depressive patients and demonstrated an antidepressant action superior to any drug available at that time, but drug company Ciba did not recognize a market for such a product and chose to market the drug as a neuroleptic instead (Healy, 2004). It seems unlikely that Schildkraut was unaware of this study. Subsequent studies have shown that only around 6% of patients given reserpine develop depression (Irving, 2010a, p. 88)

Table 1. ***Most commonly prescribed antidepressant drugs based on number of prescriptions in the US, 2007 (Drug Topics, 2008) and their US FDA approved indications.*** *Approved indications for each drug in the USA is based on information from www.FDA.gov; each drug has its own prescribing information pages. Indications may vary in other countries. Plasma half-life figures from Nierenberg et al., 2008 and FDA prescribing information pages.*

Drug	Brand Names	Class	2007 US Prescriptions	FDA Approved Indications	Plasma Elimination Half Life (approx.)
Sertraline	Zoloft	SSRI	29,652,000	MDD, OCD, Panic Disorder, PTSD, PMDD, SAD	26 hours
Escitalopram	Lexapro, Cipralex	SSRI	27,023,000	MDD, GAD	27-32 hours
Fluoxetine	Prozac, Serafem	SSRI	22,266,000	MDD, OCD, Bulimia Nervosa, Panic Disorder. Also in combination with the antipsychotic olanzapine for bipolar I and treatment-resistant depression. Sarafem for PMDD.	4-6 days
Bupropion	Wellbutrin, Budeprion, Zyban	NDRI	20,625,000	MDD, Seasonal Affective Disorder, Zyban for smoking cessation.	21 hours
Paroxetine	Paxil, Seroxat, Aropax, Loxamine, Pexeva	SSRI	18,141,000	MDD, OCD, Panic Disorder, SAD, GAD, PTSD	21 hours
Venlafaxine	Effexor	SNRI	17,200,000	MDD, SAD, GAD, Panic Disorder	5 hours
Citalopram	Celexa, Cipramil	SSRI	16,246,000	Depression	35 hours
Trazodone	Desyrel	TeCA	15,473,000	Depression	3-6 hours
Amitriptyline	Elavil	TCA	13,462,000	Depression	10-50 hours (average 15)
Duloxetine	Cymbalta	SNRI	12,551,000	MDD, GAD, pain management from fibromyalgia	12 hours
Mirtazapine	Remeron	TeCA	5,129,000	Depression	20-40 hours
Nortriptyline	Pamelor	TCA	3,105,000	Depression	1-4 days

Doxepin	Adapine, Deptran, Sinequan	TCA	2,072,000	Depression, Anxiety	8-24 hours
Imipramine	Tofranil	TCA	1,524,000	Depression	9-20 hours

MDD-Major Depressive Disorder; OCD-Obsessive Compulsive Disorder; PTSD-Post-traumatic Stress Disorder, PMDD-Premenstrual Dysphoric Disorder, SAD-Social Anxiety Disorder, GAD-Generalized Anxiety Disorder
SSRI-Selective Serotonin Reuptake Inhibitor; NDRI-Norepinephrine Dopamine Reuptake Inhibitor; SNRI-Serotonin Norepinephrine Reuptake Inhibitior; TCA-Tricyclic Antidepressant; TeCA-Tetracylic Antidepressant

Whereas the TCAs and MAOIs were discovered more or less by accident, the SSRIs were deliberate creations. Schildkraut's 1965 catecholamine theory pointed to inhibition of norepinephrine as the essential *modus operandi* of antidepressant drug function, but Swedish researcher Arvid Carlsson proposed that antidepressant compounds that would act selectively on the serotonin system might be as effective as the TCAs and have fewer side effects (Healy, 2004). In 1978, he trialled two new compounds, zimelidine and citalopram, identified as "selective 5-HT[13] reuptake inhibitors," in rats (Carlsson & Lindqvist, 1978), and human trials soon followed. Zimelidine was launched onto the European market as Zelmid in 1982, becoming the world's first commercially available SSRI, but was removed shortly thereafter following reports linking it to development of the paralyzing neurological disease Guillain Barré syndrome, liver damage, and suicidal ideation (Healy, 2004, pp 18-19; Shorter, 2009, pp 173-174). Citalopram was not made commercially available until 1989 in Europe and 1998 in the U.S. (Shorter, 2009, p. 174).

In *Let Them Eat Prozac*, David Healy (2004, pp 30-39) tells the story of the development of the first SSRI blockbuster drug, Prozac (fluoxetine), summarized here. Adapted from the antihistamine diphenhydramine (trade name Benadryl) by

[13] 5-HT, or 5-hydroxytryptamine is serotonin (MedTerms, 2003a)

researchers in the Eli Lilly laboratories in the 1970s, the new product did not block the sedative action of reserpine as other antidepressants did, but it did stimulate aggression in rats, which suggested it had some "activating" properties. Lilly was keen to develop a new antidepressant to replace their best-selling TCA nortriptyline, marketed under the trade name Pamelor, but the new drug did not show efficacy for use with severe depression, causing distress and agitation in patients, nor did it work for schizophrenia, pain relief, hypertension or obesity. Finally, adjuncted with benzodiazepines to quell subjects' ensuing agitation, it was trialled with a group of five mildly depressed individuals (Breggin, 2008, pp 247-248). All five responded positively[14]. It was a small success, but enough to initiate the launch of the next blockbuster drug (Healy, 2004).

Prozac underwent numerous clinical trials over the next few years, enough of which yielded results adequate (but just barely) for FDA approval[15] in 1987. The marketing team launched the drug with much fanfare onto the American market in 1988 under a one-pill-a-day-fits-everyone banner in an attempt to expand beyond the psychiatric prescribing market into the much larger sales arena of general practitioners. Promoted as "a breakthrough drug in the treatment of depression", Prozac made the cover of *Newsweek* in 1990 (Wong, Bymaster & Engleman, 1995). Ironically, it took six more years for the drug to pass German regulators for use there, one regulator noting "Considering the benefit and the risk, we think this preparation totally unsuitable for the treatment of depression."

[14] They likely were responding, at least in part, to the benzodiazepine (Healy, 2004, p 44).

[15] The US FDA requires lodgement of two trials demonstrating superiority to placebo; data from unsuccessful trials need not be lodged (Medawar, Hardon, & Herzheimer, 2004). Of Lilly's three submitted placebo-controlled trials for fluoxetine, one showed no effect, one showed a very small superiority over placebo but inferiority to the TCA imipramine, and the third showed efficacy but had only 11 completers of the 4-week trial (Healy, 2004, p. 35). Furthermore, Lilly trial subjects who experienced drug-induced agitation were co-prescribed benzodiazapines during the trials, although this was not reported in published results (Breggin, 2008, pp. 247-248).

(internal Eli Lilly communication reported in Healy, 2004, p. 39). Nevertheless, Prozac proved enormously popular, with sales for that one drug alone accounting for 30% of Eli Lilly's company profits (McLean, 2001). Although the patent for the drug expired in 2001, generic fluoxetine remains a popular antidepressant drug choice for many today.

Five other SSRIs have joined fluoxetine on the US market: fluvoxamine, citalopram, paroxetine, sertraline, and escitalopram oxalate (Table 1, p. 16). Touted as safer than the TCAs because of lower cardio-toxic reactions in overdose, and safer than the MAOIs with their liver toxicity and "cheese reaction", easy for general practitioners to prescribe, and applicable to an ever-growing list of applications, both on- and off-label, SSRIs have dominated the antidepressant market for two decades.

The TCAs, MAOIs, and SSRIs all work in different ways, but provide similar antidepressant actions (Leventhal & Antonuccio, 2009). Clearly, no one theory or chemical structure has proved fundamental for an understanding of how antidepressants work, although all of these products appear to cause an alteration of the neurotransmitter system to achieve effect. Several other drugs with slightly different mechanisms, known collectively as atypical antidepressants, are also currently prescribed.

Modern dual-action drugs that affect the reuptake of both serotonin and norepinephrine (SNRIs) include duloxetine, nefazodone, trazodone, venlafaxine and desvenlafaxine. SNRIs are thought to be effective because of serotonin's moderating effect on mood and norepinephrine's positive effect on drive and energy levels (Hindmarch, 2001). Eli Lilly brought duloxetine to the market under the brand name Cymbalta in 2004 after agreeing to FDA requirements to indicate

clearly on the label the drug's propensity for liver damage (Eisenberg, 2005). Liver damage is also an issue for nefazodone, first marketed by Bristol-Meyers Squibb in 1994 under the trade name Serzone; various generic versions are now available (Galson, 2004). Nefazodone inhibits reuptake of serotonin and norepinephrine and selectively blocks the 5-HT_{2A} receptor; it is considered particularly useful where insomnia is comorbid with depression (Julien, 2001, p 301; Papacostas & Fava, 2007;). Venlafaxine, introduced by Wyeth in 1993 under the trade names Efexor and Effexor, inhibits the reuptake of dopamine to some extent as well as serotonin and norepinephrine (Hindmarch, 2001; Julien, 2001, pp 294-295). Wyeth added desvenlafaxine, synthesized from the active metabolite in venlafaxine, to their product line in 2008 under the brand name Pristiq for treatment of major depressive disorder (MDD) and menopausal symptoms (Medinews.direct, 2008). Clomipramine, first developed by Giegy in the 1960s and marketed as Anafranil, is structurally a TCA, but functions as an SNRI; it is used primarily for treatment of obsessive compulsive disorder (OCD) but also depression and phobic disorders (Julien, 2001, p 294).

The tetracyclic mirtazapine was brought to the market in 1994 by Organon International under the trade name Remeron. Now out of patent, there are many generic version of the drug. It does not act as a reuptake inhibitor like the SSRIs or TCAs but instead works as an antagonist of norepinephrine and serotonin autoreceptors and blocker of histamine receptors (Julien, 2001, pp 301-302).

Trazodone (trade name Desyrel), also a tetracyclic, does not significantly block the reuptake of serotonin or norepinephrine, but appears to down-regulate some of the serotonin receptors (Julien, 2001, p. 293). It was approved for

treatment of depression by the FDA in 1981, and an extended-release formula was approved in 2010 (Waknine, 2010).

Bupropion, patented by GlaxoSmith Kline, was approved for use as an antidepressant by the FDA in 1985 under the trade name Wellbutrin, and as a tablet for smoking cessation and nicotine addition in 1997 under the brand name Zyban (FDA, 2009a). Now available in generic form, it selectively inhibits dopamine and norepinephrine reuptake and is a nicotinic antagonist, but does not appear to affect serotonin (Julien, 2001, pp 293-294; Slemmer, Martin, & Damaj, 2000).

Quetiapine (trade name Seroquel), is an antipsychotic primarily used for treatment of schizophrenia and bipolar disorder. It has recently been approved by the US FDA as an adjunctive medication for use with patients diagnosed with major depressive disorder who are already taking another antidepressant (AstraZenica, 2010). Lithium, a mood-stabilizer approved by the US FDA in 1970 for treatment of mania and bipolar disorders, is also sometimes co-prescribed with antidepressants for treatment-resistant patients (Bauer & Döpfmer, 1999).

Several other drugs have come and gone, overtaken by market conditions or safety concerns. What does seem clear is that although many antidepressants interact with the serotonin (or cholinergic) system, a point pharmaceutical companies often reiterate, there are no studies that show depression caused by any sort of deficiency or malfunction in those systems (Lacross & Leo, 2005). In spite of the inability to induce depression via serotonin depletion, or to alleviate depression through increased serotonin, the low-serotonin-causes-depression concept has become such an integral cornerstone of product marketing for modern

antidepressants (Lacrosse & Leo, 2005) that it seems almost sacrilegious to question it (Kresser, 2009).

Given that every drug and drug combination has the same, relatively small general effect as any other, with no stand-out performers (Leventhal & Antonuccio, 2009), Kirsch (2010a) hypothesized that any positive anti-depressive action perceived as a result of these various chemical agents is simply a product of their role as active placebos.

Chapter 3

Antidepressant Side Effects, Long-term Use, Off-label Use, Compliance, and Dependency

> *When you make a medicine, you are trying to disrupt the fundamental biological process. That's a pretty profound change. You can't do that without producing some unwanted effects.*
>
> Patrick Vallance, Head of Drug Discovery, GSK (2010)

If antidepressants were merely placebos with no negative effect, and if people found they worked to alleviate depression and anxiety, there would not be a problem with their use. Unfortunately, antidepressants often produce a range of unpleasant side effects and, for some users, the risk of drug dependency.

Side Effects

Up to 70% of patients discontinue their antidepressant before their prescribing physician believes they should, 28% within the first month. The most common reason given for premature discontinuation is bothersome side effects (Khawam, Laurencic, & Malone, 2006). In clinical trials, dropout rates varied between 7% and 44% for the TCAs, and 7% and 23% for the SSRIs (Khawam et al., 2006).

The TCAs were originally tested as neuroleptics, and share some of the same side effects due to suppression of the cholinergic system (Breggin, 1991). According to Breggin (1991) and Khawam et al. (2006), common side effects reported by patients prescribed TCAs include blurred vision, dry mouth, urinary retention, constipation, sleep disturbances, weight gain, lowered blood pressure,

impaired cardiac function and cardiac arrhythmias, sedation, lethargy, anxiety, sexual side effects and emotional blunting. Because of their cardiac effect, the TCAs are particularly dangerous when taken in overdose, or when combined with other drugs that suppress the central nervous system such as sleeping pills, tranquillizers, some analgesics, and alcohol (Breggin, 1991). It is this cardiac danger and somewhat greater side effect profile that have made the TCAs, which demonstrate otherwise similar levels of efficacy to the SSRIs (Anderson, 2000), less attractive prescribing options.

According to Khawam et al. (2006), the SSRIs selectively block serotonin reuptake, at least in theory, with citalopram and excitalopram demonstrating the most selective effect. Paroxetine, like the TCAs, is also anticholinergic, while fluoxetine and sertraline also inhibit norepinephrine reuptake, and sertraline weakly inhibits dopamine reuptake. All of the SSRIs are metabolized in the liver, where they inhibit the hepatic enzymes that break down other drugs, leading to a possibly toxic increase in a variety of co-prescribed drugs (Khawam et al., 2006). SSRIs should not be combined with other serotonin-enhancing drugs, including most other antidepressants, or blood thinners such as warfarin or aspirin (Khawam et al, 2006). Itemized drug reactions can be found on manufacturer-supplied patient leaflet sheets for specific drugs, most of which are available on the internet.

Eighty-six percent of SSRI patients reported at least one troublesome side effect in telephone interviews conducted 75-105 days after initiation of an SSRI prescription, a figure significantly underestimated by physicians surveyed (Hu et al, 2004). Zimmerman et al. (2010) found patients reported 20 times more side effects when responding to a checklist than what their dispensing psychiatrists had noted in their records. The most commonly reported side effect of the SSRIs is

sexual dysfunction, which presents as delayed ejaculation, anorgasmia, and decreased libido in as many as 60-73% of patients according to Khawam et al (2006) and Bahrick & Harris (2009). They report this can impact negatively on patient recovery and well-being by increasing anxiety and destabilizing intimate relationships, yet prescribers often neglect to discuss these issues with their patients. Furthermore, the sexual dysfunction often lingers long after treatment has ceased, a point extolled by the pharmaceutical industry who advocate [off-label] SSRI treatment for premature ejaculation as having "a lasting post-treatment effect" (Bahrick & Harris, 2009). Antonuccio (2008) raised a subsidiary issue regarding the prescribing of SSRIs and SNRIs to children and adolescents, voicing a concern that the drugs may alter pubertal development.

Nausea and diarrohea are also common side effects. The anorexia as a result of nausea and appetite suppression that can occur early in treatment lead early clinical trial evaluators to speculate on the value of SSRIs for weight loss; with time, however, weight gain becomes a common side effect of SSRI treatment, possibly due to desensitization of serotonin receptors responsible for appetite control (Khawam et al., 2006). Long-term use of antidepressants with subsequent weight gain is associated with an increased risk of diabetes (Andersohn, Schade, Suissa, & Garbe, 2009).

SSRIs also negatively impact the central nervous system, resulting in increased anxiety, insomnia, nightmares, and sedation for about 25% of users (Khawam et al., 2006), hence Eli Lilly's decision to co-prescribe Prozac with benzodiazapines in clinical trials. Akathisia, a sort of inner agitation that can range from uncomfortable to torturous, affects up to 25% of fluoxetine users, with lesser rates for the other SSRIs (Breggin,2003/2004) and can result in irritability,

violence and suicidality (Healy, Herxheimer & Menkes, 2006). SSRIs also inhibit blood platelet function which can cause prolonged bleeding and gastrointestinal bleeding (Khawam et al, 2006). Serotonin plays a significant role in lens transparency, and recent studies have linked SSRI use to the development of cataracts, with fluvoxamine, venlafaxine, and paroxetine demonstrating the highest risk (Etminan, Mikelberg, & Brophy, 2010). Although some research has suggested SSRIs might be useful for treating alcoholism (Swift, 1999), or the depression that is often concurrent with alcoholism (Pettinati, 2004), anecdotal reports from forum websites such as www.paxilprogress.org support Breggin's (2008, p. 112) claim that antidepressants can drive some people to increase their alcohol consumption as a method of calming drug-induced anxiety and over-stimulation.

Not all side effects are physical. In a qualitative study utilizing interviews and examination of internet postings, Price, Cole and Goodwin (2009) identified eight key emotional themes reported by SSRI users: 1) general reduction of emotional intensity; 2) reduced intensity and frequency of positive emotions; 3) reduced intensity of negative emotions; 4) emotional disconnection with people and events; 5) general feelings of indifference towards things and people that used to matter; 6) altered personality, which persisted even after medication was discontinued; 7) short-term positive but long-term negative impact on everyday life in terms of responsibilities, relationships, creativity, and decision-making; and 8) emotions affected by dose and adherence: a sense that who you are becomes controlled by a pill.

Regarding the atypical antidepressants Khawam et al. (2006) report the most common side effects for venlafaxine are nausea, dizziness, insomnia,

somnolence, dry mouth, sexual dysfunction, and hypertension. Mirtazapine causes sedation and weight gain, and may affect the liver. Dizziness, dry mouth, constipation, and disturbing dreams have also been reported. Bupropion can cause increased irritability and agitation as well as insomnia, headache, tremors, and nausea, and carries a small risk of seizure. It is not recommended for patients who are heavy users of alcohol, who have liver or kidney disease, or who have a history of seizures. Duloxetine is associated with nausea, dry mouth, constipation, fatigue, sweating, and increased blood pressure. Sexual dysfunction is less common with duloxetine than with the SSRIs.

Many countries have a body which records reports—usually from physicians—of adverse drug reactions. In the US, it is MedWatch, a branch of the FDA; in the UK it is the Medicines and Healthcare products Regulatory Agency (MHRA); in New Zealand, it is the Centre for Adverse Reactions Monitoring (CARM), a branch of MedSafe. In spite of having what the World Health Organization describes as "the highest number of [adverse reaction] reports submitted per capita" which are "of the highest quality", it is estimated that only 10% of adverse reactions are reported in New Zealand (MedSafe, 2009).

In 1999, Spigset analyzed the 1861 SSRI adverse reactions reported to the Swedish Adverse Reactions Advisory Committee. The most commonly reported adverse symptoms were neurological (22.4%), including paraesthesias (a burning or prickling skin sensation), headache, dizziness, tremor and seizures. There are only slightly more commonly reported than psychiatric symptoms (19.5%) which included anxiety, confusion, hallucinations, and disturbed sleep. Gastrointestinal symptoms accounted for 18% of reports, consisting primarily of nausea, vomiting and abdominal pain. Elevated liver enzyme levels were reported in 25 cases after

long-term use. Dermatological reactions such as rashes accounted for 11.4% of reports, most made within a few weeks of the beginning of treatment. Fatigue and weight gain were also commonly reported. Spigset observed that the majority of reported adverse reactions were in response to standard doses.

Off-label prescribing and contraindications

Antidepressants are sometimes prescribed "off label", meaning they are prescribed for indications for which they have not been approved or licensed, prescribed to patients who have not been approved to receive them, or prescribed at dosage levels beyond approved levels. According to Evans (2009), pharmaceutical companies actively promote off-label prescribing, although doing so is illegal, tossing off the court fines as part of the cost of doing business. Pfizer, for example, has paid US$2.75 billion in fines for off-label drug promoting since 2004, just over 1% of the company's revenue. Because of cross-over advertising, many doctors are unaware of which indications are tested and approved for a drug, and which are not (Evans, 2009). In the U.S., it is not illegal for a doctor to prescribe medication off-label, nor is it compulsory that the patient be informed that a prescribed drug is not approved for a particular use, but the issue creates ethical and liability conundrums (Wilkies & Johns, 2008). In New Zealand, the Medicines Act 1981 does require doctors to inform patients if a medicine is being prescribed for an unapproved use, and s/he is obligated to discuss the potential risks and benefits of the medication with the patient (MedSafe, 1998).

Examples of off-label prescribing of antidepressants for non-approved conditions are the tricyclic amitriptyline for pain relief or as a sleep aid (Mayhew, 2009), paroxetine and other SSRIs for premature ejaculation (Waldinger, 2007),

and a variety of antidepressants for anxiety, back pain, migraine headaches, bulimia, anorexia nervosa, fibromyalgia, irritable bowel syndrome, chronic fatigue and attention deficit disorder (ADD) (Pomerantz et al., 2004; Leydon & Raine, 2006). It is also common for dose increases to go beyond recommended guidelines in the case of treatment-resistant conditions, a strategy which may be helpful with TCAs[16] and venlafaxine (Adli, Baethge, Heinz, Langlitz, & Bauer, 2005) but which has proved ineffective and likely to cause significantly increased side effects with the SSRIs (Adli et al, 2005; Ruhé et al., 2006).

The most common type of off-label prescribing occurs with paediatric patients, elderly patients, pregnant patients, and patients with contraindicated disorders or medications. Although most clinical trials of antidepressants have been conducted with adults, these medications are often prescribed for children and adolescents who are experiencing depression, OCD and other disorders (Baldwin & Kosky, 2007). Twelve of the 15 SSRI paediatric trials submitted for FDA approval failed to adequate show efficacy (Whitaker, 2010, p. 230). Only Eli Lilly's results from two short-term paediatric trials on Prozac with participants aged over 8 years old demonstrated adequate efficacy over placebo to the FDA (Lilly, 2006), making fluoxetine the only antidepressant approved for paediatric treatment of depression and OCD in the US, although many critics suggest this is more a tribute to clinical trial manipulation than to a superior product[17]. No SSRI

[16] In contrast to Adli et al.'s findings, in a meta-analysis of 41 TCA trials that evaluated dose levels, Furukawa, McGuire, and Barbui (2002), found TCAs in general more effective at treating depression and less likely to cause significant side effects when prescribed at levels below recommended doses.

[17] Earlier fluoxetine trials failed to show efficacy in paediatric groups. The two "successful" studies involved extensive screening of participants prior to the trial for placebo response, and exclusion of data from those who responded adversely during the trial from the final reported results (Healy, 2006).

antidepressants are approved for use with children or adolescents in New Zealand (Jessamine, 2008).

Although antidepressants are prescribed to children as young as one year old (Leslie, Newman, Chesney & Perrin, 2005), almost nothing is known about the long-term impact of antidepressant use on children's motor, cognitive, emotional, social, or sexual development (Wohlfarth et al., 2009). Children and adolescents are involuntary patients dependant upon wise decision-making from their parents and medical practitioners who must weigh up the values of short term efficacy with potential side effects and safety issues when prescribing antidepressants. In the TADS study of 439 depressed adolescents, March et al., (2004) compared placebo with fluoxetine alone, cognitive behavioral therapy (CBT) alone, and fluoxetine plus CBT. At 12 weeks, the combination treatment was found most effective for depression; however by 36 weeks, all three treatments (excluding placebo) showed similar results (Kennard et al., 2009). The authors acknowledged the study "was designed to minimize the placebo response," and data on the placebo group was not taken after 12 weeks. Twenty-four (5%) of the participants experienced a "suicide-related adverse event" in the first 12 weeks, although participants had been pre-screened for suicidality. When considering the safety of the four treatment conditions, Antonuccio (2008) concluded CBT the best treatment choice, followed by placebo.

Fluoxetine is the only antidepressant drug approved for use with patients over 65 years of age (Ables & Baughman, 2003). The elderly may be as vulnerable as the pediatric population to antidepressant side effects, given their decreased blood-brain barrier protection, lower metabolism, and decreased renal clearance of chemical agents (Crumpacker, 2008). Nevertheless, many patients

over 65 take antidepressants. The daily use of SSRIs within the elderly population is correlated with lower bone mineral density and a 2-fold increased incidence of falls resulting in fractures over non-SSRI users (Richards et al., 2007), while TCAs can aggravate glaucoma, prostatic hyperplasia, and coronary diseases (McLeod, Ruang, Tamblyn & Gayton, 1997; Zellwegar et al., 2004). Because the elderly are more likely to have concurrent health issues, co-prescription of drugs which are contraindicated by antidepressants is also a risk.

Although no antidepressants are approved for use during pregnancy or for breast-feeding mothers, it is not uncommon for women who are taking antidepressants to become pregnant. A 20% increased risk of pre-term births and subsequent low birth weight is associated with both depression and maternal antidepressant use (Wisner et al., 2009), and Einarson, Choi, Einerson, and Koren (2009) found a 3-fold increased risk of miscarriage (spontaneous abortion) among antidepressant-using mothers, yet the risk of increased or returning depressive symptoms with drug discontinuation during pregnancy is also significant (Cohen et al. 2006). Transfer of SSRIs and SNRIs across the placenta is “substantial” (Rampono et al, 2009) and a neonatal withdrawal syndrome has been associated with maternal SSRI use, especially of paroxetine (Sanz, De-las-Cuevas, Kiuru, Bate, & Edwards, 2005).

Long-term use

There is some controversy regarding the value of long-term maintenance on antidepressants. Psychiatric practice guidelines recommend long-term maintenance for patients with recurrent depressive disorder (Holma, Holma, Melartin & Isometsä, 2008) but primary physician guidelines for antidepressants,

as reported in Petty et al. (2006), recommend withdrawal of antidepressant treatment following six months of remission. In practice, many patients remain on antidepressant treatment for much longer, an average of 5.7 years (Petty et al., 2006). Although intractable long-term distress may demand long-term treatment, Petty et al. found patient use of antidepressants poorly monitored by many health practitioners, with patients without regular documented reviews of their medication use tending to have the longest treatment times. In a literature review, Fava and Offidani (2010) identified numerous studies linking long-term use of antidepressants with increased drug tolerance, more frequent depressive episodes, worsened long-term outcomes and exacerbated manic symptoms in bipolar patients. Petty et al. (2006) and Fava and Offidani (2010) found long-term antidepressant use as maintenance therapy both ineffective and inappropriate.

Antidepressants, suicide, and violence

> *Suicidal ideation is not an adverse effect.*
>
> (Heiligenstein, a Lilly psychiatrist, as quoted in Healy, 2004, p. 151, from the Wesbecker deposition)

The use of antidepressants has been linked with incidences of suicide and violence. According to Khawam et al. (2006) and Stone et al. (2009), following the 2004 analysis of all FDA lodged short-term placebo-controlled antidepressant trials which revealed a two-fold increase in reported suicidal thoughts and behaviors in treatment groups over placebo in trial participants under 25, no significant difference in patients aged 26-65, and a minor decrease in suicidal

behaviors in those over 65,[18] the FDA mandated a black box warning on all antidepressants sold in the US advising patients and doctors of the increased risk of suicidal thoughts and behaviors, especially when starting or stopping treatment or changing dose levels. Although children and adolescents were specifically mentioned in the 2004 warning, and young adults under 26 were added to the warning in 2006, the black box currently states

> *"Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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." (*FDA, 2009b).

Since 1990, numerous case reports of patients developing "intense suicidal preoccupation" and violent fantasies following administration of antidepressants, especially SSRIs, have been recorded in the literature (Breggin, 2003/2004; Breggin, 2008; Healy & Whitaker, 2003; Liebert & Gavey, 2008). Over 3,500 cases of suicide and/or violence involving SSRIs are documented online at www.ssristories.com with links to relevant media reports. In court testimony, Glenmullen (2007) accused pharmaceutical manufacturer GlaxoSmithKline of deliberately concealing the 8-fold increase in suicidal acts that occurred with paroxetine over placebo revealed in clinical trials[19], and confidential Eli Lilly files

[18] Clinical trials were testing drugs primarily for efficacy, and none were designed to test for suicidality. Potentially suicidal participants were screened out. Nevertheless, suicidality rates of 4% on treatment versus 2% on placebo were evident from trials (Khawam et al., 2006). This high placebo rate is due, at least in part, to trial patients "on placebo" actually being in a "washout" phase after drug use (Healy, 2004, pp. 238-241). Even higher suicidality rates were "hidden" by researchers who recoded "suicidal ideation" as "depression" or "no response" or who removed the suicidal participant from the study, a fact revealed in pharmaceutical litigation (Breggin, 2004; Whitaker, 2010, p. 286).

[19] In an examination of 1989 clinical trial data for paroxetine obtained from GlaxoSmithKline under subpoena in 2007, Glenmullen found 7 completed suicides, 5 of which occurred during drug treatment or washout (withdrawal), and 40 attempted suicides among treatment groups. He accused GSK of hiding the suicide risk by allocating suicides and attempted suicides that occurred during drug washout periods (withdrawal) to "placebo" in the trial results supplied to the US FDA. Glenmullen's report was made publicly available in January 2008. GSK has paid out an average $2

revealed a 1.6% incidence of hostility and 0.8% incidence of self-injury in fluoxetine clinical trials, figures first exposed during the much touted Joseph Wesbecker murder/suicide trial[20] (Watkins, 2005). Although numerous analyses of larger data groups (post-clinical trials) have failed to definitively establish antidepressant causation, given the inherent risk of suicidality in untreated depression[21] (Gunnell, Saperia, & Ashby, 2005), Healy and Whitaker (2003) regard it impossible to sustain a null hypothesis given the data.

Jick, Kaye and Jick (2004) examined medical records of 159,810 antidepressant users prescribed variously amitriptyline (TCA), fluoxetine (SSRI), paroxetine (SSRI) and dothiepin (TCA) and found no significant difference in risk of suicidal behaviors between the four drugs, although there was a non-significant higher rate for paroxetine; their study did not incorporate a comparative placebo group. They identified non-fatal suicidal behavior as 4 times more likely in the first 9 days after the initial prescription, and 3 times more likely in the first month than it was 90 days after the initiation of treatment. They also reported a higher risk for patients who had previously demonstrated suicidal behavior and those who had been prescribed one or more antidepressants at a previous time, an observation that was echoed by Tiihonen et al. (2006).

Tiihonen et al.'s Finnish study of death records and hospital registers examined data from 15,390 patients admitted to hospital following suicide

---

million per settlement in around 150 suicide cases, and $300,000 per settlement in around 300 attempted suicide cases (Feeley & Kelley, 2010).

[20] Wesbecker killed eight people and then himself following a brief course of Prozac; in the civil suit brought against Eli Lilly, the prosecution claimed that the drug company was negligent in not warning doctors and patients of the drug's propensity to induce violent and suicidal acts. The drug company settled just prior to the jury verdict for "an astonishing sum of money". (Healy, 2004).

[21] The risk of suicide with depression is often quoted as a lifetime risk of 15%, a potentially misleading figure based on data from hospitalized patients diagnosed with melancholic depression in the 1970s, not those being treated as outpatients by primary care physicians as are most users of modern antidepressants (Healy & Whitaker, 2003; Simon et al., 2006; Healy, 2004, p. 98).

attempts and found a significantly increased risk of a severe suicide attempt among antidepressant users compared to non-users, but a lower overall completed suicide rate. A lower overall mortality rate for SSRI users was attributed primarily to a decrease in cardiovascular-related deaths in that group. In their study, no significant difference in suicide risk was observed between drug classes (e.g, TCAs, SSRIs, atypicals), but the specific drugs venlafaxine and paroxetine were associated with the highest mortality rates and unusual levels of violence.

In a similar study, Simon, Savarino, Operskalski, & Wang (2006) examined computerized medical records of 65,103 patients treated with antidepressants and found 31 completed suicides and 76 serious suicide attempts during the first six months of treatment within that patient group, yielding an overall risk rate of roughly one in 3000 for completed suicide and one in 1000 for serious attempt. The group at highest risk of suicide and suicide attempt was less than 18 years of age, showing a risk level four times as high as that seen in adults in the sample. The highest risk period for suicide in the group, however, was during the month preceding initiation of treatment, probably because a serious suicide attempt is likely to prompt drug treatment. They did not find any difference in suicide risk between prescribed drugs.

Studies examining general population suicide statistics with population antidepressant use often find that as antidepressant use goes up, overall suicide rates go down. In a summary of international suicide rates and antidepressant use, Gibbons, Hur, Bhaumik, and Mann (2005) reported a decrease in suicide rates with increased antidepressant use in the U.S., most of Europe, Australia, and Scandinavia, but the opposite effect in Japan and Iceland. Their analysis of US health statistics revealed a decrease in completed suicides with SSRI and atypical

prescriptions, but TCAs were associated with an increased suicide rate. In a later study, Gibbons et al. (2007) analyzed data from 226,866 veterans diagnosed with depression and compared suicide attempt rates between those treated with SSRIs, TCAs, atypicals and those who received no treatment at all and found lower suicide attempt rates among veterans treated with antidepressants in general, and a significant protective factor with SSRI use in all adult age groups with 346 suicide attempts per 100,000 with SSRIs compared to 1057 per 100,000 for those not treated with SSRIs.

In contrast, in a sample of 57,361 New Zealand patients who received prescriptions for antidepressants, Didham, McConnell, Blair and Reith (2005) found "significantly increased incidence rates for self harm with SSRIs as a group compared with TCAs", and little difference between the SSRIs, but oddly concluded that self-harm and suicidal ideation were greater risk factors for suicide than antidepressant use.

In summary, it appears that SSRI use seems to lower the risk of completed suicide in large sample populations, but during the first few weeks or months of a new SSRI prescription, the risk of suicidal ideation, self harm, and serious suicide attempts is significant (Hall & Lucke, 2006). TCAs may or may not increase suicide risk, but do not seem to lessen it.

Compliance

In spite of this cornucopia of drug-induced side effects and complications, concerns about compliance are pervasive among prescribers (e.g., Aikens, Nease, & Klinkman, 2008; Akerblad, Bengtsson, Holgersson, Knorring, & Ekselius, 2008; Malpass et al., 2009). Liebert (2006, pp 61-68) interviewed several health

professionals in New Zealand who expressed concerns about antidepressant compliance. They explained how they modified their language and delivery of information to patients to deliberately play down antidepressant side effects and risks and enhance possible benefits, stating that patient awareness of risks created a barrier to treatment. Many highlighted the risks of *not* taking antidepressant medication: “Look, depression’s a terminal illness”. In her analysis, she found some who utilized their position of trusted authority to induce compliance while others saw compliance as a control issue. While iterating the importance of compliance, Malpass et al. (2009) acknowledge that “compliance with medication is not a meaningful concept from the patient’s perspective.” Although analysis of American healthcare insurance claims showed a significant correlation between antidepressant compliance and higher medication costs, no significant difference on other healthcare costs between compliant and non-compliant depressed patients was shown (Birnbaum et al., 2009), suggesting that antidepressant-compliant patients are not significantly healthier (or sicker) than non-compliant patients, but they—or their insurance companies—may be more out of pocket.

Antidepressant withdrawal and drug dependency

Antidepressant withdrawal symptoms were first reported with the TCA imapramine more than fifty years ago, and are common with all antidepressants (Haddad, 2005). Up to 80% of patients taking amitriptyline (TCA) report withdrawal symptoms, and 100% report withdrawal symptoms with imapramine (TCA) (Haddad, 2005; Haddad & Anderson, 2007). The SSRIs are somewhat less likely to generate withdrawal symptoms upon discontinuation (Haddad, 2005).

A gradual reduction in antidepressant dose is recommended to reduce symptom severity (Glenmullen, 2005; Shatzberg et al., 2006). In most cases, withdrawal symptoms are mild and self-resolving, peaking 7-10 days after a dose drop and disappearing within 2-3 weeks (Glenmullen, 2005, p. 41; Haddad & Anderson, 2007; Fava & Offidani, 2010). If a severe reaction occurs, experts advise the previous dose be resumed, which quickly mitigates symptoms, and a more gradual taper be undertaken (Schatzberg et al., 2006). Some doctors switch patients from short plasma-life agents to long-life fluoxetine to create a more gradual withdrawal experience, although success rates utilizing this technique are unknown (Haddad & Anderson, 2007).

Common TCA withdrawal symptoms include abdominal pain, diarrhoea, nausea, vomiting, headache, fatigue, weakness, and a general sense of malaise (Rosenbaum, Fava, Hoog, Ascroft, & Krebs, 1998). In a randomized clinical trial sponsored by Eli Lilly which employed a 5-8 day double blind placebo substitution in patients' maintenance SSRI therapy, Rosenbaum et al. (1998) found 60% of sertraline patients (n=63) reported withdrawal symptoms on a Discontinuation Emergent Signs and Symptoms (DESS) checklist, as did 66% of paroxetine patients (n =59). In contrast, only 14% of patients on fluoxetine[22] (n = 63) reported symptoms, a result which the authors suggest may reflect fluoxetine's long plasma half life of up to 6 days, as compared to sertraline (26 hours) and paroxetine (10-21 hours) (Rosenbaum et al., 1998). Fava, Mulroy, Alpert, Nierenberg and Rosenbaum (1997) reported a 78% incidence of reported withdrawal symptoms three days following the discontinuation of the SNRI

[22] This was a positive marketing result for Eli Lilly, who could use the trial as promotional evidence of Prozac's unusually low withdrawal effects profile.

venlafaxine, which has an even shorter half-life (5-7 hours). (See Table 1, p. 16, for a list of drug plasma half lives).

Withdrawal symptoms reported in Rosenbaum's SSRI study, in order of report frequency, were worsened mood, irritability, agitation, dizziness, confusion, headache, nervousness, crying, fatigue, emotional lability[23], trouble sleeping, abnormal dreams, anger, nausea, amnesia, sweating, depersonalization, muscle aches, unsteady gait, panic attacks, sore eyes, diarrhoea, shaking, muscle tension, and chills. A third of paroxetine and sertraline patients experienced depressive symptoms at a level of a major depressive episode during the placebo period. Three of the paroxetine patients pulled out of the study during the placebo period due to severity of withdrawal effects.

In a similar study (double blind placebo interruption of SSRI maintenance therapy), Michelson et al. (2000) revealed the most commonly reported withdrawal symptom across all drug agents was dizziness or vertigo, and the most severe withdrawal symptom response was associated with paroxetine: paroxetine patients experiencing statistically significant worsened severity of nausea, disturbing dreams, fatigue, irritability, unstable moods, difficulty concentrating, muscle aches, sleep disorders, agitation, and diarrhoea; they also experienced a statistically significant increase in standing heart rate during the placebo period. In addition, paroxetine patients reported significant deterioration in social and workplace interactions, while some sertraline patients reported minor deterioration in social function, and fluoxetine patients reported no change in social function during the placebo portion of the trial. Supporting Rosenbaum et al. (1998), the authors found a statistically significant correlation between plasma half of the

[23] Emotional lability refers to extreme and often unmanageable emotions or dramatic swings of emotion. In some clinical trials, suicidality was coded as emotional lability (Healy, 2006).

drug agent and severity of withdrawal response, but observed that plasma half life did not correlate with any particular symptoms, and further observed that plasma concentration of the drug may not accurately reflect brain exposure, a reminder that psychotropic drugs affect the whole organism.

Glenmullen (2005, p. 205) created a withdrawal symptom checklist for patients which included several items not assessed with the DESS such as hallucinations, self-harm, suicidal thoughts, suicide attempts, homicidal urges, tinnitus, electric "zap" like brain sensations, changes in appetite, abnormal sense of taste or smell, vomiting, stomach bloating, chest pain, tremor, restless legs, elevated mood (feeling high), and manic behaviours. Many of these symptoms are also noted by Haddad and Anderson (2007) who add to the list rare reports of mania, Parkinsonian symptoms, dystonia (involuntary repetitive movements) and akathisia. Sexual dysfunction, including anorgasmia, erectile dysfunction, and diminished libido are common during antidepressant use and sometimes linger long after discontinuation (Csoka & Shipko, 2006).

Although it is not clear why antidepressant withdrawal symptoms occur, studies suggest that sustained blockade of receptors may result in receptor desensitization, which in the event of withdrawal could lead to an acute hyposerotonergic (or other receptor) state which may also affect the norepinephrine and dopamine systems (Schatzberg et al., 2006). The severity of the paroxetine withdrawal experience is often attributed to cholinergic and well as serotonergic rebound (Rosenbaum et al., 1998).

There are numerous case reports of antidepressant withdrawal syndrome sometimes severe enough to discourage or prevent discontinuation of the drug. Fava, Bernardi, Tomba and Rafanelli (2007) reported three out of twenty

outpatients who discontinued their antidepressant and were still experiencing worsened mood, fatigue, emotional lability and sleep problems more than a month after discontinuation of paroxetine; one resumed the drug within a year, resolving symptoms. Tonks (2002) noted GlaxoSmith Kline's acknowledgement that paroxetine "can cause intolerable withdrawal symptoms" and quoted Haddad regarding a minority of patients experiencing severe withdrawal symptoms "treatable only by restarting the drug."

An analysis of calls to a national (UK) medication helpline between 1997 and 2005 revealed 7.8% of all calls were regarding antidepressant withdrawal, of which 40% were in reference to paroxetine, and 14% were in reference to venlafaxine (SNRI) (Taylor, Stewart, & Connolly, 2005). Websites like www.paxilprogress.com, a forum site for individuals withdrawing from paroxetine and other antidepressants, offer numerous first-hand accounts of severe and prolonged withdrawal experiences.

In semi-structured interviews with 17 patients regarding antidepressant withdrawal, Leydon, Rodgers, and Kendrick (2007) identified three key themes: concern about the benefit of continuation, fear of withdrawal symptoms and relapse, and the importance of the GPs role in cessation of medication. For some, the risks of discontinuation were identified as greater than the unknown risks of long-term use.

The current Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA, 2000) identifies 11 classes of substances that cause dependence: alcohol, amphetamines, sedatives and anxiolytics, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, and phencyclidine, but not

antidepressants. To qualify as a dependency-causing substance, according to the DSM-IV-TR, the substance must elicit three or more of the following symptoms:

- tolerance, defined as a need for increased amounts of the substance to achieve the desired effect;
- withdrawal symptoms which cause psychological or physical changes that remits when the drug is reinstated;
- the substance is taken for longer than was intended;
- there is a desire to reduce or quit taking the drug but efforts to do so are unsuccessful;
- time is spent obtaining the drug or recovering from its effects;
- use of the drug affects social, occupational and/or recreational activities;
- use of the substance is continued in spite of precipitating physical or psychological problems.

Glenmullen (2005, pp 17-27) observed that antidepressant users may encounter any or all of these symptoms when they attempt to withdraw from the drug, and he observes that antidepressants clearly cause dependence in some patients. He believes the terms “dependence” and “addiction” in this context be used interchangeably.

The concept that prescribed drugs can cause dependence at therapeutic doses has been controversial. The benzodiazepines demonstrated signs of tolerance and physical dependency upon withdrawal from high doses in numerous studies and case reports in the 1960s and early 1970s but the general belief among physicians was that patients on lower doses could continue to take the drugs safely and indefinitely (Lader, 1991). However, several seminal studies in the mid 1970s demonstrated up to 25% of long-term users of benzodiazepines showed signs of

physical dependency, and that withdrawal symptoms were identical regardless of dose size; furthermore, studies suggested withdrawal could be prolonged or associated with major depressive disorder (Lader, 1991). As a consequence, both doctors and patients became more wary of benzodiazapines. UK guidelines now recommend the prescribing of benzodiazepines for short-term use only (Lader, 1991).

The situation with antidepressants remains more controversial. Most pharmaceutical companies have chosen to market antidepressants as non-addictive, pointing out that antidepressants do not cause drug cravings in the same way that alcohol, nicotine, or opioids do. Haddad & Anderson (2007), both consultants for pharmaceutical companies, defended the corporate claim, arguing that the existence of a withdrawal syndrome is not indicative of drug dependence. However, in response to a huge public outcry following two BBC documentaries on GlaxoSmithKline's SSRI Seroxat (paroxetine) in the UK in 2002 and 2003, the company agreed to remove all references to non-addictiveness of the drug in their advertising and literature, acknowledging the claim "causes confusion" (Glenmullen, 2005, pp 23-27). Other pharmaceutical companies continue to hedge the issue.

It seems likely that the new DSM-V, due out in 2013, will address the antidepressant dependency issue in some way. In a private correspondence, Charles O'Brian, a member of the DSM-V task force, wrote, "For DSM-V, we are discussing a section on neuroadaptation and discontinuation syndromes from prescribed medication such as opioid analgesics, SSRIs, tricyclics, benzodiazepines and beta blockers," (O'Brian, 2009).

Chapter 4

The Power of the Internet

The internet has been more than a bit-player in the development of the antidepressant story. By the late 1990s, the internet had become a forum and opportunity for antidepressant users to begin to compare notes, share experiences, support one another, and exchange information about the mental conditions and drugs that had come to impact upon their lives (Cohen, 2008; Houston, Cooper & Ford, 2002; Medawar & Hardon, 2004). A patient-empowering tool, the internet also provided opportunities for patients to do their own research about conditions and the drugs used to treat those conditions.

For pharmaceutical companies, mental health providers and other related industries and government bodies, the internet provides opportunities for access to potential patients, clients and customers in a way that appears direct and personal, but which can be handled as a mass-market, low-cost, easily-managed promotion. When Graber and Wedkmann (2002) examined website information given by nine pharmaceutical companies, they found most of the companies came up on the first page (first ten links) of internet searches and all company websites contained information that was advertorial and emotive. None of the company websites mentioned drug costs, only one offered efficacy statistics, adverse effects were minimized, and other drugs or types of therapy received minimal mention, making it difficult for consumers or doctors to compare drugs or make educated treatment choices based on company website information. Many modern drug companies

now include web links to government-body-authorized data sheets about the drugs they market.

Not all advertorial material appears on obvious company websites, however. In an analysis of 50 depression websites, Wattignar and Read (2009) found those backed by pharmaceutical company funding—22 of the 50 examined—were more likely to covertly espouse biomedical causes and treatments for depression while minimizing the possibility of psycho-social causes, even if specific products were not promoted; similar results were obtained in an analysis of PTSD sites (Mansell & Read, 2010). Examples of innocuous-sounding sites financially backed by drug companies include depression.com, mentalhelp.net, psychcentral.com, webmd.com, healthcentral.com, depression.com.au, and everybody.co.nz (Wattignar & Read, 2009).

The internet also provides access to patient groups and information for researchers on a variety of medical and social topics. In a one-year cohort study of internet depression support group use by depressed patients, Houston, Cooper and Ford (2002) found the median age of participants was 40 years, 42% were unemployed, 79% were female, 73% had at least some tertiary education, 86% had been treated with counselling, 96% had been treated with antidepressants, and 23% were dissatisfied with their depression care. Sixty-two percent of participants had been influenced enough by their internet forum participation to query their doctor about their care and medication, resulting in a medication change for 26% of patients—proof of the power of internet group participation to influence medical and prescribing decisions. Although a causal relationship could not be drawn from their data, individuals who had more frequent contact with an internet

depression support group were more likely to resolve their depression symptoms over the year than those who had lesser contact.

In a qualitative analysis of postings on internet message boards, Pestello and Davis-Berman (2008) found an interesting paradox: although prescription of an antidepressant implied a mental illness which led posters to refer to themselves as unhealthy, defective, or damaged, it also empowered posters to share their experiences and offer first-hand advice to others, demonstrating a good deal of experiential knowledge. Many posters challenged diagnoses and treatments, not only their own but those of other posters, and many expressed criticism of their physicians, claiming that their doctors often behaved with profession arrogance, dismissing patient concerns, experiences, and opinions. Many posters reported years of struggle with antidepressant medications and their symptoms, belying the PhRMA tenant that psychiatric medication is a reliable solution to alleviate mental anguish.

Although their study focussed on antipsychotics rather than antidepressants, Moncrieff, Cohen and Mason (2009) utilized subjective, self-reported comments from 439 users posted at www.askapatient.com regarding older antipsychotics, risperidone, and olanzapine. Quantitative and qualitative analyses of symptoms and comments posted on the site indicated considerable concern regarding sedative effects, impaired cognition, emotional flattening, increased anxiety and depression, akathisia and resultant suicidality, sexual impairment, and weight gain with all of these drugs, side effects that are likewise reported by some antidepressant users during treatment or during a withdrawal period. The authors addressed the issue of skewed results that could occur given self-selected reporting and possible motivation due to unusually negative

experiences by comparing their results to those obtained in studies based on questionnaire responses. They found only slightly higher rates of subjective adverse reporting in conventional prevalence studies than in the spontaneous internet reports and concluded any difference to be negligible.

In 2008, I undertook an analysis of postings from www.paxilprogress.org of 24 individuals who had been off SSRI antidepressants for over six months and were still reporting (spontaneously on this internet forum) significant after-effects that they attributed to withdrawal from their antidepressant (Thrasher, 2008). Four of the posters had been on an antidepressant for six weeks or less; nine had taken antidepressants for more than nine years. Most participants had been on low or average doses and none had been on unusually high doses, although several had taken more than one psychoactive medication. Seven of the participants had been drug-free for more than two years. The majority had been taking paroxetine, but given the website name paxilprogress--Paxil is the trade name for paroxetine in the US--that may reflect a site bias, although paroxetine is generally considered the most notorious SSRI for withdrawal difficulties (Haddad, 2005). More than half of these posters reported increased anxiety, worsened mood or depression, mood swings (emotional lability), disturbing thoughts, poor stress tolerance, fatigue, impaired ability to concentrate and memory lapses. Fewer than 50%, but more than 17% reported tremor or twitching, headaches or head pain, obsessive thoughts, suicidal thoughts, low energy, appetite changes, panic attacks, agoraphobia, and impaired sexual function. None of these posters attributed symptoms to a return of pre-medication conditions, and most stated that symptoms first occurred during drug administration or upon cessation of medication. All

expressed surprise and concern that their symptoms of withdrawal continued to linger for months or years.

The internet also provides researchers a platform for data collection, as is done in this study, by way of an on-line survey.

Chapter 5

The Research Questions

> *More research needs to be done which looks at the patient's experience of taking psychiatric medication to further examine side effects and the impact of these drugs on the sense of self. Although this work is beginning, the complexity of taking psychiatric medications needs more exploration...*
>
> (Pestello & Davis-Berman, 2008)

The aim of this study is to understand the patient's subjective experience of antidepressant drug-taking and withdrawal and the role of antidepressants in general patient perception of health and well-being. Several recent meta-analyses compared results from the many clinical trials on antidepressants (Kirsch et al, 2008; Stone et al, 2009; Fourier et al., 2010), challenging the validity of positive trial result perceptions and raising significant questions regarding the efficacy and safety of modern antidepressants. Anecdotal reports from antidepressant users on web forums (e.g., www.paxilprogress.org, www.drugs-forum.com, and www.depressionforums.org) suggest that our understanding and appreciation of drug side effects and withdrawal issues based on trial studies and physician-provided adverse reaction reports may not accurately reflect what happens in "real life" where patients are not regularly monitored and other factors such as life stressors, diet, and concurrent drug intake—all part of normal living—are prevalent. It is likely that minor annoyances caused by the drugs routinely go unreported to adverse reaction bodies, and that some relatively major side effects, even if reported—and keeping in mind that at least 90% go unreported (MedSafe, 2009)--may not be recognized as attributable to an antidepressant drug reaction.

Life, after all, is complicated. Although it is commonly assumed that antidepressants enhance the lives of those individuals who take them, and that a potential antidepressant withdrawal syndrome at some point in the future should not be regarded as a detrimental factor when assessing the appropriateness of a prescription (Leder, 2007), these assumptions have yet to be adequately proved. Indeed, in discussions and interviews with 49 GPs and 15 mental health practitioners, Leydon and Raine (2006) found prescribers cited the implied need to do something that would be perceived as helpful, the limited availability of other treatments, and the ability to take action within the constraints of a brief consultation period as the primary motivations for antidepressant prescription, rather than any perceived belief in the effectiveness or safety of the medication. Many had not considered any potential harm that could be caused: "I hadn't actually thought…about the side effects," reported one mental health worker, and a GP commented, "I deal them out like Smarties" (Leydon & Raine, 2006).

There have been a few studies where antidepressant users were asked directly about their experience with the medication. Bogner, Cahill, Frauenhoffer, and Barg (2009) performed a thematic study on interviews with adults over 65 regarding their antidepressant medication and identified six major themes: 1) the importance of adherence to the prescription; 2) antidepressants are beneficial, but 3) medication is just a partial fix; 4) finding the right medication is a trial-and-error process rather than an exact science; 5) elderly patients are more vulnerable than younger adults; and 6) concern over the addictive nature of antidepressants. In another study utilising interviews, Grime and Pollock (2004) found most patients using antidepressants reported frustration with side effects, disconcertion

over the appearance of a “new self” as opposed to the “normal self” that existed before using antidepressants, and anxiety about difficulties in stopping the drug.

In 2002, Vanderkooy, Kennedy and Bagby developed the Toronto Side Effect Scale (TSES), a frequency and severity scale of 32 symptoms associated with antidepressant use, and trialled it on 193 depressed patients receiving antidepressant treatment. Although they found individual side effect differences between various antidepressants (e.g., sertraline produced the most tremor and sweating, bupropion caused the most nervousness, paroxetine caused delayed ejaculation) there was no significant difference found between types of antidepressants regarding the total burden of side effects. Lack of a placebo group in their study limited any conclusion about prevalence of these side effects as a result of antidepressant use, but the authors advised using the TSES to increase antidepressant side-effect evaluation and reporting.

Medication side effects provide the most commonly reported reason for antidepressant discontinuation (Zimmerman et al., 2010), a point of frustration for many physicians who, seeking treatment compliance (Aikens et al., 2008; Akerblad et al., 2008), significantly underestimate the frequency and bothersome nature of these side effects (Hu et al., 2004). When Zimmerman et al. (2010) compared the TSES results from 300 depressed psychiatric patients being treated with antidepressants with their medical records, they found patient reports of side effects on the TSES to be 20 times higher than the number of side effects noted by the treating psychiatrists in their records. Each of the 31 items on the TSES were reported by more than 10% of patients in the study, with number of symptoms reported $M = 7.7$, $SD = 6.1$. A quarter of those side effects were reported by patients as occurring often or daily. The psychiatrists in the study all reported

using an open-ended general question when asking patients about side effects. The authors suggested that use of a checklist heightens patient awareness and concerns about their antidepressant use and could lead to greater levels of discontinuation, but use of such a checklist also allows doctors to treat patients more effectively because they are more cognisant of problems.

Some patients have chosen to quit taking their antidepressant medication, perhaps because they are feeling better, because their circumstances have changed, or because the side effects are too onerous—there are a variety of reasons. While some patients have not found that difficult, most have found quitting their antidepressant a short-term minor challenge, and some have found it very difficult indeed (Glenmullen, 2005). For a few, getting off the drugs has become a handicap and goal that can dominate lives and families for many months, and sometimes years.[24] A better understanding and appreciation of the challenges faced by patients unable to easily quit taking a drug, and the impact that this can have on families and associates, might make it easier to help those who choose to go through the withdrawal process in the future.

In spite of these issues and concerns, studies assessing the role of these drugs and how they affect the ordinary lives of outpatient individuals who are the majority of antidepressant-users, are rare. In a previous unpublished study (Thrasher, 2008), I examined the internet postings of 24 adults who were experiencing prolonged withdrawal symptoms following an SSRI discontinuation (more than six months post-drug), but this is not a representative group of antidepressant users (or ex-users in this case) either.

[24] See www.paxilprogress.org for a sample of forum postings by just such a group.

The purpose of this study was to learn more about the antidepressant experience by soliciting subjective responses from ordinary users, addressing a number of key questions: Do antidepressant users find the drugs helpful? Are side effects a problem? Does use of the drugs enhance or undermine quality of life for users? Is iatrogenic suicidality an issue? Is withdrawal a significant issue for users? What is the likely occurrence of severe or prolonged withdrawal symptoms? Do ex-users experience a long-term post-withdrawal impact? Does use of antidepressants alter the perception of value and effectiveness of the drugs? Given an opportunity to comment on their antidepressant use experience, what issues and themes are raised by users and ex-users?

On one hand, this study was exploratory, and in that sense qualitative and bottom-up. Never-the-less, the survey itself was designed to address several hypotheses: 1) There is a difference in mood, symptoms, behaviours, and attitudes reported between groups of antidepressant users, non-users, ex-users, and those currently withdrawing from an antidepressant. It is anticipated that those actively withdrawing from a drug will experience the most—and most extreme—alterations from health and normality, and that those who have never taken an antidepressant will experience the least. 2) Current antidepressant users are not likely to report a significant reduction in anxiety, stress, or depression, and will report some side effects. Nevertheless, current users may feel the drugs are helpful. (If they didn't, one surmises, they wouldn't still be taking them.) 3) Some of the participants who used antidepressants in the past will report experiencing long-term negative effects from their drug use. 4) Responses to some individual items will be of particular note such as feeling suicidal, weight changes, and emotional flattening.

Chapter 6

Method

Study Design

According to Johnson and Onwuegbuzie (2004), quantitative research is based on deduction, hypothesis testing, prediction, data collection, and statistical analysis—the epitome of the scientific paradigm—to reach a numbers-based conclusion that can be generalized to the wider case. Qualitative research, on the other hand, utilises induction, discovery, hypothesis generation, and qualitative analysis for a more open and in-depth study of a complex phenomena. Both paradigms used together, often called a mixed-methods study, can provide insight into broader research questions through convergence and collaboration of findings (Johnson & Onwuegbuzie, 2004).

This is a mixed-methods study, combining statistical data and subjective reports from antidepressant users and ex-users, along with a "baseline" group of participants who have never used antidepressants. The study endeavoured to explore antidepressant use and withdrawal through the reported experiences of four different groups of participants: those who are currently using antidepressants, those who are currently withdrawing from an antidepressant, those who used to take an antidepressant but who no longer do so, and a "control group" of individuals who have never taken an antidepressant or other prescription psychotropic drug.

All participants completed a survey about their own antidepressant use with most responses reported on 5- or 6-step Likert scales (ultimately, a subjective

quantification of a qualitative measure [Jick, 1979]), followed by an open-ended opportunity to add additional comments, providing an opportunity to explore a single issue through two different types of data from the same group of participants. Participation was completely anonymous.

Based on side effects and withdrawal symptoms noted in previous studies and symptom checklists like the DESS (Rosenbaum et al., 1998), TSES (Vanderkooy et al., 2002) and Glenmullen's antidepressant withdrawal checklist (Glenmullen 2005, p. 205) and withdrawal symptoms reported in Thrasher (2008)[25], an anonymous on-line survey was designed to test participant well-being, symptomology, and perceived changes between medicated and un-medicated states, and giving them an opportunity to add additional comments. This combination of quantifiable and qualitative data provided the basis for a mixed-methods analysis to elicit insight into the experience of antidepressant users within a naturalistic, "real-life" setting.

Following a first reading of the comments to get a feel for the general trends of thought and identify any potential problems with the quantitative survey data that might become apparent from the comments, a quantitative analysis of the survey data was undertaken. This was followed by a thematic analysis of the comments.

Survey Design

All participation was voluntary and anonymous; no information was collected that could be linked back to a specific participant.

[25] Items identified in Thrasher (2008) and not included on the TSES, DESS, or Glenmullen's checklist but included in this survey were an increased need for sleep, emotional flattening, body pain, head or facial pain (not headache), food and/or chemical sensitivity, impaired judgement, and bladder or urinary problems.

The initial section of the survey gathered demographic data (sex, age group, country of origin, medication and dosage[s] as applicable, reason for prescription, length of time on drug and [where applicable] time since withdrawal, and co-prescribed drugs), and also a likert-type question to establish the participant's overall attitude towards antidepressants. This section was followed by 21 6-point likert-type questions regarding mood to evaluate the level of depression experienced by the participant at the time of filling out the survey. This section incorporated all five questions from the WHO-5 well-being index (Newnham, Hooke, & Page, 2010) and some questions from the Major ICD-10 Depression Inventory (MDI) (Bech, Rasmussen, Olsen, Noerholm, & Abildgaard, 2001); the remainder of the MDI questions were placed elsewhere in the survey such as those asking about increased or decreased appetite and sleep issues (put under symptoms). Several additional questions were incorporated into this mood section such as "I have felt like I wanted to harm someone else" and "I have had mood swings" which were based on previous literature as possibly linked to antidepressant use. Because there were more negatively-worded questions than positively-worded questions, some statements were reversed to create a balanced range of statements. Typical questions were "I have felt calm and relaxed" (from the WHO-5) and "I have had difficulty concentrating"[26] (from the MDI).

The WHO-5 well-being index is recommended by the World Health Organisation as a quick initial screen for depression, and compares well with other depression screening instruments (Löwe et al., 2004; Newnham et al., 2010). It consists of 5 6-point Likert questions like "I have felt cheerful and in good spirits" assessed on a 25-point scale ("at no time" counts as zero). Scores are added up,

[26] The actual initial wording in the MDI is "Have you…" suggesting the questions are being asked by someone else. Since this survey is a self-report, MDI questions were reworded with an initial "I".

and a score below 13 is considered indicative of depression risk (Psychiatric Research Unit, ND). The MDI functions as a simple, widely-accepted, brief self-rating 6-point Likert-scale instrument for diagnosis of depression that when compared with the DSM-IV and the WHO's Schedules for Clinical Assessment in Neuropsychiatry (SCAN) criteria, gives a 0.90 sensitivity score sufficient for evaluating levels of depression (Bech et al., 2001).

The next section of the survey consisted of a list of 37 antidepressant side effect and withdrawal symptoms based on those reported and assessed by Rosenbaum et al. (1998), Vanderkooy et al. (2002), and Glenmullen (2005) as well as additional items highlighted by Thrasher (2008). Using the format of the TSES (Vanderkooy et al., 2002), participants rated frequency of each symptom during the past two weeks on a 5-point Likert scale from "never" to "all the time". If a symptom had been experienced, participants were asked to rate the severity of the symptom on a 5-point Likert scale from "very minor" to "very severe". Examples of symptoms included nausea, chest pain, dizziness, fatigue, and insomnia. Participants were also asked about weight gain or loss.

The fourth section on emotion and behaviour asked participants to compare their current likelihood of feeling or behaving in a certain way to how they would have done so in the past (e.g., on medication now compared to before being on medication). Items were rated on a 5-point Likert scale from "much more likely to" to "much less likely to". Typical items included "act impulsively," "worry about things," and "show affection," and were based on anecdotal reports (e.g., Breggin, 2008), loosely-related research papers (e.g., Goodman, Murphy &

Storch, 2007, Harmer, 2008)[27] and on-line forums. This author is not aware of any studies which have examined self-reported behavioural or emotional changes among antidepressant users.

A final section gave participants the opportunity to add any additional information about the survey, their experience, or their thoughts on antidepressants. None of the questions in the survey were compulsory.

Following approval by the Victoria University of Wellington School of Psychology Human Ethics Committee (SoPHEC) the survey (Appendix A) was posted on www.surveymonkey.com, a web-based survey tool.

Participants

Participants were recruited over a 5-month period through a variety of methods including local posters inviting participation, local residential letterbox drops, invitations to participate on internet forums[28], and email notifications to friends and colleagues who might be willing to participate or pass on the link to someone who would. Clearly, this is much more of a shotgun snowball approach than random sampling, but the difficulties of recruiting participants through more "official" channels such as doctors or public mental health providers, given patient confidentiality policies, are not insignificant (Pestello & Davis-Berman, 2008). Extrapolating results from this study to the general population must be done with the caveat in mind that a bias towards greater reporting of adverse reactions could

[27] The former paper examines concerns over the activation of aggressive and suicidal tendencies in 1-3% of youths prescribed antidepressants, and the second speculates on alterations in emotional processing caused by serotonin enhancers.

[28] This proved more difficult than anticipated with most forum administrators refusing to allow a link to the survey. Links were posted at www.drugs-forum.com, www.beyondblue.org.au, www.paxilprogress.org, and www.quitpaxil.info, although the latter link was not posted on line until a week before the final download of data from the survey.

exist given self-selective participation and the use of a survey in the form of a checklist (Moncrieff et al., 2009; Zimmerman et al, 2010). Participants received no payment or reward for participation, but were invited to send email details for notification of study results at the completion of the project if interested. Fifty participants requested such notification.

Analytic Strategy

The analytic strategy for this study was to integrate both hypothesis testing and hypothesis generation. Initially, demographic data was assessed and categorized. This was followed by an initial reading of comments in response to the final survey prompt: "If there is anything else you would like to add about your antidepressant experience, or about this survey, please share your comments in the box below." An initial quantitative analysis was then undertaken to compare groups on the mood data, frequency and severity of symptoms, and examine participant perception of drug effects reflected in their perceived behaviour and mood changes between "then" and "now." SPSS 16.0 was used for all of the statistical data analysis in this research. Finally, comments at the end of the survey were coded and a thematic analysis was undertaken to identify recurring issues.

Two issues were raised by the comments regarding the quantitative analysis. It became clear that many of the "current users" had, in fact, changed their prescription or dose recently, suggesting that this group lacked uniformity. Although treated as a single group in the initial analysis, the group was also split into "stable" and "unstable" users based on the survey question "Have you changed your antidepressant or dose in the past three months?" to identify any

significant differences within that subgroup. It also became clear from the comments that many of those in the “ex-user” group continued to suffer from what they perceived as withdrawal more than 2 months following complete drug cessation. Because no specific question allowed an easy split of this group into “stable” and “unstable” factions, following the initial general group comparison analysis, comments were assessed to identify those ex-user participants who chose to report ongoing health issues they ascribed to antidepressant drug use or withdrawal. Although not an ideal method for splitting the group, it was felt that an assessment of any statistically significant differences between these two sub-groups would increase understanding and expand the relatively meagre existing literature regarding the prolonged antidepressant withdrawal experience and help to illustrate the kinds of effects that might be residual in those individuals sensitive to a prolonged withdrawal syndrome.

Chapter 7

Results I

The Quantitative Analysis

The survey was completed by 509 participants. No questions were compulsory, and data from participants who did not complete more than half of the survey were not included in the analysis. Missing data for individual questions throughout this study were excluded analysis by analysis, such that a missing response to one item did not preclude analysis of that participant's responses to other items.

Demographics

Sex, age, information about drug types taken and duration of medication time within each group (current users, actively withdrawing from antidepressants, ex-users, and never used) are presented in Table 2.

Depression was the most common self-reported diagnosis or reason reported for the antidepressant prescription (212 participants), and anxiety came a fairly close second (176), plus another 10 participants specifically reported GAD. Panic disorder (53) was also commonly reported, along with OCD (19), social phobia/anxiety (16), PTSD (12), insomnia (12), stress (11), and post-natal depression (10). As noted in Chapter 2, antidepressants are approved treatment for a variety of anxiety disorders as well as depression. Many participants reported more than one cause for the prescription (e.g., "depression, anxiety and mild

OCD"), and 20 offered reasons or qualifiers (e.g., "going through a stressful life period" and "situational depression due to family death").

Table 2. ***Participant group profiles showing number of participants in each category.*** *Several participants reported taking more than one antidepressant. Non-antidepressant medication included contraceptives, gastric reflux medication (two most commonly reported) as well as mood-altering drugs including sleeping medications, benzodiazepines, Lamictal, Depakote, lithium, quetiapine, buspirone and dextroamphetamine[29].*

	Current users (n = 176)	Withdrawing (n = 181)	Ex-users (n = 108)	Never used (n = 44)
Sex				
Male	48 (27%)	45 (25%)	29 (27%)	16 (36%)
Female	128 (73%)	136 (75%)	79 (73%)	28 (64%)
Age				
<20	10 (6%)	6 (3%)	4 (4%)	1 (3%)
20-39	105 (60%)	99 (55%)	59 (55%)	27 (61%)
40-60	47 (27%)	64 (35%)	39 (36%)	12 (27%)
>60	13 (7%)	12 (7%)	5 (5%)	4 (9%)
Time on antidepressants				
<3 months	13 (7%)	6 (3%)	11 (10%)	
3-12 months	28 (16%)	35 (19%)	30 (28%)	
1-3 years	30 (17%)	34 (19%)	28 (26%)	
3-8 years	43 (25%)	49 (27%)	17 (16%)	
>8 years	62 (35%)	57 (32%)	21 (20%)	
Drug type taken				
SSRI (eg. paroxetine, fluoxetine)	139 (79%)	174 (96%)	89 (82%)	
SNRI (eg. venlafaxine)	20 (11%)	6 (3%)	16 (15%)	
NDRI (e.g. bupropion)	16 (9%)	3 (2%)	1 (1%)	
TCA (e.g. imipramine)	6 (3%)	(0%)	3 (3%)	
Other (e.g. mirtazapine, trazodone)	9 (5%)	3 (2%)	24 (22%)	
Taking more than one AD	13 (7%)	10 (6%)	16 (15%)	
Concurrent non-AD medication	91 (52%)	24 (13%)	36 (33%)	15 (34%)

Other reasons given for antidepressant prescriptions included suicidal ideation (8), bipolar (7), low mood or sadness (7), PMS/PMDD (5), pain relief (4),

[29] Both lithium and quetiapine are approved by the US FDA as antidepressant augmentation for drug-resistant depression, and benzodiazepines were used in some SSRI clinical trials to quell iatrogenic agitation as noted earlier in this thesis. Lamictal (lamotrigine) and Depakote (valproic acid) are anti-seizure medications sometimes used for treating the manic phase within a bipolar disorder; buspirone is an anti-anxiety drug; dextroamphetamine is used for treatment of ADHD.

irritable bowel syndrome (4), and anger management (4). A few participants said their antidepressant prescription was to help them deal with the side effects of other drugs, e.g., “for insomnia caused by other medications”. Diagnoses including Seasonal Affective Disorder, menopausal symptoms, anorexia nervosa, ADHD, chronic fatigue syndrome, and fibromyalgia were cited by fewer than 3 participants. Seven participants stated that they did not know why they had been prescribed antidepressants.

Some interesting things to note in general about participants in this study (Table 2): Although varying in size, the groups are roughly comparable in terms of sex and age: when a chi-square analysis for sex was conducted, no significant difference was found between groups, and results of an ANOVA for age likewise revealed no significant difference between groups. Almost three-quarters of respondents were women, which is not unrealistic given women are twice as likely to be prescribed psychotropic drugs as men (Currie, 2005; Ussher, 2010). The most common age-range in all four groups was 20-39. The majority of antidepressants used by participants in this study were SSRIs, not surprising given the dominance of SSRIs in the modern pharmaceutical market (Table 1, p. 16). More than a quarter of participants, not including the never-used group, had taken antidepressants for more than eight years.

Of the 108 participants who used to take antidepressants, four could not remember what drug(s) they had taken. The majority of this group (67%) reported no prescription drug use now, but of those that did, 14% reported regular or occasional use of a benzodiazepine. Thirty percent of this group had been off their antidepressant for less than a year (but more than 2 months), 37% had been off for 1-3 years; 20% had been off the medication for 3-5 years, and 13% had been off

antidepressants for over five years. Regarding the use of other mood-altering medications such as benzodiazepines co-prescribed with antidepressants, some participants commented that these drugs helped them cope with antidepressant side-effects or withdrawal symptoms.

Forty-four percent of participants withdrawing from their antidepressant reported 2-5 attempts to stop taking it, and 10% reported more than 5 attempts to do so. Current users were not asked this question, but many reported in their comments at the end of the survey about unsuccessful attempts to withdraw from the drug. Of those currently withdrawing and ex-users, 42% reported an abrupt stopping (cold turkey), 30% reported taking less than 3 months to taper the drug, 14% reported taking 3-5 months, 6% took 6-12 months, and 8% reported spending over a year tapering off their antidepressant.

Perceived helpfulness of antidepressants

Participants were asked how helpful they believed antidepressants to be in general, with a Likert score of 6 being “very helpful” and a score of 1 being “very harmful”. Results of a one-way ANOVA between participant groups are shown in Table 3. A significant difference was found between groups, except between those withdrawing and the never-used groups regarding antidepressants “in general”, based on Tukey-Kramer post hoc tests. Current users expressed the most positive attitude towards antidepressants in general and personally, with the highest mean group scores, while ex-users expressed the least positive attitude with the lowest mean group scores. In all three user groups, the evaluation of personal

Table 3. Attitude towards antidepressants: Mean based on a Likert scale where 6 = "very helpful" and 1 = "very harmful". 3.5 is the neutral point. ANOVA results show a significant difference between groups; a Tukey-Kramer post hoc analysis supports a significant difference between all groups except between participants withdrawing and those who have never taken antidepressants on the "in general" question.

Attitude towards ADs	Current users N = 176		AD withdrawal N = 179		Ex-users N = 108		Never used N = 42		F
	M	SD	M	SD	M	SD	M	SD	
I believe that antidepressants In general are…	4.77	0.97	4.27	1.42	3.14	1.80	3.76	1.27	F(3, 501) = 33.44***
For me, the antidepressant(s) I am taking is/are	4.73	1.15	3.99	1.65	3.07	1.86			F(2, 458) =38.71***

*** significant at p < .001

antidepressant experience was lower (less helpful) than the belief of antidepressant value in general.

Mental health and mood

Following the demographic data, the survey fell into three data segments followed by the opportunity to leave comments. The first data segment contained 21 statements about mood.

WHO-5 well-being survey.

The five items that comprise the WHO-5 well-being questionnaire were extracted from the mood data and, following establishment of normal distribution between groups, a between-subject groups ANOVA was conducted on the scores. Results are reported in Table 4.

A significant difference was found between groups, although a Tukey-Kramer post hoc test established no significant difference between group means for current users and ex-users. The means for all three antidepressant-experienced groups, however, fell below 13. The WHO advises that a raw score below 13 is indicative of poor well-being and indicative of possible depression. Participants in the currently-withdrawing group reported the lowest mean. Although one cannot attribute use of antidepressants as a cause of low WHO-5 scores, these results suggest that neither use of antidepressants, nor withdrawal from them, are adequate interventions to establish a normal state of well-being.

Table 4. WHO-5 Well-being assessment. The WHO advises that a raw score below 13 indicates a poor level of well-being and possible depression. ANOVA results demonstrated a significant difference between groups. A Tukey-Kramer post hoc test found no significant difference between current users and ex-users, but all other group differences were significant.

	Current users N = 176		AD withdrawal N = 179		Ex-users N = 108		Never used N = 42		F
	M	SD	M	SD	M	SD	M	SD	
WHO-5 survey results	11.05	4.54	9.76	4.18	11.38	5.21	15.34	3.63	F(3, 493) = 18.47***

*** significant at $p < .001$

The US FDA warns that clinical worsening and suicidality may occur at times of dose changes, either increases or decreases, as well as during early treatment (FDA, 2009b). To test this, the current user group participants were asked if they had altered their dose up or down, or changed their medication within the past two months. 42% had done so. To test if dose stability was reflected in WHO-5 results, an independent samples t-test was run comparing those antidepressant users on stable doses with those who had recently changed their dose. No significant effect was found between these two subgroups.

Complete set of mood items.

In the interests of data management and to provide a usable summary of the complete mood data set, an exploratory principal components analysis of the 21 mood items in the survey was undertaken. A KMO of .94 and small residuals indicated a strong level of factorability. Initial analysis yielded four factors with eigenvalues greater than 1, explaining 43.2%, 10.7%, 6.4%, and 4.8% of the variance respectively; three or four principle components were evident from the scree plot. A reasonably high factor correlation between the second and third component of .45 suggested an Oblimin rotation would be more appropriate than Varimax, which assumes factors to be uncorrelated (Pallant, 2005, p. 185). A three-component solution was chosen as more succinct, with factors of “positive energy”, “agitation”, and “aggressive depressive” all showing a number of strong loadings. Results are shown in Table 5. All component loadings over .30 are shown in bold. Cross-loadings occur for “feeling calm” for positive energy and

agitation, and for "sad" for positive energy and life sucks; "agoraphobia" loads at a similar level in all three categories. Percent of variance attributable to each factor cannot be calculated if components are correlated.

Table 5. ***Summary of exploratory components extraction analysis for mood question****—pattern matrix, Oblimin rotation converged in 13 iterations. (N = 509).*

	Factor Loadings		
Item	Positive Energy	Agitation	Aggressive/ Depressive
Feeling Energetic	**-.89**	-.01	.07
Feeling Vigorous	**-.83**	.08	.04
Feeling Fantastic	**-.78**	-.10	-.10
Wake feeling refreshed	**-.73**	-.20	.17
Feel self-confident	**-.69**	.07	-.04
Feel interested in life	**-.65**	.09	-.28
Feel cheerful	**-.64**	-.08	**-.31**
Feel subdued	**.38**	.30	.06
Mind is racing	-.25	**.88**	-.25
Feeling restless	-.09	**.76**	.04
Feeling agitated	.10	**.73**	.10
Experiencing mood swings	.03	**.72**	.06
Feeling anxious	.17	**.67**	.07
Having difficulty concentrating	.30	**.61**	-.05
Feeling calm	**-.44**	**-.50**	-.00
Feeling angry	.09	**.43**	**.31**
Agoraphobia (fear of going out)	**.31**	**.32**	.28
Suicidal or self-harm feelings	.02	.00	**.83**
Feeling homicidal (harm others)	-.19	.07	**.76**
Feel like life is not worth living	.23	.03	**.72**
Feel sad	**.32**	.17	**.51**
Cronbach's Alpha for component	.90	.89	.80

Note: Factor loadings over .31 appear in bold.

Regression factor scores generated by SPSS were used to undertake a one-way multivariate analysis (MANOVA) between subject groups to examine the effect of drug use and/or withdrawal/history on mood. A significant effect between groups was observed (Wilks' $\lambda = .83$, $F(3, 455) = 9.46$, $p < .001$) for the

first two components: "positive energy," $F(3, 455) = 15.89$, $p < .001$ and "agitation," $F(3, 455) = 18.43$, $p < .001$. Post hoc comparisons using the Tukey-Kramer test for "positive energy" indicated that the mean score for participants who had never taken antidepressants ($M = -.93$, $SD = .74$) was significantly different ($p < .001$) from the other three groups, but those groups were not significantly different from each other (current users, $M = -.02$, $SD = .93$; currently withdrawing, $M = .23$, $SD = .93$; ex-users, $M = -.02$, $SD = 1.12$). Post hoc comparisons using the Tukey-Kramer[30] test for "agitation" indicated that the mean scores for current users ($M = -.14$, $SD = .93$) and ex-users ($M = -.28$, $SD = .96$) were not significantly different, but participants currently withdrawing ($M = .37$, $SD = 1.00$) scored significantly higher on this factor than the other three groups ($p < .001$), and those who had never taken antidepressants ($M = -.65$, $SD = .62$) scored significantly lower than those withdrawing ($p < .001$) and current users ($p < .05$). No significant difference was found between groups on the aggressive/depressive factor.

In summary, those who have never used antidepressants appear to have significantly more positive moods than the three antidepressant-experienced groups, and participants withdrawing from their antidepressants have a significantly greater degree of anxiety and agitation than the other groups.

Results from a multivariate ANOVA comparing stable-dose and unstable-dose user subgroups found a significant effect between groups, $F(1, 166) = 2.76$, $p < .05$, Wilks' $\lambda = .95$ with a significant difference between the subgroups on the aggressive/depressive component, $F(1, 166) = 7.48$, $p < .01$ with the unstable subgroup ($M = .19$, $SD = 1.09$) scoring significantly higher on this component

[30] All calculations were done on SPSS which automatically converts the Tukey HSD post hoc test to the more conservative Tukey-Kramer in the event of uneven group sizes (Newsom, 2006)

than the stable subgroup (M = -24, SD = .89), suggesting antidepressant users who have recently increased or decreased their dose, or changed to a different antidepressant, are significantly more likely to harbour aggressive and depressive (including suicidal and/or homicidal) feelings than their counterparts on more stable doses. This supports the FDA warning regarding increased risk of suicidality, aggressiveness and hostility that may occur during dose adjustment (FDA, 2009b). No difference was found between these two subgroups on the other two mood components.

Symptoms

The terms "side effects" and "symptoms" have been used somewhat interchangeably within this thesis. MedTerms (2000) defines "side effects" as "problems that occur in addition to the desired therapeutic effect," while symptom is defined as "subjective evidence of disease" (MedTerms, 2003b). When describing withdrawal effects, most researchers refer to them as symptoms (e.g., Vanderkooy et al, 2002; Rosenbaum et al 1998; Glenmullen, 2005) even though they are essentially the side effects of a therapy manipulation. Complicating the issue with antidepressants is the overlap between disease symptoms such as anxiety, insomnia, fatigue, and changes in appetite which are common markers of depression (APA, 2000), recognized side effects of the drugs (see Chapter 3), and symptoms of withdrawal (Chapter 3). Taking a semantic approach with "disease" defined as "illness or sickness often characterized by patient problems (symptoms)" (Medterms, 1998b), and following the lead of other researchers examining withdrawal, I have chosen to use the word "symptoms" whether referring to

primary symptoms of illness, patient problems caused by drug side effects, and patient problems caused by therapy manipulation such as drug withdrawal. The purpose of the symptom analysis in this study is to identify any significant difference in frequency and intensity of experienced symptoms and types of symptoms between antidepressant users, those in the throes of drug withdrawal, and those who have been off antidepressant medication for at least two months, and to compare those results with survey participants who have never taken antidepressants.

In the survey, participants were asked to identify the frequency during the past fortnight, if any, of 37 different symptoms that have been associated with antidepressant use or withdrawal, and to evaluate the severity of any experienced symptoms. Symptom frequency was rated on a scale of 1 (have not experienced this symptom within the past two weeks) to 5 (have experienced this symptom constantly within the past two weeks), and severity on a scale from 1 (very minor) to 5 (very severe) where 3 is "impacts upon daily routine".

An assessment of the raw data revealed some issues which were corrected prior to analysis. In cases where a participant recorded no "1's" for frequency (didn't experience) for some symptoms but had filled in scores of 2-5 for other symptoms, frequency blanks were re-coded with "1" (didn't experience) as a default value. Several participants did not enter a severity value for any items. In all cases where frequency was coded as 1 (didn't experience), severity was coded as 0 (no severity). If a frequency other than "1" (didn't experience) was indicated, the item group mean was used for the severity value. Following these data adjustments, the score for

frequency was added to the score for severity, yielding a combined score range of 1-10. This means, of course, that a participant who experienced a very mild symptom often might score 5 overall, the same as a participant who experienced a severe symptom briefly.

An exploratory principle component analysis of symptoms was attempted which yielded 9 components showing eigenvalues greater than 1, but 8 of those components each accounted for less than 5% of variance, and 35 of the 37 symptoms showed a principle loading on the first component[31]. A general picture of the overall symptom experience between groups was examined briefly by performing a one way between subjects ANOVA on the single extracted factor, which showed a significant difference between groups, $F(3, 449) = 24.75$, $p < .001$. Although a Tukey-Kramer post hoc examination showed no significant difference in overall symptom loading between antidepressant users ($M = -.07$, $SD = .84$) and ex-users ($M = -.04$, $SD = 1.17$), a significantly higher frequency/severity of symptoms was found for the withdrawal group ($M = .39$, $SD = .92$) compared to the other three groups, and a significantly lower frequency/severity of symptoms for the untreated group ($M = -1.00$, $SD = .44$).

To explore in greater detail the role of individual symptoms and identify symptom experience changes that might occur as participants journey from users through withdrawal to ex-users, and to compare those results with the experience of never-used participants, a one-way multivariate analysis (MANOVA) between subject groups was employed on the frequency plus severity for all of the symptoms, and a significant effect

[31] The two exceptions were increased appetite and increased libido.

between groups was observed, $F(3, 450) = 3.21$, $p < .001$, Wilks' $\lambda = .469$, partial eta squared = .223. Only 2 of the 37 symptoms, "rash" and "suicidal ideation," did not reveal a significant difference between groups. Results of this analysis are reported in Table 6. Post hoc comparisons of symptom results between groups using the Tukey-Kramer test are also reported in Table 6. The lack of any identifiably significant difference between any two groups for body pain, based on post hoc results, is attributed to compensation for the uneven group sizes through use of the relatively conservative Tukey-Kramer post hoc test.

With all symptoms except "increased libido", the control group (having never used antidepressants or other prescribed psychoactive drugs) reported the lowest mean score (lowest frequency plus severity), and those actively withdrawing from antidepressants reported the highest mean scores for the majority of symptoms; however, the current user group recorded the highest mean scores for constipation, increased appetite, and decreased libido, and the ex-users group reported the highest mean scores for chest pain, food and chemical sensitivity, and tinnitus.

All groups recorded their highest symptom frequency/severity score for fatigue. Current users and those in withdrawal both rated an increased need for sleep as second, while ex-users and those who had never used antidepressants rated nervousness as the second most onerous symptom they experienced. Decreased libido ranked third for both current users and ex-users, while those in withdrawal put nervousness in third place and those who had never used antidepressants put insomnia third.

Table 6. ***Group mean, standard deviation and MANOVA results for symptoms demonstrating a significant effect between groups.*** *Scores reflect symptom frequency range between 1 (haven't experience this symptom in the past two weeks) to 5 (experience this symptom constantly) PLUS severity range between 1 (very minor) to 5 (very severe), with 3 defined as "moderate, impacts upon daily routine". If F = 1, then S = 0. Subscripts indicate Tukey-Kramer post hoc comparisons, p < .05: a—significantly different from current user group; b—significantly different from currently withdrawing group; c—significantly different from ex-user group; d—significantly different from never used group. Items are listed by highest reported mean in any group (bold).*

Symptom	Current users n = 158		AD withdrawal n = 158		Ex-users n = 99		Never used n = 38		F
	M	SD	M	SD	M	SD	M	SD	
Fatigue	5.40$_{d}$	2.19	**5.75$_{cd}$**	2.32	4.85$_{bd}$	2.54	3.10$_{abc}$	1.65	F(3, 450) = 14.96***
Increased need for sleep	5.06$_{cd}$	2.62	**5.09$_{cd}$**	2.61	3.72$_{ab}$	2.53	2.66$_{ab}$	1.96	F(3, 450) = 14.82***
Decreased libido	**4.85$_{d}$**	1.10	4.25$_{d}$	3.08	4.27$_{d}$	3.10	1.65$_{abc}$	1.46	F(3, 450) = 11.29***
Nervousness	4.08$_{bd}$	2.14	**4.84$_{ad}$**	2.06	4.40$_{d}$	2.15	2.97$_{abc}$	1.57	F(3, 450) = 9.40***
Dizziness, vertigo	3.19$_{bd}$	1.94	**4.82$_{acd}$**	2.44	2.83$_{b}$	2.15	2.00$_{ab}$	1.25	F(3, 450) = 30.61***
Agitation	3.70$_{bd}$	1.95	**4.70$_{acd}$**	2.13	3.85$_{cd}$	2.19	2.71$_{abc}$	1.58	F(3, 450) = 12.68***
Disturbing dreams	3.48$_{bd}$	2.32	**4.52$_{acd}$**	2.82	3.06$_{b}$	2.18	1.89$_{ab}$	1.25	F(3, 450) = 15.84***
Headache	3.61$_{bd}$	2.02	**4.49$_{ad}$**	2.36	3.83$_{d}$	2.35	2.37$_{abc}$	1.68	F(3, 450) = 10.89***
Insomnia	4.08$_{d}$	2.47	**4.43$_{d}$**	2.66	4.25$_{d}$	2.73	2.79$_{abc}$	1.89	F(3, 450) = 4.33**
Excessive sweating	3.60$_{cd}$	2.48	**4.06$_{cd}$**	2.37	2.48$_{ab}$	1.94	1.53$_{ab}$	1.10	F(3, 450) = 19.18***
Weakness	3.25$_{bd}$	2.09	**4.04$_{acd}$**	2.42	3.26$_{bd}$	2.56	1.66$_{abc}$	1.19	F(3, 450) = 12.09***
Nausea	2.67$_{bd}$	2.05	**3.85$_{acd}$**	2.41	2.38$_{b}$	2.04	1.63$_{ab}$	1.20	F(3, 450) = 18.64***
Emotional flattening	3.46$_{d}$	2.50	3.55$_{d}$	2.39	**3.80$_{d}$**	2.93	1.84$_{abc}$	1.42	F(3, 450) = 5.99**
Excessive thirst	3.58$_{d}$	2.36	**3.77$_{cd}$**	2.23	2.86$_{b}$	2.17	2.45$_{ab}$	1.74	F(3, 450) = 6.05***
Body pain	3.17	2.28	**3.69**	2.42	3.56	2.28	2.68	1.69	F(3, 450) = 2.76*

* Significant at p < .05; ** significant at p < .01; *** significant at p < .001

Symptom	Current users N = 158		AD withdrawal N = 158		Ex-users N = 99		Never used N = 38		F
	M	SD	M	SD	M	SD	M	SD	
Brain zaps	2.22$_{b}$	2.06	**3.66$_{acd}$**	2.89	1.84$_{b}$	1.72	1.32$_{b}$	1.12	F(3, 450) = 20.79***
Panic attacks	3.05$_{d}$	2.36	**3.47$_{d}$**	2.34	2.84$_{d}$	2.26	1.16$_{abc}$	0.71	F(3, 450) = 11.06***
Increased appetite	**3.41$_{cd}$**	2.36	2.84	2.15	2.58	1.87a	2.21$_{d}$	1.63	F(3, 450) = 5.18**
Diarrhoea	2.59$_{b}$	1.91	**3.41$_{acd}$**	2.30	2.62$_{b}$	1.98	1.82$_{b}$	1.43	F(3, 450) = 8.42**
Reduced appetite	2.75$_{d}$	2.30	**3.32$_{d}$**	2.29	2.63	2.25	1.66$_{ab}$	1.15	F(3, 450) = 6.43***
Dry mouth	2.91$_{d}$	2.02	**3.18$_{d}$**	2.25	2.66	2.31	1.79$_{ab}$	1.34	F(3, 450) = 4.78**
Vision abnormalities	2.19$_{b}$	1.79	**3.10$_{ad}$**	2.22	2.75$_{d}$	2.38	1.29$_{bc}$	0.87	F(3, 450) = 10.64***
Food or chemical sensitivity	2.25$_{c}$	2.15	2.53	2.45	**3.04$_{ad}$**	2.86	1.74$_{c}$	1.43	F(3, 450) = 3.58*
Tinnitus	2.18$_{bc}$	2.01	2.96$_{ad}$	2.34	**3.01$_{ad}$**	2.40	1.87$_{bc}$	1.53	F(3, 450) = 5.93**
Abdominal pain	2.70$_{d}$	2.05	**2.96$_{d}$**	2.16	2.85$_{d}$	2.26	1.63$_{abc}$	1.96	F(3, 450) = 4.27**
Head or facial pain	1.90$_{b}$	1.52	**2.94$_{ad}$**	2.23	2.52$_{d}$	2.18	1.52$_{bc}$	1.43	F(3, 450) = 10.36***
Impaired judgement	2.04$_{bc}$	1.66	**2.89$_{ad}$**	2.14	2.78$_{ad}$	2.36	1.40$_{bc}$	0.94	F(3, 450) = 9.44***
Constipation	**2.68$_{d}$**	2.26	2.49$_{d}$	1.95	2.45$_{d}$	1.97	1.39$_{abc}$	1.03	F(3, 450) = 4.22**
Restless legs	2.65$_{d}$	2.08	**2.67$_{d}$**	2.11	2.49$_{d}$	2.02	1.44$_{abc}$	0.97	F(3, 450) = 4.15**
Twitching	1.80$_{c}$	1.53	2.08$_{d}$	1.55	**2.43$_{ad}$**	2.00	1.21$_{bc}$	0.62	F(3, 450) = 6.49***
Chest pain	2.09	1.83	2.18$_{d}$	1.68	**2.43$_{d}$**	1.88	1.31$_{bc}$	0.84	F(3, 450) = 3.89**
Increased libido	1.41$_{b}$	1.10	**2.22$_{a}$**	1.93	1.91	1.65	1.95	1.68	F(3, 450) = 6.76***
Bladder or urinary problems	1.96	1.98	**2.20$_{d}$**	2.22	2.09	2.09	1.18$_{b}$	0.65	F(3, 450) = 2.67*
Tremor	1.88$_{d}$	1.74	**2.20$_{d}$**	1.84	1.96$_{d}$	1.67	1.05$_{abc}$	0.32	F(3, 450) = 4.83**
Vomiting	1.35	1.08	**1.62$_{d}$**	1.46	1.28	0.83	1.08$_{b}$	0.49	F(3, 450) = 3.49**

* Significant at p < .05; ** significant at p < .01; *** significant at p < .001

There is a great deal of data here regarding symptoms commonly associated with antidepressant use and withdrawal, and the reader is invited to explore individual symptoms through a close examination of the tables. For example, the reported frequency/severity increase in many symptoms such as nausea, vertigo, and agitation experienced by participants withdrawing from antidepressants appears to abate with time (ex-users), although other symptoms such as tinnitus and food or chemical sensitivity appear to increase as participants move from user though withdrawal to the ex-user stage.

Lastly in the "symptoms" section of the survey, participants were asked about weight gain and loss. A one-way ANOVA between subject groups was run examining weight gain since the onset of the antidepressant prescription (first three groups) or within the last year (never-used group), although the latter is not necessarily comparable[32]. A significant difference between groups was found, $F(3,451) = 11.16$, $p < .001$. Participants currently taking antidepressants reported a mean weight gain just over 10 pounds (4.5 kg) ($M = 3.22$, $SD = 1.58$, where "3" is defined on the survey as "less than 10 pounds [4.5 kg]"), as did participants withdrawing ($M = 3.09$, $SD = 1.59$), and ex-users just a bit below that ($M = 2.95$, $SD = 1.71$). The "never used" group, however, reported a mean of 1.65 ± 0.89 where "1" = no weight gain and 2 = "less than 5 lbs./2.3 kg". A Tukey-Kramer post hoc test revealed a significant difference between the never-used group and each of the user groups ($p < .001$), but no significant difference between the user groups

[32] The latter group is referring to a one-year period; the other three groups are "since the onset of prescription" which could mean a few months or ten years. Results, therefore, are inconclusive at best. However comments regarding iatrogenic weight gain were common (see Chapter 8).

themselves. There was no significant difference found between groups for weight loss.

The results of a multivariate analysis of stable and unstable user subgroups over the total combined symptoms revealed no significant difference between groups, $F(1, 156) = .93$. $p > .05$, Wilks' Lambda = .78, partial eta squared - .22, suggesting that the symptom profile is not significantly different between these two subgroups.

Subjectively perceived changes: That was then, this is now.

For the final segment of statistical data collected, participants were asked to compare their moods and behaviours between their present state and a previous one. Participants currently taking antidepressants were asked to compare being on antidepressants with how they felt or behaved before going on antidepressants. A one-sample t-test was employed to examine self-perceived change on 23 emotional and behavioural elements where a value of "3" indicates a no-change response. Significant results are shown in Table 7. Items where feelings or behaviours are perceived to have increased are shown in bold. Because of the risk of a type-one error with this many items in the analysis, a Bonferroni correction was utilised and a statistical significance level of less than .001 was set.

On the basis of these self-perceived changes, the antidepressant users in this study felt positive overall, experiencing fewer negative emotions and displaying fewer negative behaviours than prior to taking medication, and experienced more positive emotions and behaviours (except, perhaps, "crave junk food") since taking antidepressants.

Table 7. ***Current users comparing "now" (on antidepressants) with "then" (before antidepressant use).*** *Significant responses to the prompt* "Since *being on antidepressants, I have been more/less likely to…" "3" indicates no change based on a 5-point likert rating scale, with means over 3 indicating increased likelihood, and those less than 3 a decreased likelihood.*

Behaviour or mood	M	SD	t
Find the positive in a negative event	3.42	.90	t(153) = 5.83***
Feel happy	3.42	.91	t(153) = 5.65***
Feel good about myself	3.43	1.06	t(154) = 4.99***
Enjoy social events	3.42	1.06	t(153) = 4.95***
Crave "junk" food	3.36	.94	t(153) = 4.79***
Feel empathy for others	3.26	.83	t(154) = 3.88***
Lose temper	2.69	1.01	t(153) = -3.77***
Remember things	2.63	.91	t(154) = -5.02***
Worry about things	2.56	.88	t(153) = -6.24***
Gamble	2.52	.92	t(149) = -6.44***
Cry	2.39	.99	t(152) = -7.61***
Feel depressed	2.34	1.04	t(153) = -7.80***

***significant at p < .001

Participants currently withdrawing from antidepressants were asked to compare how they felt and behaved while withdrawing from antidepressants with how they felt or behaved when taking antidepressants. As with current users, a one-sample t-test was employed to examine the self-perceived change on a variety of emotional and behavioural elements. Significant results are shown in Table 8. Items where feelings or behaviours are perceived to have increased are shown in bold. Again, because of the risk of type-one error with this type of analysis, a statistical significance level of less than .001 was set. Overall, while withdrawing from their antidepressant, participants reported increased negative emotions and behaviours and a decrease in social activity participation and mental agility.

Table 8. Participants currently withdrawing from antidepressants *comparing "now" (in withdrawal) with "then" (when taking antidepressants).* *Significant responses to the prompt* "Now that I am withdrawing, *I have been more/less likely to…" "3" indicates no change based on a 5-point likert rating scale, with means over 3 indicating increased likelihood, and those less than 3 a decreased likelihood.*

Behaviour or mood	M	SD	t
Cry	3.80	.96	t(147) = 10.20***
Feel depressed	3.62	.92	t(146) = 8.12***
Lose temper	3.66	1.02	t(148) = 7.88***
Worry about things	3.52	1.00	t(149) = 6.36***
Drink alcohol	2.67	1.10	t(143) = -3.58***
Enjoy social events	2.66	.97	t(148) = -4.30***
Think clearly	2.59	1.03	t(148) = -4.87***
Remember things	2.59	.91	t(147) = -5.42***
Gamble	2.43	.92	t(139) = -7.39***

***significant at p < .001

Participants who had not taken an antidepressant for at least two months were asked to compare their feelings and behaviours post-AD with how they were feeling and behaving on antidepressants, and also how their current state compared with how they felt and behaved before taking any antidepressants. As with current users, a one-sample t-test was employed to examine self-perceived change on the same emotional and behavioural items as was examined in the user group and withdrawing group. Significant results comparing how they felt now with how they felt on antidepressants are shown in Table 9. Items where feelings or behaviours are perceived to have increased are shown in bold. Again, because of the risk of type-one error with this type of analysis, a statistical significance level of less than .001 was set (Bonferroni correction). Items where feelings or behaviours are perceived to have significantly increased are shown in bold.

The ex-user participants report significant positive improvements in feeling and behaviour over how they felt and behaved while on antidepressants. There appears to be a slight shift in the kinds of significant positive feelings and behaviours reported in this group compared to the antidepressant users, however, with a greater focus among ex-users on caring about others, spending time with family (as opposed to users' "enjoy social events"), and showing affection.

Table 9. ***Ex-users comparing "now" with when they were taking antidepressants.*** *Significant responses to the prompt* "Compared to when I was taking antidepressants, now I am more/less likely to…" *"3" indicates no change based on a 5-point likert rating scale, with means over 3 indicating increased likelihood, and those less than 3 a decreased likelihood.*

Behaviour or mood	M	SD	t
Care about others	3.53	1.11	t(84) = 4.40***
Find the positive in a negative event	3.51	1.10	t(83) = 4.25***
Laugh	3.47	1.14	t(84) = 3.81***
Show affection	3.50	1.21	t(83) = 3.80***
Gamble	2.49	.91	t(83) = -5.15***

***significant at p < .001

Interestingly, results of a one-sample test on ex-users asked to compare how they feel and behave now with how they felt and behaved prior to taking antidepressants revealed no items showing a significant differences between then and now at the p < .001 level, suggesting that group participants felt—as a group—that they had returned to pre-drug levels on all items. This is a curious paradox: although users reported feeling better than before they took antidepressants, and ex-users report

feeling better than while they were on antidepressants, ex-users did not report feeling better than they did before the antidepressant prescription.

A problem with the ex-users group—the prolonged withdrawal factor

At the end of the survey, participants were invited to leave comments about their antidepressant use or withdrawal experience, or about the survey. Although the survey was designed around the assumption that antidepressant withdrawal symptoms would more-or-less be resolved two months following a 0 gram dose (Haddad & Anderson, 2007; Fava & Offidani, 2010), 23 (21%) of participants in the ex-users category commented on their ongoing issues with protracted withdrawal[33]. It is possible that some of the other participants within that group also suffered from protracted withdrawal but did not comment to that effect, and this figure does not include those who wrote of having experienced a protracted withdrawal experience that they reported eventually resolved itself.

This is an important issue because it compromises the integrity of the ex-user group to some extent, especially when used in comparison with the group of participants who are currently withdrawing. Since this research is exploratory as well as hypothesis-driven, and gaining a better understanding of the antidepressant withdrawal experience is one of the stated goals of the study, a closer examination of the two ex-user subgroups was undertaken. It is also important because the existence of a prolonged withdrawal experience with antidepressants is generally perceived as rare—see Chapter 3—but this current study suggests a prolonged withdrawal experience might

[33] The next chapter of this thesis covers a thematic analysis of participant comments. Participant reports of withdrawal and the prolonged withdrawal experience are addressed there.

be more prevalent, and last longer for some individuals (see Chapter 8), than previously supposed.

As was done with the group of antidepressant users—in that case it was between those with stable and destabilized antidepressant dosage—the ex-users group was split into two subgroups, one of participants who spontaneously self-identified themselves as currently suffering from a prolonged withdrawal syndrome (PWD) in their comments and the other of participants who did not do so (NoPWD). Participant comments like "I am still not out of the woods from withdrawal and it has been 1.5 years,", "at nearly five years off Paxil, I feel like my central nervous system has still not fully recovered," and "I am still experiencing some withdrawal symptoms" are typical of comments used to identify ex-users reporting ongoing drug or withdrawal symptoms (PWD) from within the ex-user group. Anyone who did not make a specific reference in a comment to currently experiencing symptoms they attributed to withdrawal were considered NoPWD. In retrospect, a specific question in the survey would have sorted these ex-user sub-groups much more precisely, but lacking that, it was felt that this method of division would at least allow a preliminary exploration into the prolonged withdrawal experience. All results reported regarding these two subgroups must be assessed with the caveat of subgroup division limitations in mind.

A multivariate analysis comparing PWD and NoPWD ex-user subgroups on the three mood factors "positive energy", "agitation" and "aggressive/depressive" found a significant effect between groups $F(1, 70) = 5.92$, $p < .01$, Wilks' $\lambda = .80$. When the dependent variables were

considered separately, a significant difference was found between these two subgroups on all three mood components (Table 10).

Table 10. ***Mood components showing a significant difference between ex-users who reported prolonged withdrawal symptoms (PWD) in their comments and ex-users who did not (NoPWD).***

Mood Component	PWD n = 23 M	SD	NoPWD n = 53 M	SD	F
Positive Energy	.68	1.10	-.36	1.09	$F(1, 75) = 13.49, p < .001$
Agitation	.25	1.04	-.44	0.85	$F(1, 75) = 7.17, p < .005$
Aggressive/Depressive	.52	1.01	-.18	0.77	$F(1, 75) = 10.42, p < .005$

These results suggested that ex-users who are still suffering a prolonged drug withdrawal reaction more than two months after they ceased taking the medication are more likely to feel substantial mood volatility characterized by greater levels of positive energy, agitation, and aggressive/depressive feelings than more stable participants who are no longer feeling the results of drug withdrawal.

An independent samples t-test was also run on the WHO-5 well-being questions, and a significant difference was found between the PWD ex-user subgroup ($M = 8.36$, $SD = 4.91$) and the NoPWD ex-user subgroup ($M = 13.21$, $SD = 4.91$), $t(79) = -4.21$, $p < .001$. The WHO advises that a raw score below 13 is indicative of poor well-being and a signal of possible depression (Psychiatric Research Unit, ND), suggesting that participants undergoing a prolonged withdrawal experience are experiencing a poor level of well-being indicative of significant depression risk. Ex-users not currently experiencing a prolonged withdrawal response are not showing a depression

risk based on the WHO-5. Together, these results suggest a lack of homogeneity within the ex-user group.

A multivariate ANOVA comparing PWD and NoPWD ex-user subgroups on the 37 symptoms was performed and a significant effect between groups was found, $F(1, 82) = 2.30$, $p < .005$, Wilks' $\lambda = .35$. When the dependent variables were considered separately, a significant difference was found between these two subgroups on 27 of the 37 symptoms (Table 11).

There was no significant difference found between these two subgroups on digestive symptoms (nausea, vomiting, diarrohea, constipation, increased or decreased appetite), nor on non-dream sleep issues (insomnia, need for more sleep). There was also no significant difference found for the symptoms of excessive sweating and increased libido. In all cases, the ex-user sub-group experiencing prolonged withdrawal recorded a higher mean symptom response than the ex-user subgroup not experiencing a prolonged withdrawal reaction. An examination of individual symptoms with high group means suggest that even more than two months post-drug, many onerous symptoms remain for some users: reported as particularly bothersome were fatigue, decreased libido, and nervousness. This is an important observation not only for antidepressant users and their doctors, but also for clinical trial researchers who assume a drug washout period of a week or two adequate when testing new drug or placebo results.

Table 11. ***Symptoms (frequency plus severity) showing a significant difference between ex-users who reported prolonged withdrawal symptoms (PWD) in their comments, and ex-users who did not (NoPW.*** *All ex-users reported being antidepressant-free for at least 2 months. Mean scores reflect a symptom frequency range between 1 (haven't experience this symptom in the past two weeks) and 5 (experience this symptom constantly) PLUS severity range between 1 (very minor) and 5 (very severe), with 3 defined as "moderate, impacts upon daily routine". If F = 1, then S = 0. Symptoms are listed in order of highest mean.*

Symptom	PWD n = 23		NoPWD n = 61		
	M	SD	M	SD	F
Fatigue	6.43	2.59	4.36	2.29	F(1, 83) = 12.76**
Decreased libido	5.96	3.10	3.80	2.95	F(1, 83) = 8.64**
Nervousness	5.91	1.98	3.87	1.94	F(1, 83) = 18.42***
Emotional flattening	5.61	3.13	3.23	2.62	F(1, 83) = 12.34**
Food/chemical sensitive	5.48	3.00	2.18	2.13	F(1, 83) = 31.78***
Body pain	5.26	2.45	2.97	1.91	F(1, 83) = 20.57***
Weakness	5.13	2.77	2.57	2.06	F(1. 83) = 21.14***
Headaches	5.04	1.97	3.46	2.17	F(1, 83) = 9.34**
Agitation	4.78	2.43	3.61	2.03	F(1, 83) = 5.03*
Tinnitus	4.61	2.55	2.33	1.91	F(1, 83) = 19.63***
Vision abnormalities	4.48	2.64	2.10	1.80	F(1, 83) = 22.35***
Impaired judgement	4.48	2.78	2.16	1.79	F(1, 83) = 20.26***
Disturbing dreams	4.43	2.19	2.49	1.95	F(1, 83) = 15.53***
Panic attacks	4.30	2.44	2.20	1.93	F(1. 83) = 17.16***
Twitching	4.00	2.35	1.95	1.55	F(1, 83) = 21.55***
Dizziness/vertigo	4.00	2.35	2.44	2.06	F(1, 83) = 9.63**
Thirst	3.96	2.48	2.36	1.80	F(1, 83) = 10.61**
Head or facial pain	3.91	2.50	2.00	1.74	F(1, 83) = 15.67***
Dry mouth	3.91	2.64	2.11	1.94	F(1, 83) = 11.66**
Abdominal pain	3.91	2.47	2.48	2.13	F(1, 83) = 6.99*
Suicidality	3.70	2.36	1.87	1.55	F(1, 83) = 17.07***
Restless legs	3.61	2.23	2.00	1.74	F(1, 83) = 12.06**
Chest pain	3.43	1.80	2.03	1.85	F(1, 83) = 9.70**
Bladder/urinary problem	3.09	2.81	1.70	1.67	F(1, 83) = 7.68**
Tremor	3.04	2.18	1.62	1.25	F(1, 83) = 13.87***
Brain zaps	2.83	2.29	1.51	1.30	F(1, 83) = 10.99**
Rash	2.52	2.17	1.39	1.23	F(1, 83) = 8.97**

*Significant at $p < .05$; ** significant at $p < .01$; *** significant at $p < .001$

A significant difference between PWD and noPWD on suicidality is of some note since no difference was found on this symptom between the

four intact groups. Although an increased risk of suicidality is linked with both antidepressant use and withdrawal (see Chapter 3), this author is not aware of any studies examining the possibility of an increased suicide risk post-withdrawal for some patients.

It is possible, of course, that those patients reporting ongoing withdrawal issues more than two months after their terminal antidepressant dose are simply responding to a return to their original illness, but their comments indicate that they do not believe this to be the case, and many made the point in their comments of feeling “WAY better off before taking any meds” (ex-user).

Chapter 8

Results II

An Examination of Comment Themes

> *Qualitative health research is research with a focus on the social world, not the world of nature. ...When researching the natural world the phenomena can be treated as objects or things, and from careful observation, natural laws may be generated. But in the social world, we are dealing with subjective experiences, and understanding of reality can change over time and in different social contexts.*
>
> --Kevin Dew, 2007

Although including a comment was optional, 65% of participants included personal comments at the end of the survey where invited to do so[34]; those who were withdrawing from antidepressants were the most likely to respond with a 76% return rate, while participants without antidepressant experience showed the lowest response to this invitation at just 22%. The longest response was 959 words; the shortest 3 words, and the median response length was 72 words.

All quotes from participants used as examples in this chapter are as written, including the use of capital letters for emphasis. Obvious typographical errors have been corrected (e.g., remember instead of rememeber), and punctuation has been amended for clarity (e.g., commas to separate items in a series). An ellipsis (…) is used to indicate portions of the comment that have been omitted for brevity.

A thematic analysis was conducted of the comments using Braun and Clarke (2006) as a guide. The data set was read through several times to identify repeated patterns of meaning. Notes were made in the margins and text passages

[34] Actual invitation: "If there is anything else you would like to add about your antidepressant experience, or about this survey, please share your comments in the box below."

highlighted with different colours to facilitate the coding process. A series of thematic maps were generated and items clustered and consolidated. A general trend differentiating the three user groups was observed, and six key themes that occurred across all three user groups were identified along with three subsidiary issues that were raised indirectly by the comments. This trend, the key themes, and the subsidiary issues are discussed below. Comments from the never-used group were different in tone to those made by the antidepressant-experienced groups and are addressed briefly near the end of this chapter.

The antidepressant experience as a whole can be seen as a sort of journey, moving from a perceived need for a pharmaceutical intervention, through the user experience, through the withdrawal experience, and arriving eventually at an ex-user endpoint. The majority of participants in this study were exploring this journey, and their responses were, understandably, coloured by their current stage and progress in that journey. None of the participants focussed primarily on the pre-prescription stage, although several commented in passing on their diagnosis:

> My depression is a manifestation of my PTSD which was triggered due to a number of social and work stressors. (Current user)

> They are supposed to clear my head and make it easier for me to be motivated towards positive change. In reality, I'm not sure that has happened. (Current user)

Of those participants with antidepressant experience, an overall impression is that those who currently take the drugs were generally the most positive about antidepressant use, those withdrawing less so, and ex-users were the most negative. Each group tended to focus on issues peculiar to their stage in the journey. Typical examples:

> All the antidepressants I've taken have helped me get through daily life, but I've become more numb to life itself. (Current user)

> Don't take them if your issues aren't severe. The process of getting off them is painful and terrible. (Currently withdrawing)
>
> I thought Paxil was a wonder drug for the first 12 years I was on it. However, after hitting "poop out", my entire last 3 years has been the most difficult experience I have ever faced. I am left with severe nerve pain after a 2½-year taper. (Ex-user)

Although almost all of the comments were about individual antidepressant experiences, a variety of issues were explored by respondents under this general umbrella. For this analysis, six themes were identified: 1) the effects of antidepressants; 2) antidepressant withdrawal; 3) issues with medical authorities; 4) regret; 5) the role of the internet; and 6) comments on the survey itself. Some of these themes incorporated several sub-themes.

The effects of antidepressants

Most of the comments dealt with some aspect of antidepressant effectiveness or problems perceived as a result of antidepressant use. 16 participants (5%)[35] commented on the helpfulness of their antidepressant in an unqualified way:

> They did make a vital difference when the walls were essentially closing in on me and I was severely clinically depressed. (Ex-user)
>
> I used to stress about this but now take things in my stride. I feel able to continue working and enjoy my work. (Current user)
>
> My thinking is steady and the previous cloud has lifted. It doesn't make life easier…but I am able to handle the feelings and emotions… If it weren't for my pills I don't know where I would be now. (Current user)

However, the majority of participants who reported positively about their antidepressant use also included a significant "but":

> Paroxetine increases confidence and feeling of contentment. Decreases creativity, motivation and general energy level. Emotions are blunted,

[35] Of participants who left a comment; all percentages given in this chapter are of those who left comments, not of the survey group as a whole.

> unable to feel excited or passionate about anything. (Currently withdrawing)
>
> Antidepressants certainly stopped my panic attacks and depression, but this came at a cost. Weight gain, emotional blunting, and fatigue. Functioning well, but feeling nothing. Trying to get off has been a nightmare. (Currently withdrawing)
>
> I was able to be more social at first and landed my husband at 25 (I'd probably still be a virgin if not) but it was almost as bad as doing a real drug substance. I lost my academic and career goals, my artistic talents… (Current user)
>
> I felt like my depression and mood was getting better whilst taking antidepressants, and it was. However, it became very hard to show empathy. I severed relationships…became more selfish… (Currently withdrawing)

Many participants went on to itemize a variety of difficulties and unpleasant symptoms they experienced as a result of antidepressant use, both short-term and long-term:

> Citalopram has made me very anxious and restless, cannot concentrate, have developed insomnia, caused me to fall quite behind in uni work. (Current user)
>
> I was not too bad in the beginning but it pooped out. Was so ill, plus think it was poisoning me. Liver gave out, eyesight went, stomach bleed, cysts of ovaries, Parkinsonism. I became a different person for the 18 years I was on them…. (Ex-user)
>
> While I was on Paxil for 4 months, I gained 50 pounds and I haven't been able to loose this weight even though I switched medications. (Current user)

Four participants (1%) recounted details of severe adverse reactions after brief exposure, treated by increased doses or additional drugs.

> I was WAY better off before taking any meds. One dose of an SSRI caused SEVERE, INTRACTABLE, CHRONIC insomnia, horrific electric-shocks in my head and heart, nightmares, a complete loss of thirst and appetite, shaking and tremors. On multiple doctors' advice, was poly-drugged with more ADs, benzos, and anti-psychs which created non-stop anxiety, massive weight loss, and a host of other symptoms like severe allergies, hypersensitivities and suicidal ideation. (Ex-user)

Several participants reported experience with a variety of antidepressants and identified how their responses changed with subsequent prescriptions, how they reacted differently to different drugs, and reported that generic versions of a drug do not necessarily elicit the same response as a brand-name drug. The use of sequential or multiple drugs was a fairly common sub-theme with two predictable outcomes: either acceptable medication was found by this trial and error method, or nothing seemed to provide satisfaction.

> Although my most recent antidepressant prescription was for bupropion, I was previously placed on various serotonergic antidepressants. These included mirtazepine, trazodone, nortriptyline, sertraline, fluvoxamine and fluoxetine. The SSRIs all induced a semi-psychotic state (paranoia, delusions, auditory hallucinations) while the other antidepressants had a "distant/dissociative" sort of feel to them, which caused me to drop every single one immediately after the effects set in. (Currently withdrawing)

> I have been on antidepressants since I was 18 years old. Hated the tricyclics for somnolence and weight gain, Prozac for the tremor, citalopram stopped working; so far venlafaxine is very good. (Current user)

> "Since Aropax [paroxetine] isn't funded anymore, I tried the generic brand Loxamine but found it gave me headaches. (Current user)

An unsuccessful sequence of drugs prompted one responder to query the fundamental assumption of biomedical causation and belief that a chemical cure can be found if one only tries hard enough:

> I have been on almost every medication over a 22 year period, including Prozac, Welbutrin, Celexa, Buspar, Paxil, Lexapro, Zoloft, Cymbalta and many others. I was told I had been prescribed all available medication. Yet I still was depressed… EXACTLY what is MEDICALLY wrong with me if NO DRUGS are working? (Currently withdrawing)

These examples also highlight one of the subsidiary issues—by that I mean issues not directly addressed by participants in the comments but revealed by them: long-term use of antidepressants and the use of sequential medication.

An overall impression is that these are factors that influence participants' understanding of the antidepressant use process, affecting attitudes and decisions, and resulting in particular physical responses to the drugs. For example, reference to "poop out"—the drugs ceasing to work without increased dosage as in the extract above—implies a long-term use effect which may lead to a decision to increase the dose, withdraw from a now-not-working drug, or try a different drug. Behind this is a fundamental belief that depression will be cured (resolved) if the right medicine can be found. Although recent studies suggest that long-term use is more likely to be detrimental than helpful (see Chapter 3), little awareness of this is revealed in comments, except in a vague way.

> I was told that I would have to take Paxil for the rest of my life and after almost 10 years have had enough. Quit cold turkey and suffering the side effects is worth it. (Currently withdrawing)

Antidepressant withdrawal

Although many issues were raised in the comments, withdrawal was the most commonly-addressed topic in all experienced groups, with 43% of current users' comments about attempts to withdraw or concerns about quitting, 73% of comments from those withdrawing adding additional information about their personal withdrawal experience, and 59% of ex-users' comments addressing withdrawal issues in their responses. Although my initial instinct was to incorporate this theme under the theme "effects of antidepressants", I decided to give it a classification in its own right, given it is a particular focus area of this study and a primary focus of so many participant responses.

It is difficult to clearly identify and count participants for whom the withdrawal experience has been minor because many participants understandably did not elaborate in their comments about what they did not experience. A few, however, did comment:

> My withdrawals were not as extreme as I thought they were going to be. I researched a lot before I stopped taking them. I was prepared for the worst and sailed through VERY slowly with only minor effects! (Currently withdrawing)

A change of circumstances changed the withdrawal experience dramatically for one participant:

> Withdrawal was horrible. No warning. First time CT'd and lasted a week before the horror came on suddenly. Second time I made sure I was overseas staying with good friends and doing new stuff that made me happy and it was a doddle. (Ex-user)

The rest ranged from brief summaries:

> Coming off venlafaxine sucks (Current user)

To itemized lists of withdrawal symptoms:

> Cold chills at times, difficulty concentrating, social discomfort, numb hands at times, internal vibrations, sleep apnoea… (Ex-user)

> It was 8 weeks of vomiting, crying, headaches and the worst nightmares imaginable. I thought I would never survive it. (Ex-user)

> As I was on a "considered low dose", the physician said I could just stop the Zoloft. Within 48 to 72 hours, I had severe abdominal symptoms (pain, nausea, and vomiting), became very dehydrated, and ended up in hospital for 24 hours for pain control… Abdominal scans were negative. (Ex-user)

> Those initial three weeks…were, by a large margin, the worse days of my life… I considered suicide every day and for a large part of the day. I was extremely depressed. I could barely eat anything. I had severe acid reflux, hallucinations (both visual and auditory), akathisia, horrendous mental fog (I would often forget mid-sentence what I was talking about), I was exceptionally sensitive to stimuli, light, perfumes. I couldn't even watch television due to rapid movements. I had dizziness, extreme balance issues, I couldn't walk up a flight of stairs… (Ex-user)

In their responses, many participants gave reasons for discontinuing their antidepressant, which included problems with side effects, lack of efficacy, pregnancy, and seeking an un-medicated self:

> After 40 pounds, lack of emotion, and absolutely no libido, I am looking forward to see who I am again after so much time (Currently withdrawing)

> In no time over the past 10-12 years while I've been switched from one so called anti-depressant to the next have I made any tangible progress in my inner battle …not only have they not helped in any meaningful way but also contributed to worsening symptoms. (Currently withdrawing)

> I am 6 weeks pregnant... Now that my hubby and I are having another there was no way I would go through pregnancy taking that sort of medication. The health of our baby is more important. (Currently withdrawing)

Four current users expressed a general fear of quitting, either because of fear of withdrawal effects or fear of a return of pre-drug symptoms (a common theme according to Leydon, Rodgers, and Kendrick [2007]),

> I am frightened to stop (Current user)

> Would like to stop taking Paxil, but also concerned that this might result in recurrences of the anxiety that led me to take it in the first place. (Current user)

but 35 (30% of current users) commented specifically on unsuccessful attempts to quit taking the drugs in the past or on unpleasant and concerning withdrawal symptoms when medication was inadvertently stopped:

> I want to stop. I will go a few days without taking the drug, but it is hard for me to control the withdrawals so I get back on it every time. (Current user)

> I have attempted to come off paroxetine several times without success. The last time I tried was 5 years ago and I was hospitalised… (Current user)

> A recent hospital visit landed me with an extremely inexperienced hospitalist who cancelled my Paxil without me knowing it and I immediately felt the side effects. (Current user)

Many of those currently withdrawing had also made previous attempts to quit

> I have attempted to quit antidepressants more than 10 times in the past 22 years, unsuccessfully. …The physical symptoms are painful and the mental and emotional symptoms are terrifying. The withdrawal caused me to believe that "this is my REAL behaviour…" I quickly went back on them for fear of what might happen. (Currently withdrawing)

Also disturbing is the number of ex-users (29, 42% of those who left a comment[36]) reporting severe withdrawal symptoms months or years after discontinuing their antidepressant.

> After almost six years off antidepressants, I still have lots of withdrawal problems, mainly neurological in the form of rapidly shifting muscle tone problems (from spasms and stiffness throughout the body to extreme weakness) plus the so often reported so-called brain zaps. These symptoms are still severe and very disabling and refuse to go away. Improving by about 5-10 percent per year only. I'd like to mention that I didn't have any of these problems before taking SSRIs. Before the ADs I never had any kind of physical symptoms. (Ex-user)

> It's been 19.5 months and I'm STILL experiencing some pretty bad withdrawal symptoms like tinnitus, tremor, anxiety, akathisia/agitation, occasional depersonalization/derealization, rage, bran zaps, tingling, depression, sensitivity to light and noise, and INTENSE brain fog. It used to actually be worse. (Ex-user)

Participants experiencing long-term withdrawal problems filled out the survey as "ex-users" since "currently withdrawing" was confined to those currently dropping doses or within the two months following drug cessation. It became apparent from comments such as these that the "ex-user" group was hardly a drug-symptom free group and that many participants experienced withdrawal symptoms for much longer than two months following dose cessation, although not all participants in the group reported experiencing long-term lingering effects when taking the survey:

> I am now off 11 months and feel pretty stable. (Ex-user)

[36] This is 34% of total ex-users including those who did not leave a comment

> It took a long time for the withdrawal symptoms to fade. Once off the medication, I believe it was close to a year before I felt none of these effects anymore. (Ex-user)

Issues with medical authorities.

A third theme raised by respondents regarded issues with medical authorities[37]. Many participants wrote of anger and frustration with their doctors and the medical profession in general, citing lack of sufficient or appropriate information about their antidepressant medication prior to being given the prescription:

> I was not told much about the side effects, and I don't think I was told anything about the withdrawal. It took me years to figure out that I needed to take it at the same time every day. (Currently withdrawing)

> I am very angry that I wasn't told that this drug is addictive. (Currently withdrawing)

Others decried the lack of support—indeed, sometimes of belief—when distressed by side effects or withdrawal, and expressed a sense of betrayal that professional advice and ongoing prescribing had led to unanticipated and unwanted long-term problems. Some of this frustration involved compliance issues as discussed earlier in this thesis: pharmaceutical companies and some medical professionals push drug compliance hard, iterating that the underlying disease is the greater problem, not the drug(s) used to treat it, a view that is challenged by many of these experienced users.

> My GP tells me I need to be on medications for life. I truly believe a lot of my prior failed attempts to be AD free were actually severe withdrawal. (Currently withdrawing)

> I became a different person for the 18 years I was on them, always trying to quit and being told withdrawal was something else. I would

[37] See Liebert & Gavey, 2009 for a development of this theme as perceived by medical professionals.

> get another antidepressant to treat it. Have been told I had fibromyalgia, depression, anxiety disorder. I had none of these before ADs, only had leg pain. I believe these drugs caused all these things. (Ex-user)

> There are probably hundreds of thousands of individual reports of AD withdrawal and side-effects on the internet. I've read a small fraction of them, perhaps 10-20,000. They tally with each other, and science, and physiology and pharmacology and p450s and the past history of serotonergic drugs, and half-lives, and dopamine down-regulation, and dependence, and stimulant drugs, and hyper-stimulative states. Unfunnily, doctors still disagree with them. (Ex-user)

> I had multiple serious on-drug side-effects which were ignored, being told it was "the disease and not the drug." The AD doses were upped, and benzos were added for the drug-induced insomnia… (Ex-user)

> My psychiatrist said he had never heard of anyone being so sensitive to the medication and basically accused me of lying or exaggerating. (Currently withdrawing)

Lack of awareness on the part of doctors, according to one participant, can be compounded by lack of awareness in the patient:

> The thing is, you are too subsumed and destroyed by the adverse effects TO BE ABLE TO RECOGNISE WHAT IS HAPPENING TO YOU. That's a key point of which doctors are still unaware. Their patient may be so cognitively-crippled by the drug that their body's twitching and rattling, lethargy, eyesight changes, skeletal pain, etc. simply doesn't REGISTER. …Doctors MUST know the true side-effects profile and be able to competently work though each of the standard categories of side-effects with their patients. This is most emphatically NOT HAPPENING. (Ex-user)

In a similar vein, another participant expressed concern that drug impairment affects patient-doctor communication:

> Due to the fact the drugs can affect cognition in a negative way it becomes difficult to get the understanding of the medical community… Many of my doctor's appointments may have gone differently had I been able to properly communicate what was happening. That doctors regularly refused to help me when I reported akathesia nearly cost me my life. (Ex-user)

Several participants indicated a concern that antidepressants are over-prescribed:

> It seems like you just have to say you are "sad" to be put on a pill. (Current user)
>
> When my doctor prescribed me antidepressants and I was reluctant, she said she was prescribing about 10 of her patients a day with them. I think this is shocking… (Current user)

Many participants advocated more research into antidepressants and their effects, as well as improved education of doctors, nurses and patients regarding drug-related side effects, withdrawal, and long-term risks.

> Gained about 25 pounds since taking Paxil… Quit Paxil slowly over the last 3 weeks…symptoms of zaps, roaring in ears and dizziness with turning head. Absolutely miserable today… I am an RN! They didn't teach us this in school… (Currently withdrawing)
>
> I think there needs to be much more research done on antidepressants and the long term effects they have on not only the brain but on other parts of the body as well. (Ex-user)
>
> Not enough education is given to GPs on the constant side effects and the awful withdrawal symptoms (Current user)

Regret

In their comments, several participants expressed regret over their use of antidepressants:

> If I knew the things I know now when I was first prescribed the meds, I wouldn't have taken them (Currently withdrawing)
>
> I wish I had been given a chance at learning how to live when I was 19 instead of being put on this medication and left on it for 12.5 years. As I try to withdraw for the fourth time, I am finding it very difficult to know who I am or what I stand for. (Currently withdrawing)

Many participants reported being worse off now than before they started taking antidepressants, which they perceived as a burden in their lives. An initial attempt to quantify this general observation was abandoned because of the difficulty in deciding, based on an undirected comment, whether a given participant necessarily felt that way or not, but many examples are explicit:

> I regret ever taking an ssri as now I am addicted to them and they are EXTREMELY difficult to get off of. (Current user)
>
> I cannot get off Effexor. I have tried but the withdrawals are too severe and frightening. I also believe that Effexor has caused my weight gain, body pain, fuzzy thinking, etc. I feel like a prisoner to this medicine. (Current user)
>
> One day I hope to be able to walk away from all this medication and have some normality in my life. (Current user)

Many ex-users expressed regret that their antidepressant drug use had damaged their lives, leaving them in a sort of limbo:

> I took Paxil for an anxiety condition but was happy with other aspects of my life. I worked, had a good social life and was generally happy. I never felt that the pills helped, but every time I stopped I felt worse. I thought and was told that this was my original condition worsening. I believe it now to have been caused by the meds themselves. I now have much more severe mental problems that I didn't have before as a direct result of taking these pills. I can no longer work, rarely socialise or leave the house and feel these pills have destroyed my life due to the effects that they have had on my body and mind. (Ex-user)
>
> It's really hard to find my place in the world again. Who am I? What are my goals in life? I feel like a totally different person compared with pre-and during Paxil…the meds make you stand still, no emotional development, not learning to live with your problems… (Ex-user)
>
> I feel effexor has ruined my health. (Ex-user)
>
> I feel considerably diminished physically and mentally. All in all, medication made me worse. (Ex-user)
>
> I now have amnesia, the beginnings of tardive dyskinesia, severe hair loss, severe acne, trouble with balance, trouble with eyesight, loss of imagination and creativity… I have lost many friends, have alienated my family, lost my apartment and job… I feel very strongly that these drugs do not belong on the market. (ex-user)

Only one person expressed regret about not being prescribed antidepressants earlier, and implied possible support for paediatric prescribing:

> I would have liked to have been prescribed it years earlier. Children at school should be taught to be mindful of depressive symptoms before they lose insight into their condition. (Ex-user)

The role of the internet

This survey was only available on-line, so it is not surprising that many participants appeared to be savvy users of the internet. Lacking satisfactory information from their medical advisors, many accessed information and found support from internet sources, in some cases acting on that information. Others simply advocated the internet as an accessible and appropriate source of information about antidepressants that they felt was superior to standard medical advice. No one expressed concerns about inappropriate advice retrieved from the internet.

> I have spent a fortune on tests and doctors trying to find out what's wrong with me and I had to find out on the net through paxilprogress and drugs.com that my symptoms are common on SSRIs and in withdrawal…so I decided to wean off the drug after reading info on both those sites. (Currently withdrawing)

> A few hours internet searching can provide families/partners with answers to their loved one's deterioration/death/emotional blunting/ twitching/anger/mania/shopping sprees/ insomnia/obesity etc., nearly all of which will be subsequently denied by their doctors. (Ex-user)

Comments on the survey itself

Some participants expressed thanks for the survey, expressing a hope that results might find their way to medical authorities.

> The dependence is awful and very few members of the medical community are aware of this important and vital fact. It's just scandalous. Thank you for participating in spreading this vital information. (Ex-user)

Others found doing the survey itself therapeutic.

> Thank you for letting me voice my thoughts and feelings. (Current user)

> Good survey! I work in mental health myself and found these useful questions. (Current user)

Subsidiary issues and the "never used" group

There were two other subsidiary issues (besides long-term and sequential use discussed earlier) raised by participants in their comments. Although participants were not asked at what age they began taking antidepressants, several reported being recipients of paediatric prescriptions.

> My experience with harmful, addictive drugs goes back to age 10½ (I will be 58 this month) when my mother took me to a doctor who gave her a prescription for me for amphetamines… (Ex-user)

> I was 13 when I first went on antidepressants, and I'm 22 now, so maybe worth bearing in mind that during the 8 plus years I used them I was also going through extreme hormonal changes related to puberty. (Ex-user)

> My parents put me on anti-depressants at age 11. I took lots of different ones. Many made me very queasy and dizzy. I stopped at about age 20, when I saw a psychologist instead of a psychiatrist. I haven't been depressed for years. I believe I probably never was. (Ex-user)

Children and adolescents are particularly vulnerable patients because their prescribed drug use is involuntary, based on decisions made by their parents and doctors. As discussed in Chapter 3, only one antidepressant is approved for paediatric use in the U.S. (fluoxetine), none are approved for use in New Zealand, and virtually nothing is known about the long-term consequences of antidepressant use in maturing bodies.

Suicidality is the second subsidiary issue, of interest because of the controversy over attribution of underlying disease or drugs as the inciting cause. Antidepressant-induced suicidality was the primary focus of only one participant's comments, but suicidality was mentioned by several participants:

> Recently, one night while I had drank over 12 beers, I tried to commit suicide by taking a lot of Tylenal. I have never had suicidal thoughts, nor had I ever tried to commit suicide before, and I truly believe it was because my Paxil had been increased to 30 mg. (Current user)
>
> I have attempted to come off paroxetine several time without success. The last time I tried was 5 years ago and I was hospitalised for 4 weeks due to being extremely suicidal. This was so unusual for me… (Current user)
>
> Fluoxetine tended to make me feel numb, unable to cry, and suicidal. (Current user)
>
> Those initial three weeks…were, by a large margin, the worse days of my life… I considered suicide every day and for a large part of the day[38]. (Ex-user, describing withdrawal experience)

None of the participant groups showed a significantly greater level of suicidality than any other in the quantitative section of this study, but there is evidence in the comments that several participants had suicidal experiences that they believed were antidepressant-related either as a result of drug use, or during drug withdrawal at some point in the past.

There were just 10 comments from the never-used group. Most justified why antidepressants hadn't been tried, some were observational of others' experiences, and they ranged from the philosophical to the practical, sometimes in a single comment:

> Several years ago I was having difficulty with my life and was recommended to see a social worker about my mental health. It was suggested that I try antidepressants. I declined, and my situation gradually improved through other means. (Never used)
>
> I've seen quite a few friends go through times of taking antidepressants, and also had a friend who was clinically depressed and suicidal. All she got out of the help she received was a dependency on pills. NO THANKS. (Never used)
>
> Friends I have known on them solve initial problems…but don't resolve the issues. If stressed or getting low, I escape by going fishing. (Never used)

[38] See extended comment, p. 94, for other withdrawal symptoms reported by this participant

The concept of the antidepressant experience being a journey of sorts makes sense in the context of the comments. Some incident or problem in a person's life leads to an antidepressant prescription, embarking that person upon a journey through drug use that may then lead to a withdrawal and post-drug experience and at any given point within this journey results in increased awareness, a change of perspective, or some other transformational change (physical, mental, and/or emotional).

> Nobody knows what is happening, how long it will last and how it will affect you. It is this uncertainty and lack of knowledge by the medical profession which makes this journey as difficult as it can be. (Ex-user)
>
> For me, anti-depressants were a part of learning to cope… (Ex-user)
>
> If I knew the things I know now when I was first prescribed the meds, I wouldn't have taken them. (Currently withdrawing)

Several participants sent me personal emails wanting to know where they could find out more about the antidepressant they were taking or asking for advice regarding withdrawal. I replied briefly, directing them—apropos to their query—to official medication information posted on pharmaceutical websites, relevant books and research papers, and www.paxilprogress.org, and suggested they consult their doctor.

Chapter 9

Discussion, Conclusions and Future Directions

This is a subjective study of self-selected participants, based on the personal responses of 465 individuals with antidepressant experience, and 44 individuals with no personal experience of antidepressant use but perhaps some awareness or observation of others' experiences (as noted in their comments). Each participant will have approached the survey differently, a reflection not only of their own antidepressant experience, but also their interpretation of that experience within the context of their lives at the time they were taking the drug(s) and the time they were taking the survey. A statistical analysis of their survey responses allows us to give some sort of operational validity to the sum total of those responses—enough to make broad empirical observations about the groups—but it is, of course, subject to the limitations of the survey design and questions and influenced by researcher decisions regarding data analysis. These "empirical" responses are supported by the thematic analysis of comments, which is even more subjective: not only have participants been given free rein to comment in any way about their experience—or any other topic for that matter—but my interpretation and analysis has allowed me to subjectively pick and choose what I think are key themes and representative or useful examples, omitting others for a myriad of reasons (e.g., tangential issue, only one example to support it, example too long or too complicated, etc.)

And of course these participant groups are not "clean"—there are a host of concurrent medications, the effect of which has not been factored into responses

and, indeed, cannot easily be factored in given their sporadic use and inherent variety. Furthermore, antidepressants are mood modifiers, but so is life in all its messy glory: relationships begin, end, and change; jobs come and go; people are born and die; economic situations alter; seasons come and go. We all make decisions and have to live with the consequences. All of these affect moods and are part of the human condition; each participant has responses affected and compromised by these life factors which may carry more weight than the effects of the antidepressants themselves. Never-the-less, as far as I am aware, this study is unique because it presents a valuable portrait of those most affected by antidepressant use, as opposed to the more familiar treatises by medical practitioners, reports from short-term clinical trials, and analyses of broad statistical trends. There is huge inherent value in understanding what the end-user thinks.

A brief summary of the results

When antidepressant users, those withdrawing from their drug(s), ex-users, and never-used participants were asked about their attitudes towards antidepressants, those currently taking them were the most enthusiastic about antidepressants in general, and about their personal use, calling them “helpful” (median response). Those withdrawing and non-users were less enthusiastic (“a bit helpful,” median response), and ex-users were quite negative, calling them “harmful” (median response). To some extent, these are not surprising results. It seems logical that participants currently taking antidepressants are likely to find them useful—one would think that if they did not, they would quit taking them (withdrawal issues aside)—and those who did not find them useful, or who found

the side effects draining, are most likely to have ceased their use. However, when it comes to self-rated mood on the WHO well-being index, users, those withdrawing, and ex-users all fell below the "13" demarcation line suggesting depression risk (based on mean responses). Only the never-used group sat comfortably above the 13 at a mean of 15, although ex-users who did not report a prolonged withdrawal reaction squeaked over the critical 13 with a mean of 13.21.

Whether or not the majority of the participants in treatment groups would have had a mean below 13 prior to treatment—and we have no way of knowing that, but given that these individuals chose to be treated with antidepressants, it is not an unreasonable supposition—it is clear that neither treatment, withdrawal from treatment, nor the post-treatment phase overall were adequate interventions to provide an elevation of well-being to a "normal" level, or depression remission. In spite of this, when participants were asked if they feel better off now than in a previous state (the "that was then, this is now" section of survey questions), users reported themselves better than before they went on the drugs, and ex-users reported themselves, in general, better than when they were on the drugs and similar to their pre-drug state. Not surprisingly, participants experiencing withdrawal reported feeling worse than when they were on the antidepressants.

It is also not surprising that the well-being levels of the three "experienced" groups is low considering the bevy of unpleasant side effects they report suffering from: increased nervousness, agitation, tremor, twitching, chest pain, nausea, food and/or chemical sensitivity, weakness, dizziness, fatigue, need for extra sleep, sweating, headaches, head or face pain, brain zaps, vision abnormalities, disturbing dreams, emotional flatness, panic attacks, impaired judgement, and decreased libido. Furthermore, many users identified large weight

gains of 40, 50, even 60 pounds in their comments, often over relatively short periods of time. This seems extraordinary: the mean frequency and severity in all three experienced groups reported for every single one of these symptoms is higher than in the control group of non-users.

One possible explanation for the seeming paradox of participants' positive assessment of antidepressant value in spite of low levels of well-being and assorted side effects is suggested by Breggin (2006). Intoxication anosognosia or "medication spellbinding" can be induced by a variety of drugs, causing users to overestimate the value of the drug and underestimate or fail to recognize drug-induced impairment. Alcohol users, for example, often overestimate their own social charm or ability to drive when drinking, but at least we are all aware that alcohol has an intoxicating effect. In the case of antidepressants, according to Breggin, intoxication anosognosia generally develops over a period of time (if it develops at all) and it is unanticipated—after all, the drugs have been approved by the government and prescribed by a doctor for a given condition and thus surely must be helping. Patients can overestimate drug benefits while underestimating or failing to perceive iatrogenic effects.

. It is important to remember that this survey data was not collected by random sampling. Participants self-selected to participate, and some may have done so because of an overall dissatisfaction with their antidepressant experience, although as noted earlier, Moncrieff et al. (2009) found no statistical difference between self-selected reporting of adverse drug effects and reports obtained by more traditional means. Nevertheless, it seems fairly clear from these results that antidepressant use does not create or restore normal well-being levels, which may be compromised by iatrogenic side effects.

The comments left by participants in general made for grim reading. Although a few spoke well of their antidepressant experience, the majority reported problems with dependency, side effects, unhelpful health professionals, and long-term struggles with medication use and a variety of affective disorders. Although official guidelines suggest that antidepressant withdrawal symptoms are generally "mild" and resolve "spontaneously between day 1 and 3 weeks after onset" (Haddad & Anderson, 2007), comments from this study's participants suggest many weeks or months often elapse before cessation of withdrawal symptoms, a process that may be extended further if a long taper is required. The post-drug impairments reported by many ex-users, in some cases years after drug cessation, highlights an important issue that has yet to be explored by researchers, other than emerging awareness of the sometimes-lingering nature of sexual dysfunction as identified by Bahrick and Harris (2009) and Csoka and Shipko (2006). Many of the long-term impairments reported by ex-users in their comments were of a neurological nature, and heightened sensitivity to stress and stimulation were commonly reported by those who had been off antidepressants for over a year. Fewer comments were made about social fallout, another theme deserving of attention in future research, but some reported on the negative impact of their antidepressant use, and subsequent withdrawal, on jobs, school performance, or relationships with family and friends. Positive comments about increased social functioning while taking the drugs were rarer still, and often involved some sort of compromise, such as creativity traded off for responsible functionality.

Contrary to expectations, given its relatively high-profile prevalence as a controversy in the media, suicidality did not present as a significant issue or

symptom in any of the groups examined quantitatively except when ex-users were split between those reporting prolonged withdrawal symptoms in their comments and those who did not. Only one participant made suicidality a primary focus in the comments, but several participants in the drug-experienced groups commented in passing on suicidality experienced in the past that they attributed to antidepressant use or withdrawal. It seems probable that individuals currently experiencing an episode of suicidality would not consider participating in a voluntary on-line survey on antidepressant use an activity of high priority, and in the quantitative section of the survey, participants were asked only about symptoms experienced within the past two weeks. However, the significant reporting of suicidality among the subgroup of ex-users experiencing a prolonged withdrawal experience highlights a point often missed when assessing the link between antidepressant use and suicidality: even a significant time after complete discontinuation of the drug, some ex-users may remain at risk. What is unknown from this data is whether these individuals were at risk of suicide prior to drug prescription, but if not, lingering drug after-effects may be missed by medical professionals and coroners in any analysis of cause of suicide attempt or death.

Answering the research questions and addressing hypotheses:

The first proposed hypothesis, that there would be some significant differences between the four subject groups in terms of mood, symptoms, behaviours has been supported by this study's findings. As anticipated, the currently-withdrawing group reported experiencing the greatest health challenges with a significantly higher level of the mood factor agitation than the other three groups, and the highest level of symptom frequency and severity for most of the

symptoms addressed when compared with the other groups. The never-used group, by contrast, had the lowest symptom severity of the four groups and scored the lowest on the agitation mood factor.

Also as hypothesized, current users were the most favourably disposed to their antidepressants, considering them, in general, “helpful”. Nevertheless, symptoms such as decreased libido, weight gain, fatigue and insomnia were commonly reported both under symptoms and in their comments, and concern over dependency and an inability to discontinue the drug reported in their comments suggest their enthusiasm is tempered by these concerns. The overall WHO-5 score for this group suggests their depression symptoms had not been ameliorated by antidepressant use, although we cannot speculate on how much worse they might have been if the medication had not been prescribed from this data. Nervousness and agitation symptoms were significantly lower for users than for those withdrawing, and significantly higher than levels reported by the never-used group, but about the same as that reported by ex-users.

The third proposed hypothesis, that some ex-users would still be experiencing effects from antidepressant use months after drug cessation was strongly supported by participant comments, although the qualitative data cannot be used to definitively prove a causal link; ultimately, teasing out the difference between the diagnosed illness, drug side effects, and withdrawal symptoms to determine causation based on a one-point-in-time data collection is inherently impossible. Never-the-less, the possibility that antidepressant drug use causes long-term health issues cannot be dismissed.

My fourth hypothesis predicted particular items of note including suicidality, weight changes, and emotional flattening. Although the group of ex-

users still reporting withdrawal symptoms showed a significantly higher level of suicidality than ex-users not reporting ongoing symptoms, there was no difference found between the four main survey groups on symptoms of suicidality, and none between drug-experienced groups on emotional flattening or weight gain, although the never-used group reported significantly less weight gain and emotional flattening than the experienced groups. No group reported significant weight loss. In short, results from these specific factors did not stand out in this study.

Coming back to the specific research questions posed in this thesis, the first one was the obvious: do antidepressant users find the drugs helpful? Based upon users' evaluations of drug effectiveness and their responses to the "now" (on antidepressants)" compared to "then" (before antidepressants) response, it seems fairly clear that the majority of users believe the drugs are helpful. Nevertheless, many of these users expressed concern over unwanted side effects, dependency issues, and long-term efficacy (poop out), and in terms of WHO-5 well-being results, this group as a whole is at risk of depression, so overall, a qualified "no". It would appear the drugs do little to enhance the quality of life. Indeed, many participants in all groups expressed regret over their drug use.

Withdrawal appears to be a significant issue to participants in all groups. The likely occurrence of severe or prolonged withdrawal symptoms is difficult to ascertain from this data, however. Many of the current users expressed experience with and concern about withdrawal in their comments: many of them are individuals who have thus far been unable to discontinue the drugs in spite of one or more attempts due to a severe withdrawal reaction. Many of those actively withdrawing hinted in their comments that they weren't sure they would succeed in quitting the drug this time, having not succeeded with previous attempts. Of

those ex-users who had succeeded in withdrawing from antidepressants, 34% were still experiencing fallout from their antidepressant experience months or years after their final dose, and in some cases symptoms were still life-invasive years after use. Although no actual figures can be gleaned from this, it seems clear from this data set at least that dependency is a greater problem than has been hitherto acknowledged in the literature, and there is a significant long-term post-withdrawal impact for some users that so far no one has examined in any depth.

Does antidepressant use alter perception of the value and effectiveness of the drugs? The specific questions about perceived value of the drugs and comments made at the end of the survey make it clear that those currently using the drugs have a more positive assessment of their value than those who no longer use them or those who have never used them. Those who are withdrawing from the drugs are less enthusiastic than users, and ex-users in general expressed a belief that any value the drugs may have is compromised by the discomfort of side effects and risk of dependency. Drug use and withdrawal, in other words, significantly eroded the perceived value of the medication.

Future directions

Further opportunities for psychological and social researchers to examine the impact of antidepressant drug use on individuals and social groups should be apparent. This study did not examine, for example, the social fallout that may come with personality changes brought on by the medication or withdrawal from it. In his book, Whitaker (2010) suggests antidepressant use has lead to the current bipolar boom and a worsening of the bipolar disorder with increased rapid cycling. The role of antidepressants in cases of violence and suicide has been examined in

a few papers (e.g., Breggin, 2003/2004, 2004) but little attention has been paid to the withdrawal and post-drug phase when iatrogenic akathesia and hypomanic states might also elicit violent or self-harm behaviours, or socially-inappropriate activities that is not so readily attributable to antidepressant use. The fundamental assumption that inappropriate thoughts or behaviours post-drug, even if those thoughts or behaviours did not exist pre-drug, indicate a need for continued drug treatment and support drug effectiveness remains to be critically examined in this light.

Another area ripe for future research involves looking at useful strategies for assisting those undertaking antidepressant withdrawal. It is generally assumed, for example, that a slow taper is better and safer than abrupt withdrawal, although a long taper may extend the withdrawal process much like pulling a sticky band-aid off slowly extends but—presumably—lessens the overall pain experience at any given time. A very quick check of data from this survey suggested no correlation between length of taper and frequency/severity of symptoms experienced, which is to be expected since health professionals and pharmaceutical manufacturers recommend resuming the original dose if withdrawal symptoms become unmanageable and a slower taper commenced if desired (Glenmullen, 2005; Lilly, 2006)—thus, it is often the severest withdrawal response that mandates the slowest taper to keep symptoms manageable[39]. It seems likely (but is untested here) that patients quit or taper as quickly as they can comfortably handle. Given the limited supervision inherent with outpatient withdrawal, a prolonged tapering makes sense if withdrawal symptoms are severe, but illicit drugs—notorious for difficult withdrawal--are often discontinued much

[39] And it seems unlikely that patients in the midst of an unmanageable withdrawal experience would volunteer to sit down at a computer and spend twenty minutes filling in a survey.

more quickly within a rehabilitation care facility, an option that is rarely if ever considered with antidepressant withdrawal. It would be interesting to examine longitudinally symptom severity, recovery rates and long-term residual symptoms in patients from the onset of the withdrawal process (initial drop, large or small, abrupt stop or gradual taper) to final resolution of drug and withdrawal symptoms.

There is also opportunity for an examination of other withdrawal support mechanisms that have been tried and perhaps found useful: changes with diet and exercise, vitamin and health supplements, meditation, acupuncture, counselling, and similar. A closer examination of those individuals experiencing a prolonged withdrawal experience or what they believe is long-term iatrogenic antidepressant disablement through interviews would help to expand the almost non-existent literature on this issue that is just now coming into public awareness.

The marginal efficacy of antidepressants and high placebo rate in clinical trials has only been acknowledged in the research literature in the past two or three years. This coupled with a growing awareness of side effects that may affect not only mood and emotions but physical functioning and social interactions, often in negative ways, along with a risk of long-term post-drug consequences, might be reason enough to make prescribers hesitate when considering the appropriateness of antidepressant treatment for a patient. The significant issues with addiction and dependency, and the very real possibility of long-term disablement as described by many of the ex-users in this study, suggest the German regulators may have been right all along. Perhaps these preparations truly are “totally unsuitable for the treatment of depression.” (internal Eli Lilly communication reported in Healy, 2004, p. 39, as mentioned earlier in this thesis).

In a very practical way, physicians today need to exercise caution when prescribing antidepressants, alerting patients to possible side effects and dependency issues, and finding ways to educate, understand and assist their patients in discontinuing the drugs should they wish to do so. Psychiatric prescribers in particular, concerned primarily with the mental health of patients, must recognize the effects these pharmaceuticals can exert on patients' physical health, and the impact compromised physical health can have on mental well-being. Our society places great emphasis on treatment and rehabilitation for individuals who are addicted to illegal drugs, alcohol, or tobacco but provides little education or support for those addicted to prescription medicines, even when those medicines are damaging to overall health and well-being.

Conclusions

"Psychiatry, for me and many of my colleagues," wrote Daniel Carlat (2010), "has become a process of corralling patients' symptoms into labels and finding a drug to match," a process that highlights "a glaring deficiency in much of modern psychiatry." We live in a world where, when problems occur, we want them fixed, and we want them fixed as quickly and as cheaply and as effortlessly as possible. The medicalization of depression and other affective disorders has been the economic response to this natural and seemingly pragmatic desire. Pharmaceutical companies can hardly be blamed for recognizing the economic goldmine that a one-pill-fits-all[40] antidepressant creates for themselves and their shareholders. After all, who wants to be depressed? And an ANTI-depressant (and

[40] Patients, diagnoses, and prescribers

the power of that prefix on our consciousness cannot be underestimated) seems a perfect fix. Unfortunately, this goldmine is also a landmine, for the collateral damage that comes from an attempt to hit the depression [anxiety/OCD/panic] button with a marginally-effective chemical agent may well cause more harm for the overall organism and community than can be gleaned in patient benefit.

Understanding the history, development, and promotion of assorted mental illnesses and their treatment with antidepressants and other mood-changing drugs provides a solid foundation for recognizing the powerful appeal of these drugs and their role in modern society. The reality, however, is less stellar than the vision, and the quick (and probably ineffective) fix for each user comes with the substantial risk of unpleasant side effects and dependency, and a potential for residual post-drug fallout.

Appendix A: Online Survey Used in this Study

The online survey used in this study is reproduced below. An attempt to copy and paste from the www.surveymonkey.com website has altered the format somewhat: what appears on a computer screen does not easily fit on an A4 page, and Word's automatic mechanism has adjusted text and survey items to fit the page width. In addition, response boxes and circles did not reproduce as full geometric shapes. The survey itself was all on a two-shade "peach sherbet" coloured background which did not pick up and transfer in all cases. However, it was felt that this method of presenting the survey questions in this appendix would more closely approximate the participant experience than recreation of a new reformatted survey with smaller typefaces and altered design specific for an A4 page.

Following the first default page, the survey divided into four separate surveys depending upon participant response on the default page. These four surveys are printed one after the other on the following pages. Introductory questions vary from survey to survey, mood and symptom pages do not vary, and the "that was then, this is now" section likewise varies. All participants were invited to leave comments.

In the symptoms section, each of the drop down boxes offered five choices. For frequency, the five choices were *never, sometimes, often, most of the time,* and *all of the time*. For severity, the five choices were *very minor, mild, moderate (affects daily routine), severe* and *very severe*.

DEFAULT SECTION

1. The surveys that follow are designed to collect comparative data between groups of people currently using antidepressants, people withdrawing from antidepressants, people who used to take antidepressants but who don't take them anymore, and people who have never used antidepressants. Information collected here will be used for a research study conducted at Victoria University of Wellington, New Zealand. The surveys have been approved by the Victoria University of Wellington Ethics Committee. All participation is voluntary and completely anonymous. It will take approximately 20-25 minutes to complete a survey.

If you wish to participate, click on the appropriate button for your survey.

- I am currently taking one or more antidepressants
- I am currently withdrawing from antidepressants, or ceased taking them less than 2 months ago
- I have taken antidepressants in the past, but I do not take them now, and I have not taken them for at least two months
- I have never taken antidepressants or other prescribed psychiatric medication

2. Introductory questions

This survey is for participants who are CURRENTLY taking one or more antidepressants (and not currently in the process of antidepressant withdrawal). If this does not describe you, please use the back browser at the bottom of this page and select another survey.

1. Please indicate your gender

☐ Male ☐ Female

2. My current age is...

☐ Under 20 ☐ 20-39 ☐ 40-59 ☐ 60+

3. Country of residence

4. Antidepressant(s) that you are currently taking and current dose(s)(e.g., Prozac, 20 mg.)

Antidepressant(s)

Dose(s)

5. What other prescription medicines are you currently taking?

6. Why were you prescribed an antidepressant? (If you don't know, please state "don't know".)

7. How long have you been taking antidepressants?

☐ Less than 3 months ☐ 3-12 months ☐ 1-3 years ☐ 3-8 years ☐ More than 8 years

8. Have you changed your antidepressant or dose in the past three months?

☐ No

☐ Yes, dose has gone up

☐ Yes, dose has gone down

☐ Yes, I've changed antidepressants

9. If you've changed antidepressants, what did you used to take?

10. Please tick the appropriate option. There are no right or wrong answers.

	Very helpful	Helpful	a bit helpful	not at all helpful	Harmful	Very harmful
I believe that antidepressants in general are...	☐	☐	☐	☐	☐	☐
For me, the antidepressant(s) I am taking is/are...	☐	☐	☐	☐	☐	☐

3. Mood

1. The following statements deal with mood. Please tick the most appropriate box to match how you have been feeling during the past two weeks regardless of the reason.

	All of the time	Most of the time	Often	Sometimes	Rarely	At no time
I feel cheerful and in good spirits	☐	☐	☐	☐	☐	☐
I feel unusually self-confident	☐	☐	☐	☐	☐	☐
I feel restless	☐	☐	☐	☐	☐	☐
I feel calm and relaxed	☐	☐	☐	☐	☐	☐
I feel anxious	☐	☐	☐	☐	☐	☐
I feel subdued and slowed down	☐	☐	☐	☐	☐	☐
I feel very angry	☐	☐	☐	☐	☐	☐
I feel active and vigorous	☐	☐	☐	☐	☐	☐

	All of the time	Most of the time	Often	Sometimes	Rarely	At no time
I feel that life isn't worth living	☐	☐	☐	☐	☐	☐
I feel sad	☐	☐	☐	☐	☐	☐
I wake up feeling fresh and rested	☐	☐	☐	☐	☐	☐
I feel agitated	☐	☐	☐	☐	☐	☐
I have difficulty concentrating	☐	☐	☐	☐	☐	☐
I feel full of energy	☐	☐	☐	☐	☐	☐
I feel like harming myself	☐	☐	☐	☐	☐	☐
I feel like I want to harm someone else	☐	☐	☐	☐	☐	☐
My life is filled with things that interest me	☐	☐	☐	☐	☐	☐
I feel like my mind is racing	☐	☐	☐	☐	☐	☐
I have mood swings	☐	☐	☐	☐	☐	☐
I feel fantastic	☐	☐	☐	☐	☐	☐
I feel reluctant to leave the house	☐	☐	☐	☐	☐	☐

4. Symptoms

1. Have you experiened any of the following symptoms during the past two weeks (regardless of the reason)? If you have experienced a symptom, please indicate how severe you would rate that symptom. If you don't know what a symptom is (for example "brain zaps"), leave it blank.

	Frequency	Severity
Nervousness		
Agitation		
Tremor		
Twitching		
Uncontrollable or "restless" leg or arm movements		
Chest pain		
Body pain		
Abdominal pain		
Nausea		
Vomiting		
Diarrhoea		
Constipation		
Decreased appetite		
Increased appetite		
Food or chemical sensitivity		
Weakness		
Dizziness		

	Frequency	Severity
Fatigue		
Insomnia		
Increased need for sleep		
Sweating		
Thirst		
Rash		
Headache		
Head or facial pain		
Brain "zaps"		
Blurred or abnormal vision		
Tinnitus (ringing or buzzing in ears)		
Dry mouth		
Disturbing dreams		
Emotional flattening		
Felt suicidal		
Panic attacks		
Impaired judgement		
Urinary or		

	Frequency	Severity
bladder problems		
Increased libido		
Decreased libido		

5. Comparing then and now

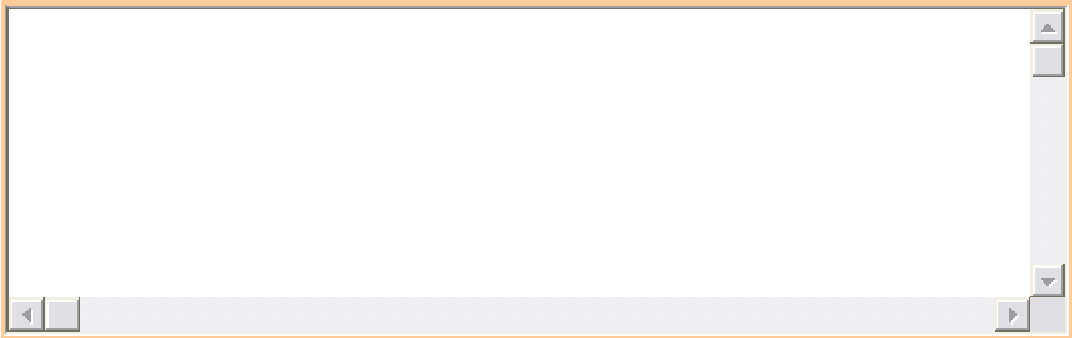
Since being on antidepressants, I have been...

	Much more likely to	More likely to	About the same	Less likely to	Much less likely to
Show affection					
Remember things					
Act impulsively					
Enjoy social events					
Care about others					
Feel good about myself					
Worry about things					
Keep a tidy environment					
Succeed at work or school					
Spend time with my family					
Lose my temper					
Feel depressed					
Feel motivated					
Cry					
Laugh					

	Much more likely to	More likely to	About the same	Less likely to	Much less likely to
Drink alcohol	☐	☐	☐	☐	☐
Be creative	☐	☐	☐	☐	☐
Crave "junk food" or sweets	☐	☐	☐	☐	☐
Think clearly	☐	☐	☐	☐	☐
Have dental problems	☐	☐	☐	☐	☐
Find something positive in a difficult situation	☐	☐	☐	☐	☐
Feel happy	☐	☐	☐	☐	☐
Gamble	☐	☐	☐	☐	☐

6. Comments

1. If there is anything else you would like to add about your antidepressant experience, or about this survey, please share your comments in the box below.



7. Thank you

Thank you very much for your participation in this survey.

If you would like to be notified of any publications utilizing data collected from this survey please send us a separate email (to susan.thrasher@vuw.ac.nz) which cannot be linked to your responses.

If you would like to share more about your antidepressant experience, we'd like to hear from you. Again, feel free to contact us via email at susan.thrasher@vuw.ac.nz

8. Survey 2 Introductory Questions

This survey is for participants who are currently withdrawing from one or more antidepressants, including individuals who ceased taking antidepressants within the last 2 months. If you ceased taking antidepressants more than 2 months ago, even if you are still experiencing withdrawal symptoms, please use the back browser link at the bottom of this page and complete the survey for participants who used to take an antidepressant.

1. Please indicate your gender

☐ Male ☐ Female

2. My current age is...

☐ Under 20 ☐ 20-39 ☐ 40-59 ☐ Over 60

3. Country of residence

4. Antidepressant(s) that you are currently taking (or were taking)and dose(s), e.g. Prozac, was 20 mg, now 5 mg.

Antidepressant(s)

Dose(s)

5. What other prescription medication(s) are your currently taking?

6. Why were you prescribed antidepressants? (If you don't know, please put "don't know".)

7. How long have you been taking antidepressants?

☐ Less than 3 months ☐ 3-12 months ☐ 1-3 years ☐ 3-8 years ☐ More than 8 years

8. How long have you been tapering off the drug(s) or, if you are now at zero, how long did it take you to taper off your drug(s)?

☐ Abrupt discontinuation (cold turkey) ☐ less than 3 months ☐ 3-6 months ☐ 6-12 months ☐ More than a year

9. Is this your first attempt to discontinue taking your antidepressant? If not, how many times have you tried to quit?

☐ This is the first time ☐ I've tried to quit 1-3 times before ☐ I've tried to quit 4+ times before this time

10. Please tick the appropriate box. There are no right or wrong answers.

	Very helpful	Helpful	A bit helpful	Not at all helpful	Harmful	Very harmful
I believe antidepressants in general are...	☐	☐	☐	☐	☐	☐
For me, the antidepressant(s) I am/was taking is(are)...	☐	☐	☐	☐	☐	☐

[Author's note—mood and symptom surveys are identical between groups. See Survey 1.]

11. Survey 2: Comparing Then and Now

1. Compared to when I was taking antidepressants, now that I am withdrawing, I am...

	Much more likely to	More likely to	About the same	Less likely to	Much less likely to
Show affection	☐	☐	☐	☐	☐
Remember things	☐	☐	☐	☐	☐
Act impulsively	☐	☐	☐	☐	☐
Enjoy social events	☐	☐	☐	☐	☐
Care about others	☐	☐	☐	☐	☐
Feel good about myself	☐	☐	☐	☐	☐
Worry about things	☐	☐	☐	☐	☐
Keep a tidy environment	☐	☐	☐	☐	☐
Succeed at work or school	☐	☐	☐	☐	☐

	Much more likely to	More likely to	About the same	Less likely to	Much less likely to
Spend time with my family	☐	☐	☐	☐	☐
Lose my temper	☐	☐	☐	☐	☐
Feel depressed	☐	☐	☐	☐	☐
Feel motivated	☐	☐	☐	☐	☐
Cry	☐	☐	☐	☐	☐
Laugh	☐	☐	☐	☐	☐
Drink alcohol	☐	☐	☐	☐	☐
Be creative	☐	☐	☐	☐	☐
Crave "junk food" or sweets	☐	☐	☐	☐	☐
Think clearly	☐	☐	☐	☐	☐
Have dental problems	☐	☐	☐	☐	☐
Find something positive in a difficult situation	☐	☐	☐	☐	☐
Feel happy	☐	☐	☐	☐	☐
Gamble	☐	☐	☐	☐	☐

[Author's note: The invitation for comments and Thank you page were the same for all groups. See Survey 1.]

14. Survey 3: Introductory Questions

This survey is for participants who used to taken an antidepressant but do not do so now (and haven't taken one for at least 2 months). If you ceased taking an antidepressant less than two months ago, please use the back browser button at the bottom of the page and fill out the survey for "currently withdrawing from antidepressants".

1. What is your gender?

☐ Male ☐ Female

2. What is your age?

☐ Under 20 ☐ 20-39 ☐ 40-59 ☐ 60+

3. What is your country of residence?

4. Antidepressant(s) that you used to take and maximum dose (e.g., Prozac, 20 mg)

Antidepressant(s)

Dose

5. What other prescription medications were you taking when you were taking antidepressants (if any)?

6. What prescription medications are you taking now (if any)?

7. Why were you prescribed antidepressants? (If you don't know, please put "don't know".)

8. How long did you take antidepressants?

☐ Less than 3 months ☐ 3-12 months ☐ 1-3 years ☐ 3-8 years ☐ more than 8 years

9. How long did you spend withdrawing from your antidepressant (reducing doses)?

☐ Abrupt discontinuation (cold turkey) ☐ less than 3 months ☐ 3-6 months ☐ 6-12 months ☐ 1+ years

10. How long ago did you quit taking antidepressants?

☐ Less than a year ago ☐ 1-3 years ago ☐ 3-5 years ago ☐ More than 5 years ago

11. How many times did you attempt to quit taking your antidepressant (including the most recent successful withdrawal)?

☐ Once ☐ 2-4 times ☐ 5+ times

12. Please tick the appropriate answer. There are no right or wrong answers.

	Very helpful	Helpful	A bit helpful	Not at all helpful	Harmful	Very harmful
I believe that antidepressants in general are...	☐	☐	☐	☐	☐	☐
For me, the antidepressant I was taking was...	☐	☐	☐	☐	☐	☐

[Author's note—mood and symptom surveys are identical between groups. See Survey 1.]

17. Survey 3: Then and Now

1. Compared to WHEN I was taking antidepressants, NOW I am...

	Much more likely to	more likely to	About the same	less likely to	Much less likely to
Show affection	☐	☐	☐	☐	☐
Remember things	☐	☐	☐	☐	☐
Act impulsively	☐	☐	☐	☐	☐
Enjoy social events	☐	☐	☐	☐	☐
Care about	☐	☐	☐	☐	☐

	Much more likely to	more likely to	About the same	less likely to	Much less likely to
others					
Feel good about myself	☐	☐	☐	☐	☐
Worry about things	☐	☐	☐	☐	☐
Keep a tidy environment	☐	☐	☐	☐	☐
Succeed at work or school	☐	☐	☐	☐	☐
Spend time with my family	☐	☐	☐	☐	☐
Lose my temper	☐	☐	☐	☐	☐
Feel depressed	☐	☐	☐	☐	☐
Feel motivated	☐	☐	☐	☐	☐
Cry	☐	☐	☐	☐	☐
Laugh	☐	☐	☐	☐	☐
Drink alcohol	☐	☐	☐	☐	☐
Be creative	☐	☐	☐	☐	☐
Crave "junk food" or sweets	☐	☐	☐	☐	☐
Think clearly	☐	☐	☐	☐	☐
Have dental problems	☐	☐	☐	☐	☐
Find something positive in a difficult situation	☐	☐	☐	☐	☐
Feel happy	☐	☐	☐	☐	☐
Gamble	☐	☐	☐	☐	☐

17. Survey 3: Then and Now

1. Compared to BEFORE I was taking antidepressants, NOW I am...

	Much more likely to	more likely to	About the same	less likely to	Much less likely to
Show affection	☐	☐	☐	☐	☐
Remember things	☐	☐	☐	☐	☐
Act impulsively	☐	☐	☐	☐	☐
Enjoy social events	☐	☐	☐	☐	☐
Care about others	☐	☐	☐	☐	☐
Feel good about myself	☐	☐	☐	☐	☐
Worry about things	☐	☐	☐	☐	☐
Keep a tidy environment	☐	☐	☐	☐	☐
Succeed at work or school	☐	☐	☐	☐	☐
Spend time with my family	☐	☐	☐	☐	☐
Lose my temper	☐	☐	☐	☐	☐
Feel depressed	☐	☐	☐	☐	☐
Feel motivated	☐	☐	☐	☐	☐
Cry	☐	☐	☐	☐	☐
Laugh	☐	☐	☐	☐	☐
Drink alcohol	☐	☐	☐	☐	☐
Be creative	☐	☐	☐	☐	☐
Crave "junk food" or sweets	☐	☐	☐	☐	☐
Think clearly	☐	☐	☐	☐	☐
Have dental problems	☐	☐	☐	☐	☐
Find something positive in a difficult situation	☐	☐	☐	☐	☐

Feel happy	☐	☐	☐	☐	☐	
Gamble	☐	☐	☐	☐	☐	

[Author's note: The invitation for comments and thank you page were the same for all groups. See Survey 1.]

!0. Survey 4: Introductory Questions--Never taken an AD

This survey is for participants who have NEVER taken an antidepressant. If you have taken an antidepressant before, please click on the back browser button on the bottom of the page and choose another survey.

1. What is your gender?

☐ Male ☐ Female

2. What is your age?

☐ Under 20 ☐ 20-39 ☐ 40-59 ☐ 60+

3. What is your country of residence?

4. What prescription medications are you currently taking?

5. I believe that antidepressants in general are...

☐ Very helpful ☐ Helpful ☐ A bit helpful ☐ Not at all helpful ☐ Harmful ☐ Very harmful

[Author's note—mood and symptom surveys are identical between groups. See Survey 1.]

1. in the past two weeks, how often have you done the following?

	I've done this every day	I've done this often	I've done this sometimes	I've done this rarely	I haven't done this
Shown affection	☐	☐	☐	☐	☐

	I've done this every day	I've done this often	I've done this sometimes	I've done this rarely	I haven't done this
Forgot things	☐	☐	☐	☐	☐
Acted impulsively	☐	☐	☐	☐	☐
Enjoyed social events	☐	☐	☐	☐	☐
Cared about others	☐	☐	☐	☐	☐
Felt good about yourself	☐	☐	☐	☐	☐
Worried about things	☐	☐	☐	☐	☐
Kept a tidy environment	☐	☐	☐	☐	☐
Succeeded at work or school	☐	☐	☐	☐	☐
Spent time with your family	☐	☐	☐	☐	☐
Lost your temper	☐	☐	☐	☐	☐
Felt depressed	☐	☐	☐	☐	☐
Felt motivated	☐	☐	☐	☐	☐
Cried	☐	☐	☐	☐	☐
Laughed	☐	☐	☐	☐	☐
Drunk alcohol	☐	☐	☐	☐	☐
Been creative	☐	☐	☐	☐	☐
Craved "junk food" or sweets	☐	☐	☐	☐	☐
Thought clearly	☐	☐	☐	☐	☐
Had dental problems	☐	☐	☐	☐	☐
Found something positive in a difficult situation	☐	☐	☐	☐	☐
Felt happy	☐	☐	☐	☐	☐

	I've done this every day	I've done this often	I've done this sometimes	I've done this rarely	I haven't done this
Gambled	☐	☐	☐	☐	☐
felt anxious	☐	☐	☐	☐	☐
Felt irritable	☐	☐	☐	☐	☐
Felt tired	☐	☐	☐	☐	☐

[Author's note: The invitation for comments and thank you page were the same for all groups. See Survey 1.]

References

Ables, A. Z. & Baughman, O. L. (2003). Antidepressants: Update on new agents and indications. *American Family Physician, 67*(3), 547-554. Retrieved from http://www.aafp.org/online/en/home/publications/journals/afp.html

Adli, M., Baethge, Ch., Heinz, A., Langlitz, N., & Bauer, M. (2005). Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed?: A systematic review. *European Archives of Psychiatry and Clinical Neuroscience, 255*(6), 387-400. doi:10.1007/s00406-005-0579-5

Aikins, J. E., Nease, D. E., & Klinkman, M. S. (2008). Explaining patients' beliefs about the necessity and harmfulness of antidepressants. *Annals of Family Medicine, 6*, 23-29. doi:10.1370/afm.759

Akerblad, A. C., Bengtsson, F., Holgersson, M., von Knorring, L., & Ekselius, L. (2008). Identification of primary care patients at risk of nonadherence to antidepressant treatment. *Patient Preference and Adherence, 2*, 379-386. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2770387/pdf/ppa-2-379.pdf

American Psychiatric Association (APA) (2000). *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, Text Revision. Virginia, USA: American Psychiatric Association.

Andersohn, F. Schade, R., Suissa, S., & Garbe, E. (2009). Long-term use of antidepressants and the risk of diabetes mellitus. *American Journal of Psychiatry, 166,* 591-598. doi:10.1176/appi/apj.2008.08071065)

Anderson, I. M. (2000). Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *Journal of Affective Disorders, 58,* 19-36. doi:10.1016/S0165-0327(99)00092-0

Antonuccio, D. (2008). Treating depressed children with antidepressants: More harm than benefit? *Journal of Clinical Psychological Medical Settings, 15*, 92-97. doi:10.1007/s10880-008-9108-9.

Ashcroft, G. & Healy, D. (2000). The receptor enters psychiatry. In *The Psychopharmachologists III: Interviews by David Healy* (pp. 189-200). London: Arnold.

AstraZenica Pharmaceuticals. (2010). Seroquel XR for major depressive disorders. Retrieved from http://www.seroquelxr.com/major-depressive-disorder/index.aspx?ux=m

Bahrick, A. S. & Harris, M. M. (2009). Sexual side effects of antidepressant medications: An informed consent accountability gap. *Journal of*

Contemporary Psychotherapy, 39(2), 135-143. doi:10.1007/210879-008-9094-0

Baldwin, D. S. & Kosky, N. (2008). Off-label prescribing in psychiatric practice. *Advances in Psychiatric Treatment, 13,* 414-422. doi:10.1192/apt.bp.107.004184

Bauer, M., & Döpfmer, B. M. (1999). Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *Journal of Clinical Psychopharmacology, 19*(5), 427-434. Retrieved from http://journals.lww.com/psychopharmacology/pages/default.aspx

Bech, P., Rasmussen, N. A., Olsen, R., Noerholm, V. & Abildgaard, W. (2001). The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *Journal of Affective Disorders, 66*(2-3), 159-164. doi:10.1016/S0165-0327(00)00309-8

Bennett, S. (1992). Shame, stigma and mental illness in ancient Greece. *Stigma and Mental Illness* (eds. Fink, P. J. & Tasman, A.) Washington D.C.: American Psychiatric Press.

Birnbaum, H., Ben-Hamadi, R., Kelley, D., Hsieh, M., Seal, B., Cremieux, P. et al. (2009). Assessing the relationship between compliance with antidepressant therapy and costs among employees in the United States. *European Psychiatry, 24,* Supplement 1, S498. doi:10.1016/SO924-9338(09)70731-X

Bogner, H.R., Cahill, E., Frauenhoffer, C., & Barg, F.K. (2009). Older primary care patient views regarding antidepressants: a mixed methods approach. *Journal of Mental Health, 18*(1), 57-64. doi:10.1080/09638230701677795.

Braun, V. and Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology, 3,* 77-101. doi:10.1191/1478088706qp063oa

Breggin, P. (1991). *Toxic Psychiatry*. New York: St Martin's Press.

Breggin, P. (2003/2004). Suicidality, violence and mania caused by selective serotonin reuptake inhibitors (SSRIs): a review and analysis. *International Journal of Risk & Safety in Medicine, 16*(1), 31-49. Retrieved from http://www.breggin.com/

Breggin, P. (2004). Antidepressant-induced suicidality and violence: More about deception than science. Observations made at the FDA hearings press conference, Sept 14, 2004. Retrieved from PDF link at http://www.breggin.com/index.php?option=com_content&task=view&id=43&Itemid=66

Breggin, P. (2006). Intoxication anosognosia: The spellbinding effect of psychiatric drugs. *Ethical Human Psychology and Psychiatry, 8*(3), 201-215. Retrieved from www.breggin.com

Breggin, P. (2008). *Medication madness: The role of psychiatric drugs in cases of violence, suicide, and crime.* New York: St. Martin's Press.

Britten, N. (2008). *Medicines and society: Patients, professionals and the dominance of pharmaceuticals.* Basingstoke, Hampshire, UK: Palgrave MacMillan.

Carlet, D. (2010, April 19). Mind over meds. *The New York Times.* Retrieved from http://www.nytimes.com/2010/04/25/magazine/25Memoir-t.htm

Carlsson, A. & Lindqvist, M. (1978). Effects of antidepressant agents on the synthesis of brain monoamines. *Journal of Neural Transmission, 43*(2), 73-91. doi:10/1007/BF01579067

Catecholamine. (2010). In Encyclopædia Britannica Online, retrieved from http://www.britannica.com/EBchecked/topic/99345/catecholamine

Cohen, D. (2008). Needed: Critical thinking about psychiatric medications. *Social Work in Mental Health, 7*(1), 42-61. doi:10.1080/15332980802072371

Cohen, L. S., Altshuler, L. L., Harlow, B. L., Nonacs, R., Newport, D. J., …Stowe, Z. N. (2006). Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *Journal of the American Medical Association, 295*(5), 499-507. Retrieved from http://jama.ama-assn.org/cgi/content/full/jama;295/5/499

Crumpacker, D. W. (2008). Suicidality and antidepressants in the elderly. *Proceedings (Baylor University Medical Center), 21*(4), 373-377. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2566907/

Csoka, A. B. & Shipko, S. (2006). Persistent sexual side effects after SSRI discontinuation. *Psychotherapy and Psychosomatics, 75*(3), 187-188. doi:10.1159/000091777

Currie, J. (2005). The marketization of depression: the prescribing of SSRI antidepressants to women. *Women and Health Protection,* 1-27. Retrieved from http://www.psychrights.org/Articles/SSRIs.pdf

Daly, R. (2009). Depression biggest contributor to global disease burden. *Psychiatric News, 44*(1), 7. Retrieved from http://www.pn.psychiatryonline.org/content/44/1/7.1.full

Dew, K. (2007). A health researcher's guide to qualitative methodologies. *Australian and New Zealand Journal of Public Health, 31*(5), 433-437. Retrieved from

http://www3.interscience.wiley.com/journal/117969640/abstract?CRETRY=1&SRETRY=0

Dewa, C. S., Hoch, J. S., Lin, E., Paterson, M. & Goering, P. (2003). Pattern of antidepressant use and duration of depression-related absence from work. *British Journal of Psychiatry, 183,* 507-513. Retrieved from http://bjp.rcpsych.org/cgi/reprint/183/6/507

Didham, R. C., McConnell, D. W., Blair, H. J. and Reith, D. M. (2005). Suicide and self-harm following prescription of SSRIs and other antidepressants: confounding by indication. *British Journal of Clinical Pharmacology, 60*(5), 519-525. doi:10.1111/j.1365-2125.2005.02480.x

Drug Topics (2008, February 18). Top 200 generic drugs by units in 2007 & Top 200 brand drugs by units in 2007. *Drug Topics.* Retrieved from http://drugtopics.modernmedicine.com/drugtopics/PharmacyFactsAndFigures/ArticleStandard/article/detail/491210 and http://drugtopics.modernmedicine.com/drugtopics/Top200Drugs/ArticleStandard/article/detail/491194

Eisenberg, P. (2005). Safety data on Cymbalta (duloxetine hydrochloride)—Hepatic effects. Letter to health care professionals. Retrieved from http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164428.pdf

Einarson, A., Choi, J., Einarson, T. R., & Koren, G. (2009). Rates of spontaneous and therapeutic abortions following use of antidepressants in pregnancy: Results from a large prospective database. *Journal of Obstetrics and Gynaecology Canada, 31*(5), 452-456. Retrieved from http://www.sogc.org/jogc/abstracts/full/200905_DrugsinPregnancy_1.pdf

Etminan, M., Mikelberg, F. S., & Brophy, J. M. (2010). Selective serotonin reuptake inhibitors and the risk of cataracts: A nested case-control study. *Ophthalmology, 117*(6), 1251-1255. doi:10.1016/j.ophtha.2009.11.042.

Evans, D. (2009, November 9). Pfizer broke the law by promoting drugs for unapproved uses. *Bloomberg.com.* Retrieved from http://www.bloomberg.com/apps/news?pid=20601109&sid=a4yV1nYxCGoA

Fava, G. A. (2003). Can long-term treatment with antidepressant drugs worsen the course of depression? *Journal of Clinical Psychiatry, 64*(2), 123-133. Retrieved from http://www.psychiatrist.com/ppp/login/login_check_1.asp?dest=/privatepdf/2003/v64n02/v64n0204.pdf

Fava, G. A., Bernardi, M., Tomba, E., & Rafanelli, C. (2007). Effects of gradual discontinuation of selective serotonin reuptake inhibitors in panic disorder with agoraphobia. *International Journal of Neuropsycopharmacology, 10,* 835-838. doi:10.1017/S1461145706007462

Fava, G. A. & Offidani, E. (2010). The mechanisms of tolerance in antidepressant action. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, In press.* Doi:10.1016/j.pnpbp.2010.07.026

Fava, M., Mulroy, R., Alpert, J., Nierenberg, A.A., Rosenbaum, J.F. (1997). Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. *The American Journal of Psychiatry, 154*, 1760-1762. Retrieved from http://ajp.psychiatryonline.org/cgi/content/abstract/154/12/1760

FDA. (2009a). The smoking cessation aids varenicline (marketed as Chantix) and bupropion (marketed as Zyban and generics): Suicidal ideation and behaviour. *FDA Drug Safety Newsletter: Postmarket Reviews, 2.* Retrieved from http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm110235.htm

FDA (2009b). Revisions to product labelling. U.S. Food and Drug Administration. Retrieved from http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273 and http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM173233.pdf

Feeley, J. & Kelley, T. (2010, July 21). Glaxo said to have paid $1 billion over Paxil suits. *Bloomberg Businessweek.* Retrieved from http://www.businessweek.com/news/2010-07-20/glaxo-said-to-have-paid-1-billion-over-paxil-suits.html

Fortune 500 (2009. May 4). Top industries: Most profitable. Retrieved from http://money.cnn.com/magazines/fortune/fortune500/2009/performers/industries/profits/

Fourier, J. C., DeRubeis, R. J., Hollon, S. D., Dimidjian, S., Amsterdam, J. D., Shelton, R. C., & Fawcett, J. (2010). Antidepressant drug effects and depression severity. *The Journal of the American Medical Association. 303*(1), 47-53. doi:10.1001/jama.2009.1943

Freud, S. (1917). Mourning and melancholia. In P. Gay, ed., *The Freud Reader*, (1995) Pp. 584-589 . New York: W.W. Norton & Co.

Galson, S. K. (2004). Docket No. 2003P-0090/CP1&SUP1. (Letter). Department of Health and Human Services, FDA. Retrieved from http://www.fda.gov/ohrms/dockets/dailys/04/June04/062404/03p-0090-pdn00001-vol1.pdf

Gartlehner, G., Morgan, L. C., Thieda, P., Thaler, K., Hansen, R. A., Gaynes, B., Lohr, K. N., & Carey, T. S. (2008). Drug class review: Second generation antidepressants. Final Report, Update 4. Portland: Oregon Health &

Science University. Retrieved from http://derp.ohsu.edu/final/AD2_final_evidence%20tables_update%2043.pdf

Gibbons, R. D., Brown, C. H., Hur, K., Marcus, S. M., Bhaumik, D. K., Mann, J. J. (2007). Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. *American Journal of Psychiatry, 164*, 1044-1049. doi:10.1176/appi.ajp.164.7.1044

Gibbons, R. D., Hur, K., Bhaumik, D. K., & Mann, J. J. (2005). The relationship between antidepressant medication use and rate of suicide. *Archives of General Psychiatry, 62*(2), 165-172. Retrieved from http://archpsyc.ama-assn.org/cgi/content/abstract/62/2/165

GlaxoSmith Kline (2008). Paxil (paroxetine hydrochloride) prescribing information. FDA. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020031s060,020936s037,020710s024lbl.pdf

Glenmullen, J. (2005). The Antidepressant Solution. New York: Free Press.

Glenmullen, J. (2007). Exhibit 0 (Part A) Case 6:07-cv-01157-MLB-DWB, Document 34-17, filed 10/25/2007 for O'Neal vs. SmithKline Beecham (GlaxoSmithKline). (Known colloquially as "The Glenmullen Report") Retrieved from http://finance.senate.gov/search/?q=Glenmullen+report&access=p&as_dt=i&as_epq=&as_eq=&as_lq=&as_occt=any&as_oq=&as_q=&as_sitesearch=&client=finance&sntsp=0&filter=0&getfields=title&lr=&num=15&numgm=3&oe=UTF8&output=xml&partialfields=&proxycustom=&proxyreload=0&proxystylesheet=default_frontend&requiredfields=&site=finance&sitesearch=&sort=date%3AD%3AS%3Ad1&start=0&ud=1&x=13&y=8

Goldberg, D., Privett, M., Ustun, B., Simon, G., & Linden, M. (1998). The effects of detection and treatment on the outcome of major depression in primary care: a naturalistic study in 15 cities. British Journal of General Practice, 48, 1840-1844. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1313290/pdf/10198504.pdf

Goodman, W. K., Murphy, T. K., & Storch, E. A. (2007). Risk of adverse behavioural effects with paediatric use of antidepressants. *Psychopharmacology, 191*(1), 87-96. doi:10.1007/s00213-006-0642-6

Graber, M. A. & Weckmann, M. (2002). Pharmaceutical company internet sites as sources of information about antidepressant medications. *CNS Drugs, 16*(6), 419-423. Retrieved from http://adisonline.com/cnsdrugs/pages/default.aspx

Grime, J. & Pollock, K. (2004). Information versus experience: a comparison of an information leaflet on antidepressants with lay experiences of treatment.

Patient Education and Counseling, 54(3), 361-368. doi:10.1016/j.pec.2004.02.003

Gunnell, D., Saperia, J., & Ashby, D. (2005). Selective serotonin reuptake inhibitors (SSRIs) and suicidality in adults: meta-analysis of drug company data from placebo controlled, randomized controlled trials submitted to the MHRA's safety review. *British Medical Journal, 330*: 385. doi:10.1136/bmj.330.7488.385

Haddad, P. M. (2005). Do antidepressants cause dependence? *Epidemiologia e Psichiatria Sociale, 14*, 58-62. Retrieved from http://www.psychiatry.univr.it/page_eps/docs/2005_2_haddad.pdf

Haddad, P. M. & Anderson, I. M. (2007). Recognising and managing antidepressant discontinuation symptoms. *Advances in Psychiatric Treatment, 13*, 447-457. doi:10.1192/apt.bp.105.001.966

Hagen, B., Wong-Wylie, G., & Pijl-Zieber, E. (2010). Tablets or talk?: A critical review of the literature comparing antidepressants and counselling for treatment of depression. *Journal of Mental Health Counseling, 32*(2), 102-124. Retrieved from http://amhca.metapress.com/app/home/contribution.asp?referrer=parent&backto=issue,2,6;journal,1,30;linkingpublicationresults,1:112203,1

Hall, W. D., & Lucke, J. (2006). How have the selective serotonin reuptake inhibitor antidepressants affected suicide mortality? *Australian and New Zealand Journal of Psychiatry, 40*(11-12), 941-950. doi:10.1111/j.1440-1614.2006.01917.x

Hansen, L. A. (1998). Metaphors of mind and society: the origins of German psychiatry in the revolutionary era. Isis, 89(3), 387-409. Retrieved from http://www.jstor.org/stable/pdfplus/237140.pdf

Harmer, C. J. (2008). Serotonin and emotional processing: Does it help explain antidepressant drug action? *Neuropharmacology, 55*(6), 1023-1028. doi:10.1016/j.neuropharm.2008.06.036

Healy, D. (1997). *The anti-depressant era*. Boston: Harvard University Press.

Healy, D. (2004). *Let them eat Prozac*. New York and London: New York University Press.

Healy, D., Herxheimer, A., & Menkes, D. B. (2006). Antidepressants and violence: Problems at the interface of medicine and law. *PLoS Medicine, 3(9)*: e372. doi:10.1371/journal.pmed.0030372

Healy, D., and Whitaker, C. (2003). Antidepressants and suicide: risk-benefit conundrums. *Journal of Psychiatry and Neuroscience, 28*(5), 331-337. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC193979/

Hertting, G., Axelrod, J., & Whitby, L. G. (1961). Effect of drugs on the uptake and metabolism of H^3-Norepinephrine. The Journal of Pharmacology and Experimental Therapeutics, 134(2). 146-153. Retrieved from http://jpet.aspetjournals.org/content/134/2/146.full.pdf+html

Hindmarch, I. (2001). Expanding the horizons of depression: beyond the monoamine hypothesis. *Human Psychopharmacologogical Clinical Experience, 16*(3), 203-218. doi:10.1002/hup.288.

Holma, I. A., Holma, K. M., Melartin, T. K., & Isometsa, E. T. (2008). Maintenance pharmacotherapy for recurrent major depressive disorder: 5-year follow-up study. *The British Journal of Psychiatry, 193*, 163-164. doi:10.1192/bjp.bp.107.045708.

Houston, T. K., Cooper, L. A., & Ford, D. E. (2002) Internet support groups for depression: a 1-year prospective cohort study. *American Journal of Psychiatry, 159*, 2060-2068. Retrieved from http://ajp.psychiatryonline.org/cgi/content/abstract/159/12/2062

Hu, X. H., Bull, S. A., Hunkeler, E. M., Ming, E., Lee, J. Y., Fireman, B., & Markson, L. E. (2004). Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. *Journal of Clinical Psychiatry, 65(7),* 959-965. Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=16006680

Jessamine, S. (2008). SSRI Antidepressants: Medsafe's response to Professor Werry's letter. *The New Zealand Medical Journal, 121*(1270). Retrieved from http://www.nzma.org.nz/journal/121-1270/2960/

Jick, H., Kaye, J. A., & Jick, S. S. (2004). Antidepressants and the risk of suicidal behaviors. *Journal of the American Medical Association, 292,* 338-343. doi: 10.1001/jama.292.3.338

Jick, T. (1979). Mixed qualitative and quantitative methods: Triangulation in action. *Administrative Science Quarterly, 24*(4), 602-611. Retrieved from http://www.jstor.org/stable/2392366

Johnson, R. B. and Onwuegbuzie, A. J. (2004). Mixed methods research: a research paradigm whose time has come. *Educational Researcher, 33*(7), 14-16. doi:10.3102/0013189X033007014

Julien, R. M. (2001). Chapter 15: Drugs used to treat depression. *A primer of drug action.* (pp. 281-310). New York: Worth Publishers.

Kennard, B. D., Silva, S. G., Tonev, S., Rohde, P., Hughes, J. L. , Vitiello, B., …March, J. (2009). Remission and recovery in the treatment for adolescents with depression study (TADS): Acute and long-term outcomes. Journal of the American Academy of Child and Adolescent Psychiatry, 48(2), 186-195. doi:10.1097/CHI:0b013e31819176f9

Khawam, E. A., Laurencic, G., & Malone, D. A. (2006). Side effects of antidepressants: an overview. *Cleveland Clinic Journal of Medicine, 73*(4), 351-361. doi:10.3949/ccmj.73.4.351

Kirsch, I. (2010a). *The Emperor's New Drugs: Exploding the Antidepressant Myth.* New York: Basic Books.

Kirsch, I. (2010b, January 24) Antidepressants, the sad reality. *New York Post*, retrieved from http://www.nypost.com/p/news/opinion/opedcolumnists/antidepressants_the_sad_reality_yj2IPLSkeQtpAd1Y5a977N

Kirsch, I., Deacon, B. J., Huedo-Medina, T. B., Scoboria, A. Moore, T. J., & Johnson, B. T. (2008). Initial severity and antidepressant benefits: a meta-analysis of data submitted to the food and drug administration. *PLoS Medicine, 5*, e45. doi:10.1371/journal.pmed.0050045

Kresser, C. (2009, November 10). The chemical imbalance myth. *Beyond Meds.* Retrieved from http://bipolarblast.wordpress.com/2009/11/10/chemical-imbalance-myth/

Kuhn, R. (1970). The imapramine story. In F. Ayd & B. Blackwell (Eds.) *Discoveries in Biological Psychiatry.* Pp. 205-217. Philadelphia: J. B. Lippincott Company.

Lacross, J. R. & Leo, J. (2005). Serotonin and depression: A disconnect between the advertisements and the scientific literature. *PLoS Medicine, 2*, e392. doi:10.1371/journal.pmed.0020392

Lader, M. (1991). History of benzodiazepine dependence. *Journal of Substance Abuse Treatment, 8(1-2),* 53-59. doi:10/1016/0740-5472(91)90027-8

Leslie, L. K., Newman, T. B., Chesney, P. J., and Perrin, J. M. (2005). The Food and Drug Administration's deliberations on antidepressant use in pediatric patients. *Pediatrics, 116,* 195-204. doi:10.1542/peds.2005-0074.

Leventhal, A. M. & Antonuccio, D. O. (2009). On chemical imbalances, antidepressant, and the diagnosis of depression. *Ethical Human Psychology and Psychiatry, 11,* 199-214. doi:10.1891/1559-4343.11.3.199

Leydon, G. M. & Raine, R. (2006). The need to act versus reluctance to act: a qualitative study of primary care antidepressant prescribing for patients with common somatic conditions of uncertain cause. *Primary Care Mental Health, 4*(2), 131-142. Retrieved from http://web.ebscohost.com.helicon.vuw.ac.nz/ehost/pdfviewer/pdfviewer?vid=1&hid=10&sid=f7198ac0-0710-46f8-97ef-0447f30d0a5f%40sessionmgr10

Leydon, G. M., Rodgers, L. and Kendrick, T. (2007). A qualitative study of patient views on discontinuing long-term selective serotonin reuptake inhibitors. *Family Practice,* 1-6. doi:10.1093/fampra/cmm069

Liebert, R. (2006). *Medicate me into madness: Knowledges of adverse effects from selective serotonin reuptake inhibitor antidepressant use*. (Unpublished master's thesis). University of Auckland, New Zealand.

Liebert, R. & Gavey, N. (2008). "I didn't just cross a line I tripped over an edge": Experiences of serious adverse effects with selective serotonin reuptake inhibitor use. *New Zealand Journal of Psychology, 37*(1), 38-48.

Liebert R. & Gavey, N. (2009). "There are always two sides to these things": Managing the dilemma of serious adverse effects from SSRIs. *Social Science & Medicine, 68*, 1882-1891. doi:10.1016/j.socscimed.2009.02.047

Lilly, E. (2006). Prozac (Prescribing label). Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018936s076lbl.pdf

Lilly, E. and Co. (2009). Sarafem. Product leaflet retrieved from http://pi.lilly.com/us/sarafem.pdf

Löwe, B., Spitzer, R. L., Gräfe, K., Kroenke, K., Quenter, A., Zipfel, S., …Herzog, W. (2004). Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. *Journal of Affective Disorders, 78*(2), 131-140. doi:10.1016/SO165-0327(02)00237-9

Malpass, A., Shaw, A., Sharp, D., Walter, F., Feder, G. Ridd, M., & Kessler, D. (2009). "Medication career" or "Moral career"? The two sides of managing antidepressants: a meta-ethnography of patients' experience of antidepressants. *Social Science and Medicine, 68*(1), 154-168. doi:10.1016/j.socscimed.2008.09.068

Mansell, P. & Read, J. (2010). Posttraumatic stress disorder, drug companies, and the internet. *Journal of Trauma & Dissociation, 10*, 9-23. doi:10.1080/15299730802488494

March, J., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., …Severe, J. (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression. Treatment for Adolescents of Depression Study (TADS) randomized controlled trial. *Journal of the American Medical Association, 292*(7), 807-820. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15315995/

Mayhew, M. (2009). Off-label prescribing. *The journal for nurse practitioners, 5*(2), 122-123. doi:10.1016/j.nurpra.2008.11.009

McGovern, P. E. (1996). Forward. *The origins and ancient history of wine.* London: Gordon and Breach Publishers.

McLean, B. (2001). A bitter pill Prozac made Eli Lilly. Then along came a feisty generic maker called Barr Labs. Their battle gives new meaning to the term "drug war". *Fortune*, 13 Aug. Retrieved 6 Nov 2009 from http://money.cnn.com/magazines/fortune/fortune_archive/2001/08/13/308077/index.htm

McLeod, P. J., Ruang, A. R., Tamblyn, R. M., & Gayton, D. C. (1997). Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *Canadian Medical Association Journal, 156*(3), 385-391. Retrieved from http://ecmaj.ca/cgi/reprint/156/3/385

Medawar, C. & Hardon, A. (2004). *Medicines out of control? -- Antidepressants and the conspiracy of goodwill.* Amsterdam: Aksant Academic Publishers.

Medawar, C., Hardon, A., & Herzheimer, A. (2004). Depressing research. *The Lancet, 363*(9426), 2087. doi:10.1016/S0140-6736(04)16463-5

Medinews.Direct. (2008, March 5). US FDA approves desvenlafaxine for the treatment of major depressive disorder. *MediNews.Direct.* Retrieved from http://www.medinewsdirect.com/?p=433

MedSafe (1998). Unapproved use of medicines. MedSafe. Retrieved from http://www.medsafe.govt.nz/profs/RIss/unapp.asp

MedSafe (2006). Paroxetine data sheet.Retrieved from http://www.medsafe.govt.nz/profs/datasheet/p/paroxetinemesylatetab.htm.

MedSafe. (2009). Launch of an adverse reaction reporting tool. *MedSafe Prescriber Update*, 30(2):7. Retrieved from http://www.medsafe.govt.nz/Profs/PUArticles/ADR%20Reporting%20Tool-May09.htm

MedTerms (1998a). Definition of bile. *MedTerms Online Medical Dictionary*. Retrieved from http://www.medterms.com/script/main/art.asp?articlekey=2459

MedTerms (1998b). Definition of disease. *MedTerms Online Medical Dictionary*. Retrieved from http://www.medterms.com/script/main/art.asp?articlekey=3011

MedTerms (2000). Definition of side effects. *MedTerms Online Medical Dictionary*. Retrieved from http://www.medterms.com/script/main/art.asp?articlekey=5489

MedTerms (2003a). Definition of 5-HT. *MedTerms Online Medical Dictionary.* Retrieved from http://www.medterms.com/script/main/art.asp?articlekey=24891

MedTerms (2003b). Definition of symptom. *MedTerms Online Medical Dictionary.* Retrieved from http://www.medterms.com/script/main/art.asp?articlekey=5610

Metzl, J. (2003). 'Mother's Little Helper': The crisis of psychoanalysis and the Miltown Resolution. *Gender & History, 15*(2), 240-267. doi:10.1111/1468-1424.00300

Michelson, D., Fava, M., Amsterdam, J. Apter, J. Londborg, P. Tamura, R., and Tepner, R. G. (2000). Interruption of selective serotonin reuptake inhibitor treatment. *British Journal of Psychiatry, 176,* 363-368. Retrieved from http://bjp.rcpsych.org/cgi/content/abstract/176/4/363

Ministry of Health (2007). Patterns of antidepressant drug prescribing and intentional self-harm outcomes in New Zealand: an ecological study. Wellington: Ministry of Health. Retrieved from www.moh.govt.nz

Mitchell, A. J. & Coyne, J. C. (2007). Do ultra-short screening instruments accurately detect depression in primary care?: A pooled analysis and meta-analysis of 22 studies. *British Journal of General Practice, 57*(535), 144-151. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2034175/

Moncrieff, J. (2008). The creation of the concept of an antidepressant: an historical analysis. *Social Science & Medicine, 66*(11), 2346-2355. doi:10.1016/j.socscimed.2008.01.047

Moncrieff, J., Cohen, D., & Mason, J. P. (2009). The subjective experience of taking antipsychotic medication: a content analysis of internet data. Acta Psychiatrica Scandanavica, 120(2), 102-111. doi:10.1111/j.1600-0447.2009.01356.x

Moore, M., Yuen, H. M., Dunn, N., Mullee, M. A., Maskell, J., & Kendrick, T. (2009). Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. *British Medical Journal, 339, b3999,* 1-7. doi: 10.1136/bmj.b3999.

Newnham, E. A., Hooke, G. R., & Page, A. C. (2010). Monitoring treatment response and outcomes using the World Health Organization's wellbeing index in psychiatric care. *Journal of Affective Disorders, 122*(1-2), 133-138. doi:10.1016/j.jad.2009.06.005

NIMH (2010, July 23). The numbers count: Mental disorders in America. Retrieved from http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america/index.shtml

Nierenberg, A. A., Ostacher, M. J., Huffman, J. C., Ametrano, R. M., Fava, M., & Roy, H. (2008). A brief review of antidepressant efficacy, effectiveness, indications and usage for major depressive disorder. *Journal of*

Occupational and Environmental Medicine, 50(4), 428-436. doi:10.1097/JOM.0b013e31816b5034

Nunn, J. F. (1996). *Ancient Egyptian medicine*. London: British Museum Press.

Oakley Browne, M. A., Wells, J. E., and Scott, K. M. (eds). 2006. Te rau hinengaro: The New Zealand mental health survey. Wellington: Ministry of Health. Available at www.moh.govt.nz

O'Brian, C. (2009). Letter quoted in a forum post at www.paxilprogress.org. Retrieved from http://www.paxilprogress.org/forums/showthread.php?t=41408&highlight=dependence

Olfson, M. & Marcus, S. C. (2009). National patterns in antidepressant medication treatment. *Archives of General Psychiatry, 66*(8), 848-856. Retrieved from http://archpsyc.ama-assn.org/cgi/content/abstract/66/8/848

Pallant, J. (2005). SPSS survival manual: A step by step guide to data analysis using SPSS version 12. 2nd Ed. Maidenhead, UK: Open University Press.

Papacostas, G. I. & Fava, M. (2007). A meta-analysis of clinical trials comparing the serotonin (5HT)-2 receptor antagonists trazodone and nefazodone with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. *European Psychiatry, 22*, 444-447. doi:10.1016//j.eurpsy.2007.01.1220

Patten, S. B. (2004). The impact of antidepressant treatment on population health: Synthesis of data from two national data sources in Canada. *Population Health Metrics, 2*(9). doi:10.1186/1478-7954-2-9

Payk, Th. R. (1994). Treatment of Depression. *Journal of Geriatric Psychiatry and Neurology, 7*, S3-S5. doi:10.1177/08918879400700102

Pestello, F. G. & Davis-Berman, J. (2008). Taking anti-depressant medication: a qualitative examination of internet postings. *Journal of Mental Health, 17*(4), 349-360. doi:10.1080/09638230701498333

Pettinati, H. M. (2004). Antidepressant treatment of co-occurring depression and alcohol dependence. *Biological Psychiatry, 56*(10), 785-792. doi:10.1016/j.biopsych.2004.07.016

Petty, D. R., House, A., Knapp, P., Raynor, T., Zermansky, A. (2006). Prevalance, duration and indications for prescribing of antidepressants in primary care. *Age and Aging, 35*(5), 523-526. Retrieved from http://ageing.oxfordjournals.org/content/35/5/523.full

Pomerantz, J. M., Finkelstein, S. N., Berndt, E. R., Poret, A. W., Walker, L. E., Alber, R. C. …Ebert, T. H. (2004). Prescriber intent, off-label usage, and early discontinuation of antidepressants: a retrospective physician survey

and data analysis. *Journal of Clinical Psychiatry, 65*(3), 395-404. Retrieved from http://www.grandrounds.com/v65n0316.pdf

Price, J., Cole, V. & Goodwin, G. M. (2009). Emotional side-effects of selective serotonin reuptake inhibitors: qualitative study. *The British Journal of Psychiatry, 195,* 211-217. doi:10.1192/bjp.bp.108.051110

Psychiatric Research Unit. (ND). Interpretation of the items of the WHO-5 questionnaire. WHO-5 Well-being index. Retrieved from http://www.who-5.org/

Rampono, J., Simmer, K., Ilett, K. F., Hackett, L. P., Doherty, A., Elliot, R., …Forman, T. (2009). Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry, 42*(3), 95-100. doi:10.1055/s-0028-1103296.

Rasmussen, N. (2006). Making the first anti-depressant: Amphetamine in American medicine 1929-1950. *Journal of the History of Medicine and Allied Sciences, 61*(3), 288-323. doi:10.1093/jhmas/jrj039

Rasmussen, N. (2008). America's first amphetamine epidemic 1929-1971: A quantitative and qualitative retrospective with implications for the present. *Public Health Then and Now, 98*(6), 974-985. doi:10.2105/AHPH.2007.110593

Richards, J. B., Papaioannou, A., Adachi, J. D., Joseph, L., Whitson, H. E., Prior, J. C., & Goltzman, D. (2007). Effects of selective serotonin reuptake inhibitors on the risk of fracture. *Archives of Internal Medicine, 167*(2), 188-194. Retrieved from http://archinte.ama-assn.org/cgi/content/abstract/167/2/188

Rosenbaum, J. F., Fava, M., Hoog, S. L., Ascroft, R. C., and Krebs, W. B. (1998). Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biological Psychiatry, 44*(2), 77-87. doi:10/1016/S0006-3223(98)00126-7

Ruhé, H. G., Huyser, J., Swinkels, J. & Schene, A. H. (2006). Dose escalation for insufficient response to standard-dose selective serotonin reuptake inhibitors in major depressive disorder: Systematic review. *British Journal of Psychiatry, 189,* 309-316. doi:10.1192/bjp.bp.105.1083225.

Rush, A. J., Fava, M., Wisniewski, S. R., Lavori, P. W., Trivedi, M. H., Sackeim, H. A. …Niederehe, G. (2004). Sequenced treatment alternatives to relieve depression (STAR*D): Rationale and design. *Controlled Clinical Trials, 25*(1), 119-142. doi:10.1016/SO197-2456(03)00112-0

Sabin, B. (2010, September 11). More Kiwis using antidepressants. *TV3 News*. Retrieved from http://www.3news.co.nz/More-Kiwis-using-anti-depressants/tabid/423/articleID/175547/Default.aspx

Sandler, M. (1990). Monoamine oxidase inhibitors in depression: History and mythology. *Journal of Psychopharmachology, 4*(3), 136-139. doi:10.1177/026988119000400307

Sanz, E. J., De-las-Cuevas, C., Kiuru, A., Bate, A., & Edwards, R. (2005). Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *The Lancet, 365*, 482-487. doi:10.1016/S1040-6736(05)17865-9.

Schildkraut, J. J. & Kety, S. S. (1967). Biogenic amines and emotion. *Science, 156*(3771), 21-30. doi:10.1126/science.156.3771.21

Schatzberg, A. F., Blier, P., Delgado, P. L., Fava, M., Haddad, P. M., Psych, M. R. C. & Shelton, R. C. (2006). Antidepressant discontinuation syndrome: consensus panel recommendations for clinical management and additional research. *Journal of Clinical Psychiatry, 67* (suppl 4), 27-31. Retrieved from http://www.psychiatrist.com/pastppp/tocs.asp?toc=t67s04

Shorter, E. (2009). *Before Prozac: The troubled history of mood disorders in psychiatry.* Oxford: Oxford University Press.

Simon, G. E., Savarino, J., Operskalski, B., & Wang, P. S. (2006). Suicide risk during antidepressant treatment. *American Journal of Psychiatry, 163*, 41-47. doi:10.1176/appi.ajp.163.1.41

Slemmer, J. E., Martin, B. R., and Damaj, M. I. (2000). Bupropion is a nicotinic antagonist. *Journal of Pharmacological Experimental Therapy, 295*(1), 321-327. Retrieved from http://jpet.aspetjournals.org/content/295/1/321.full

Spigset, O. (1999) Adverse reactions of selective serotonin reuptake inhibitors: Reports from a spontaneous reporting system. *Drug Safety, 20(3)*, 277-287 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10221856

Stone, M., Laughren, T., Jones, M. L., Levenson, M., Holland, P. C., Hughes, A., …Rochester, G. (2009). Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *British Medical Journal*, 339:b2880, doi:10.1135/bmj.b2880.

Swift, R.M. (1999). Drug therapy for alcohol dependence. *The New England Journal of Medicine, 340*(19), 1482-1491. Retrieved from http://content.nejm.org/

Szabo, L. (2009, August 4). Number of Americans taking antidepressants doubles. *USA Today*. Retrieved from http://www.usatoday.com/news/health/2009-08-03-antidepressants_N.htm

Taylor, D., Stewart, S., and Connolly, A. (2006). Antidepressant withdrawal symptoms—telephone calls to a national medication helpline. *Journal of Affective Disorders, 95*(1-3), 129-133. doi:10.1016/j.jad.2006.04.026

Thase, M. E., Trivedi, M. H., and Rush, A. J. (1995). MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology, 12*(3), 185-219. doi:10.1016/0893-133X(94)00058-8

Thompson, M. L. (2007). *Mental illness.* Westport, Connecticut, USA: Greenwood Press.

Thrasher (2008). Spontaneously Reported Prolonged Serotonin Reuptake Inhibitor (SRI) Antidepressant Discontinuation Syndrome in a Naturalistic Cohort. Unpublished manuscript.

Tiihonen, J., Lonnqvist, J., Wahlbeck, K., Klaukka, T., Tanskanen, A., and Haukka, J. (2006). Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. *Archives of General Psychiatry, 63*(12), 1358-1367. Retrieved from http://archpsyc.ama-assn.org/cgi/content/abstract/63/12/1358

Tonks, A. (2002). Withdrawal from paroxetine can be severe, warns FDA. *British Medical Journal, 324*(7332), 260. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1122195/

Turner, E. H., Matthews, A. M., Linardatos, E., Tell, R. A., & Rosenthal, R. (2008). Selective publication of antidepressant trials and its influence of apparent efficacy. *The New England Journal of Medicine, 358*(3), 252-260. Retrieved from http://www.contentnejmorg.zuom.info/cgi/content/abstract/358/3/252

Ussher, J. (2010). Are we medicalizing women's misery? A critical review of women's higher rates of reported depression. *Feminism & Psychology, 20*(1), 9-35. doi:10.1177/0959353509350213

Vallance, P. (2010) Pill poppers. *Horizon, BBC*. Retrieved from http://www.youtube.com/watch?v=QqIbUhvJve8

Vanderkooy, J. D., Kennedy, S. H., & Bagby, R. M. (2002). Antidepressant side effects in depression patients treated in a naturalistic setting: a study of Bupropion, moclobemide, paroxetine, sertraline, and venlafaxine. *Canadian Journal of Psychiatry, 47*(2), 174-180. Retrieved from http://publications.cpa-apc.org/browse/documents/3

Waknine, Y. (2010, February 11). FDA approves trazedone extended-release formulation for depression. *Medscape Medical News*. Retrieved from http://www.medscape.com/viewarticle/716502

Waldinger, M. D. (2007). Premature ejaculation: definition and drug treatment. *Drugs, 67*(4), 547-562. Retrieved from

http://adisonline.com/urolvj/Abstract/vjcs/00002/Premature_Ejaculation__Definition_and_Drug.9.aspx

Watkins, T. (2005, January 4). Papers indicate firm knew possible Prozac suicide risk. *CNN International.com*, retrieved from http://edition.cnn.com/2005/HEALTH/01/03/prozac.documents/index.html

Watters, Ethan. (2010). *Crazy like us: The globalization of the American psyche.* New York: Free Press.

Wattignar, S. D. & Read, J. (2009). The pharmaceutical industry and the internet: Are drug company funded depression websites biased? *Journal of Mental Health, 18*(6), 476-485. doi:10.3109/09638230902968183.

Whitaker, R. (2005). Anatomy of an epidemic: psychiatric drugs and the astonishing rise of mental illness in America. *Ethical Human Psychology and Psychiatry, 7*(1), 23-35. Retrieved from http://freedom-center.org/pdf/anatomy_of_epidemic_whitaker_psych_drugs.pdf

Whitaker, R. (2010). *Anatomy of an epidemic: Magic bullets, psychiatric drugs, and the astonishing rise of mental illness in America*. New York: Crown Publishers.

Wisner, K. L., Sit, D. K. Y., Hanusa, B. H., Moses-Kolko, E. L., Bogen, D. L., Hunker, D. F., …Singer, L. T. (2009). Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. *American Journal of Psychiatry, 166*, 557-566. doi:10.1176/appi.ajp.2008.08081170

Wohlfarth, T., Kalverdijk, L., Rademaker, C., Schothorst, P., Minderaa, R., & Wied, C. G. (2009). Psychopharmacology for children: From off label use to registration. *European Neuropsychopharmacology*, *19*(8), 603-608. doi:10.1016./j.euroneuro.2009.04.007

Wong, D. T., Bymaster, F. P., and Engleman, E.A. (1995). Prozac (fluoxetine, Lilly 110141), the first selective serotonin uptake inhibitor and an antidepressant drug: Twenty years since its first publication. *Life Sciences, 57*(5), 411-441. doi:10.1016/0024-3205(95)00209-O

Wong, M. & Licinio, J. (2001). Research and treatment approaches to depression. *Nature Reviews Neuroscience*, 2, 343-351. doi:10.1038/35072566

Zellweger, M. J., Osterwalder, R. H., Langewitz, W., & Pfisterer, M. E. (2004). Coronary artery disease and depression. *European Heart Journal, 25*(1), 3-9. doi:10.1016/j.ehj.2003.09.009

Zimmerman, M., Galione, J. N., Attiullah, N., Friedman, M., Toba, C., Boerescu, D. A., & Ragheb, M. (2010). Underrecognition of clinically significant side effects in depressed outpatients. *Journal of Clinical Psychiatry, 71*(4), 484-490. doi:10.4088/JCP.08m04978blu