Unrelenting: A Media-Focused Political Economy Analysis of Antidepressant Use in Canada

by

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A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfillment of the requirements of the degree of

MASTER OF ARTS

Department of Political Studies

University of Manitoba

Winnipeg, MB

August 2016

Abstract

Although extensive evidence suggests antidepressants are a non-effective treatment for the majority of depressive cases where they are prescribed and despite other developed countries taking steps to provide alternative treatments, Canada's prescription rates continue rising and no state action is being taken. The primary purpose of this study is to explore whether the media in English-speaking Canada, represented by its "newspaper of record," *The Globe and Mail*, has been performing its essential role in informing Canadians about the controversy surrounding antidepressants and the pharmaceutical system that that has made them central to treating depression. Data was collected in the form of newspaper articles from between 2000 and 2015 in order to analyze media coverage to ensure the essential facts were reported and to qualify to what degree a patient advocacy role challenging the norms of contemporary treatment has been adopted.

Keywords: antidepressants; anti-depressants; selective serotonin reuptake inhibitor; pharmaceutical industry; political economy; media; Canada

Acknowledgments

This thesis would not have been possible without my family and friends. They have always tolerated my no-doubt tedious rants with heroic patience and usually managed to keep me working even when it looked pretty nice outside.

A huge thank you to my advisor, Dr. Radhika Desai, who showed me what needed doing, where to find information, and did her best to keep me somewhat on topic – any topic. I also want to extend a sincere thank-you to my committee chair, Dr. Mara Fridell, and committee members, Dr. Karine Levasseur and Dr. Robert Chernomas, who provided advice and expertise when it was needed.

Thanks to those of my friends who have struggled with depression and were able to give me real insight into what it is like to fight that horrible force that Winston Churchill had coined the "black dog."

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The Introduction

Depression has become a major health concern worldwide. A 2001 World Health Organization (WHO) report stated that by 2020, depression will be the second leading cause of disability worldwide after heart disease (WHO, 2001 p. 6). One analysis of the large-scale Global Burden of Disease study from 2010 suggests that it already is (Ferrari et al., 2013). Canada has responded to this growing problem almost solely with pharmaceutical antidepressants. In 2012, the last year reliable data was available, Canadians would fill 42.6 million prescriptions for antidepressants, an increase of 32.3 percent since 2008 and 1331.25 percent since 1981. This made Canada the third-largest per capita consumer of antidepressant medication of the twenty-three nations surveyed from the Organization for Economic Co-operation and Development (OECD), behind only Iceland and Australia (Hemels, Koren, and Einarson, 2002; OECD, 2013; Kirkey, 2014). However, the US was not included in this analysis and previous data suggests they would be the heaviest users, pushing Canadians to the position of fourth heaviest users (Pratt, Brody, and Gu, 2011).

It is important to note that antidepressants are also prescribed for mental health issues other than major depressive disorder (MDD) such as anxiety and obsessive compulsive disorder (OCD). However, this paper will focus solely on the relationship between antidepressants and the treatment of depression and the extent to which antidepressants are used for this reason alone can be quantified. This includes depression brought about by seasonal affective disorder (SAD) and posttraumatic stress disorder (PTSD) as the similarities in symptoms to MDD means antidepressants are seen as an effective treatment. It also includes depression brought on by

bipolar disorder because even though the research shows "weak evidence for efficacy and the potential risk for excessive mood elevation" with these drugs, they are in "wide use" for the condition anyway (ISBD Task Force, 2013 p. 1250-1).

In 2012, Canada had approximately 8.175 million visits to a primary care physician where depression was reported as the primary reason for coming, making it the fourth leading cause. 83 percent of these visits for depression, roughly 6.785 million, would result in a pharmaceutical drug being prescribed to treat the condition, making antidepressants the primary and often sole method primary care physicians use to deal with depression in Canada (IMS Health, 2013). Only 20 percent of these antidepressant prescriptions were provided by specialized mental health doctors, such as psychiatrists, who generally have much greater training in psychiatric illnesses and their treatments (Mark, Levit, and Buck, 2009).

At first glance, this increased prescribing appears strictly beneficial. It has been argued that depression has been historically under-diagnosed and that the stigma of having mental health issues is finally being removed, allowing more people to seek and receive treatment (Gardner, 2009). This seems to make sense as some studies have certainly shown antidepressants to be beneficial for some people. Randomized controlled trials (RCTs) are considered the most effective methodology for showing the effectiveness of drugs. In these trials, patients are randomly given a drug to be tested or a placebo, that is, a simulated treatment with no active ingredients intended to deceive patients into believing they have been given a biologically-active treatment. The patient is not informed which they have been given and the results of the different patients are compared to demonstrate drug efficacy or lack thereof. These trials can then be combined into a meta-analysis which consists of merging the results of multiple studies so that the results of different studies can be functionally compared to provide an average effectiveness.

Some older meta-analyses of randomized controlled trials have shown that antidepressants are 20-30 percent more effective than placebos. They have been shown to lead to higher rates of remission, where a patient has their Hamilton Depressive Rating Scale (HDRS)[1] score reduced to less than eight, and have higher response rates, where the HDRS score is reduced by 50 percent or more (Davis, Wang, and Janicak, 1993; Walsh et al., 2002; Arroll et al., 2005).

However, against this evidence in favour of the use of antidepressants, there is mounting evidence arguing against their efficacy and their sometimes severe side-effects. To begin with, meta-analyses have shown that the effectiveness of antidepressants depends heavily on the severity of depression at the start of treatment and that the drugs become more effective as severity increases (Khan et al., 2002; Khan et al., 2005; Fournier et al., 2010).

This is an issue as there has been substantial evidence coming forward to suggest that the majority of antidepressants are being prescribed to patients with a level of depression severity where the drugs are typically no more effective than placebos. Studies have shown that for people with depression rated less than severe on the HDRS, the most commonly used antidepressants have no clinically significant advantage – as established by the UK's National Institute for Health and Clinical Excellence (NICE) – over a sugar pill (Kirsch et al., 2002; Kahn et al., 2005; Barbui, Furukawa, and Cipriani, 2008; Kirsch et al., 2008; Fournier et al., 2010).

A US study found that likely less than half and potentially as few as 29 percent of people receiving antidepressant medication would fall into the category of severely depressed and

[1] The HDRS has been the most commonly used scale and has long been considered the 'gold standard' of rating systems for measuring the acuity of depression. HDRS has a maximum depressive score of 50 for the 17-item scale and 62 for the 21-item scale (Worboys, 2013).

therefore be likely to benefit from the medication (Zimmerman, Posternak and Chelminski, 2002). If this can be extrapolated to Canada, this would mean that in 2012, out of the almost seven million visits to a primary care physician that resulted in antidepressant prescriptions, approximately 4.817 million will receive no clinically significant benefit from taking the drugs compared to what would be gained from a sugar pill. Another US study showed that from 2001-2003, 26 percent of Americans receiving antidepressants were prescribed them without ever being diagnosed with any of the disorders they are used to treat (Pagura et al., 2011). An additional study would show that about 69 percent of Americans taking selective serotonin reuptake inhibitor antidepressants (SSRI), the most commonly prescribed kinds, had never suffered from major depressive disorder and 38 percent have never suffered from any mental disorder that evidence shows would benefit from an antidepressant (Takayangai et al., 2015). Exactly how applicable these findings are to Canada is debatable but with our similar antidepressant usage level and exposure to US drug advertising and culture there is reason to suspect Canadians might have some issues with this prescribing to people who have no clear reason to be using them as well.

Also of concern is the notion that even the modest, approximately two-point advantage of antidepressants over placebo, witnessed in one earlier study (Kirsch et al., 2002), may not have been the result of drug efficacy. More severely depressed people generally are given higher doses which come with more side-effects. As the severely depressed have often been on antidepressants before, they know what being on antidepressants is like and will thus more likely recognize being on placebo when they do not have the normal effects. This suggests that patients are likely breaking the trial blind and realizing they have been given a placebo due to a noticeable lack of drug side-effects, thus reducing the effect (Kirsch, 2014). This is backed by

previous evidence that suggests trial participants are often capable of realizing whether they have been assigned to the drug or placebo in a trial (Rabkin et al., 1986).

In addition, a meta-analysis of the studies for antidepressant efficacy on juvenile depression has shown that they have very limited benefits with the possible exception of the SSRI fluoxetine, marketed as Prozac (Tsapakis et al., 2008). Despite this and the lack of knowledge of long-term side-effects specific to youth, there has been a consistent increase in the amount of antidepressants prescribed to Canadian youth annually, including those other than fluoxetine (Lam et al., 2013).

Another worrying trend in depression treatment for youth in Canada is the increasing use of second-generation antipsychotics for adolescents and children (Ronsley et al., 2013). This is likely due to the lack of efficacy of standard antidepressants for this demographic. These medications have dubious side-effects and, "There is no evidence to support the use of SGA [second-generation antipsychotic] medications for major depression ... in children and adolescents (Horn et al., 2012 p.78)." Clearly, when antipsychotics are being used to treat youth despite there being no evidence indicating they will help, it suggests that our medical system is simply too focused on treating depression with drugs and that after standard antidepressants have failed to help a young patient, physicians are simply prescribing whatever drug they think might potentially help instead of trying evidence-backed alternatives to drug-only treatments.

To the lack of efficacy in so many of the cases antidepressants drugs are prescribed we must add an even more problematic aspect of the over-prescription of antidepressants: their negative side-effects. Some of them run directly counter to the primary goal of antidepressants, that is, causing the remission of depression. A pair of 2011 studies would look over the available evidence and deduce that antidepressant medication appeared to throw off our natural

homeostasis so that we become more likely to go into remission when taken off of the medication than we would be if we recovered without medication or with placebo only (Andrews et al., 2011; Fava and Offidani, 2011).

A study in the Netherlands found that people who did not take antidepressants were 50 percent more likely to remain relapse-free over those who did (Weel-Baumgarten, 2000). Another study showed that someone on antidepressants whose depression has remitted is more than twice as likely to relapse within the first three months than if that remission occurred without them, likely because the brain overcompensates for the now absent drug (Andrews et al., 2012). This implies that for the large number of people with a severity level too low to benefit from the drugs, being given "antidepressants might trigger even more severe depressive episodes when they are discontinued (Andrews et al., 2012)." This means you might be given a drug that will not help for your condition but that will make you depressed enough when trying to come off them that that they actually becomes efficacious and necessary to start again. This seems to fit with the idea the evidence shows cognitive therapy – essentially any kind of talking-only therapy – has more enduring benefits than antidepressants (DeRubeis, Siegle, and Hollon, 2008).

Also, sudden withdrawal can produce side-effects such as flu-like symptoms, nausea, imbalance, hyperarousal, insomnia, sensory disturbances in addition to the return of depressive symptoms. These occur in about 20 percent of people after suddenly discontinuing use. These symptoms are more common and severe with longer duration treatments and with drugs that take longer to be broken down within the body (Warner et al., 2006). This means the people who may actually benefit from antidepressants will be the ones on longer-lasting drugs with longer treatment durations suggesting that they would likely suffer the worst withdrawal symptoms upon sudden discontinuation.

In order to help prevent relapse, antidepressant medication is usually prescribed for between four and twelve months (Geddes et al., 2003). However, evidence shows that the average duration of an untreated major depressive disorder episode is only twelve to thirteen weeks (Coryell et al., 1995; Posternak et al., 2006). This means that even if a patient's symptoms are reduced by taking the medication, they will often suffer the side-effects for as much as four times longer than the depression would generally last and all with a chance of relapse afterwards that is at least twice as high than if left unmedicated. This suggests antidepressant medication actually usually delays the resolution of depressive episodes, sometimes substantially.

The health issues from taking antidepressants are also emerging as potentially quite severe. The most common antidepressants work by altering the body's levels of serotonin, dopamine, and norepinephrine as these neurotransmitters are believed to be the primary brain chemicals that maintain mood-homeostasis. The issue is that these chemicals are present in other parts of our bodies than just our brains and control more bodily mechanisms than just our mood. This means using drugs to tweak these levels can have problematic consequences for other bodily systems.

Commonly used antidepressants have been linked to increased risk of some types of cancer (Cosgrove et al., 2011); cell death in healthy hippocampal neurons (Sairanen et al., 2005); impaired cognition (Hindmarch, 2009); increased risk of driving accidents (Gibson et al., 2009); decreased bone mineral density (Moret, Isaac, and Briley, 2009); gastrointestinal problems (Brambilla et al., 2005; Zimmerman et al., 2010); abnormal bleeding (Meijer et al., 2004); sexual impairment (Serretti and Chiesa, 2009); sperm impairment (Tanrikut et al., 2010); increased risk of diabetes (Barnard, Peveler, and Holt, 2013); child developmental impairment (Bar-Oz et al., 2007; Cole et al., 2007; Moret, Isaac, and Briley, 2009; Ellfolk and Malm, 2010); increased risk

of hyponatremia in the elderly (Jacob and Spinler, 2006; Coupland et al., 2011); increased heart disease in the elderly (O'Regan et al., 2015); and an overall increased risk of death in the elderly (Smoller et al., 2009; Almeida et al., 2010; Coupland et al., 2011).

One study (Cascade, Kalali, and Kennedy, 2009) would look at approximately seven hundred patients taking SSRI antidepressants and find that 38 percent of them reported at least one side-effect. Of the 229 patients who reported a side-effect, 56 percent would report decreased sexual functioning, 53 percent would report drowsiness, and 49 percent would report weight gain. Of the 229 patients suffering side-effects, there would be a 12-19 percent chance that they would report suffering from any of the following: dry mouth, insomnia, fatigue, nausea, light-headedness and tremors. 26 percent would rate these as "very bothersome" or "extremely bothersome." Although sexual dysfunction while on antidepressants is considered routine, there are cases suggesting that this may continue in some patients even after discontinuing and may be permanent. Looking at these cases, the researchers concluded that, "SSRIs can cause long-term effects on all aspects of the sexual response cycle that may persist after they are discontinued (Csoka, Bahrick and Mehtonen, 2008)."

There is also emotional blunting and apathy in a certain subset of patients. A 2010 study looking at this said: "As for prevalence rates, according to a study by Bolling and Kohlenberg, approximately 20 percent of 161 patients who were prescribed an SSRI reported apathy and 16.1 percent described a loss of ambition. In a study by Fava et al., which consisted of participants in both the United States and Italy, nearly one-third on any antidepressant reported apathy, with 7.7 percent describing moderate-to-severe impairment, and nearly 40 percent acknowledged the loss of motivation, with 12.0 percent describing moderate-to-severe impairment (Sansone and Sansone, 2010)."

There has also been an ongoing debate around whether antidepressants actually cause more or less suicidal ideation and actual suicides amongst youths. In 2003, the UK Medicines and Healthcare products Regulatory Agency (MHRA) warned doctors against using SSRI antidepressants in people under eighteen with the exception of fluoxetine due to concerns with a lack of efficacy and increased suicidal ideation. The US Food and Drug Administration (FDA) followed suit and warned doctors to watch for suicidal behaviour in adolescents on SSRIs, especially paroxetine, and would require this class of drugs to have 'black boxes' on the label that warned users and doctors about potential suicide risk caused by the drugs. Health Canada would put out a similar warning on seven drugs from the SSRI and SNRI classes (Mann et al., 2006).

The evidence on this matter is unclear as some studies have suggested that antidepressants do not increase the chance of suicide in youth and might actually reduce it (Gibbons et al., 2006; Gibbons et al., 2012) while other research has found the opposite (Fergusson et al., 2005; Dubicka, Hadley, and Roberts, 2006; Stone et al., 2009). What has been less controversial, however, is the notion that SSRI antidepressants lead to an increase in violent tendencies in adolescents (Breggin, 2003; Healy, Herxheimer, and Menkes, 2006). Another study found that of the top-ten pharmaceutical drugs disproportionately linked to violence, five of them are antidepressants (Moore, Glenmullen, and Furberg, 2010). In 2011, it was accepted in court that a fifteen-year-old boy who murdered his friend did so because of the influence of Prozac. The judge would state: "He had become irritable, restless, agitated, aggressive and unclear in his thinking ... It was while in that state he overreacted in an impulsive, explosive and violent way. Now that his body and mind are free and clear of any effects of Prozac, he is simply not the same youth in behaviour or character (Blackwell, 2011)." Japan's Ministry of Health, Labour, and Welfare (MHLW) would revise SSRI/SNRI labels to add warnings about potential hostility,

stating at the time: "There are cases where we cannot rule out a causal relationship [of hostility, anxiety, and sudden acts of violence] with the medication (MHLW, 2009 p. 3)."

There are also environmental consequences to an over-reliance on antidepressants. Like most things humans consume in large enough amounts, antidepressants find their way into our water bodies through our sewage in noticeable amounts as water treatment plants are not designed to remove them. Although it is assumed the quantities of pharmaceuticals are so diluted as to not be a threat to humans when they eventually make their way back into human drinking water, there is evidence they can interact with the animal and plant species within those water-bodies in ways that seem to be significant. One study showed that fish swimming in "municipal effluent-dominated streams" did indeed have significant levels of SSRI antidepressants in their tissue (Brooks et al., 2005).

Another study showed that larval fathead minnows exposed to an amount of antidepressants often found in water bodies had slower predator avoidance behaviour than those who were not exposed (Painter et al., 2009). As with humans, drugs that affect the serotonin, dopamine, and norepinephrine systems of fish will cause changes in their development, especially since they are exposed to them while still in their infantile stages. Considering that evidence shows antidepressants make fish less able to avoid their predators, it is not a huge stretch to suggest that our overuse of antidepressants may eventually cause real, potentially substantial changes in the ecosystem.

Overall, there is now a sizable body of literature demonstrating the dangers and inefficacy of mass prescribing antidepressants the way that we do. In their work, *Primum No Nocere: An Evolutionary Analysis of Whether Antidepressants Do More Harm than Good* (2012), Paul Andrews and his cohorts explain how antidepressants are generally a net-loss for

patients even in cases where they appear to work since they argue that the evidence suggests they damage our body's efforts at maintaining healthy homeostasis. Even without going that far as to say the drugs are bad for basically everyone, the numbers certainly suggest we are giving them to many people who will not benefit, would benefit significantly more from alternative treatments, or might be being harmed by the drugs.

Due to side-effects and lack of efficacy, the UK's National Institute for Health and Care Excellence (NICE) created a set of guidelines for its doctors in 2004 recommending stepped care where antidepressants would only be prescribed in patients who were moderately depressed or greater (NICE, 2004). The evidence against SSRI treatment for youth has been potent enough that the UK has now banned their use with the exception of fluoxetine due to demonstrated lack of effectiveness and an increase in suicidal ideation and violent tendencies. Doctors there have been asked to recommend cognitive behavioural therapy (CBT), a verbal, psychological treatment that has been demonstrated as effective in clinical trials (Chambless and Hollon, 1998; Richards and Borglin, 2011, Amick et al. 2015) and in real-world practice (Stewart and Chambless, 2009). To supply the therapists required, policy was developed to provide funds for the National Health Service (NHS) to train 3600 psychological therapists between 2008-2011 and another 2400 between 2011-2014 (Richards and Borglin, 2011).

Australia has taken similar steps in trying to move away from antidepressants and has discovered that for treating major depressive disorder, CBT is a cheaper and more effective form of treatment (Vos et al., 2005). This has resulted in reforming public policy so that privately-provided CBT is publicly reimbursed, partially through the Partnership Program, a program designed to improve cooperation between public and private-sector mental health service (Pirkis et al., 2004).

Japan has also been running a trial to see if it is practical to reduce their reliance on antidepressants as a first-line treatment for depression. In 2010, after CBT was added to the national insurance plan, the Japanese city of Chiba's university launched a new program called Improving Access for Psychological Therapies (IAPT) that was based on the program of the same name in the UK. The program's mandate was to, "establish national standards for certification of clinical professionals trained in the science and art of CBT, and develop a law related to national licensing of cognitive-behavioral therapists (Shimizu, 2011)."

The Netherlands have also attempted to reduce reliance on antidepressants. Their prescription rate increased by less than 25 percent between 2001 and 2013 with almost none of the growth coming after 2008. Germany, Spain, and the UK would see their prescription rates double over the same period (Rice-Oxley and Fishwick, 2013). This has been a result of the implementation of medical guidelines that suggest doctors initially attempt to treat non-severe depression through non-drug means. A study found that doctors following these guidelines decreased their antidepressant prescription rates by 23.3 percent (Franx et al., 2014). Although there are no measures coercing doctors to follow these guidelines, a cultural shift seems to have occurred in the Dutch healthcare system and their prescription rates have dropped significantly relative to their European neighbours.

Unfortunately, Canada has not taken any similar steps in this direction and the rate of antidepressant prescribing for depression is still increasing annually. Currently, none of the existing literature focuses on why the Canadian healthcare system is so out of sync with the newest research and why it is not making policy changes in concert with those being undertaken by other major developed countries. Considering the reasons for this will likely be multi-faceted and beyond the scope of a single thesis, the focus here will be on the role of Canada's English-

speaking media. As Canada is a kind of democracy, an informed population is necessary if the citizens are to wind up with a government and health care system that is going to engage in the highest quality, evidence-based policy making.

1.1 Posing the Thesis Question and Chapter Outline

This thesis will attempt to answer the question: Considering that the available evidence regarding the most popular antidepressants has caused the UK, Australia, Japan, and the Netherlands to alter or begin altering public-policy away from antidepressant treatment for the majority of depressive cases, has Canada's media been informing Canadians on the issues involved and these initiatives sufficiently well? Has it endeavored to shift the public discourse to put Canada on a similar path?

The chapter outline will be as follows:

1) Introduction

2) Theoretical Perspective and Methodology

The second chapter will provide a theoretical perspective and a methodology to be used throughout the paper. It will first explain the role and importance of the media in shaping public opinion and that of relevant stakeholders regarding healthcare issues. It will then briefly summarize and provide literary reviews for the three main theories behind the dramatic increase in antidepressant prescriptions despite significant evidence suggesting this is a dangerous and ineffective route.

The first argument is that an insufficient understanding of the placebo effect has led to an assumption of far greater efficacy on the part of antidepressants than is warranted. The second argument is that the subjective nature of depression and a desire to be akin to other health practitioners has lead a well-intentioned psychiatry to become rigid, insufficiently nuanced, and too focused on drugs in its diagnosing and treatment habits. The third argument, approached from a political economy perspective, is that economic incentives have lead the pharmaceutical industry to use various means of influencing politicians, regulators, researchers, doctors, patients, and the media in order to create a context where far more drugs are being prescribed than would happen without industry intervention.

As this thesis is analyzing the media coverage surrounding the real-world developments that are related to these arguments in order to evaluate its efficacy as a watchdog for the public good, this chapter will end with an explanation of the methodology being used in collecting primary data and measuring the performance of the media in this role.

3) Historical Chapter: The Evolution of Psychiatry in Regards to the Origins, Understanding and Treatment of Depression

The third chapter will explore depression and its treatment from the perspective of psychiatry and its practitioners as well as how the wider public knowledge and opinion has evolved on the topic. It will start by providing a historical narrative of depression as an evolutionary and social construct and will explain the difference between what has traditionally been considered normal sadness and its disordered counterpart melancholia/depression.

The chapter will then also explore the role of the pharmaceutical industry in shaping psychiatry's development including its opinions and understanding of depression as a disorder. It

will then analyze the inherent contradictions within psychiatry that make it more susceptible to opinions, fads, and outside influence than other branches of medicine as well as the developments that would make it become less nuanced and increasingly homogenized in its diagnosing and prescribing.

4) The Political Economy of Prescriptions: The Role of Big Pharma

The fourth chapter will explore the development of the pharmaceutical industry and its relationship with governments, regulators, and other medical establishment stakeholders that allowed it to become the most profitable industry for so many years and gave its companies the incentive and ability to turn antidepressants into the massively profitable products they have become in a way that was not previously possible.

For this, it will look at three main developments. The first is the introduction of an international drug patenting regime that allowed individual drugs and their producing company to go worldwide and what this meant for their relationship with national governments and regulatory agencies in addition to altering how invested pharmaceutical companies were in individual drugs. The second development was the introduction of prescription-only drugs and the change in role that this meant for the relationship between physicians and pharmaceutical companies. The third development was the move towards purely evidence-based licensing of drugs and how this requirement, under a neoliberal regime, would affect the relationship between industry and the researchers responsible for providing evidence of drug safety and efficacy.

After providing the context for the relationships between the pharmaceutical companies and the other relevant stakeholders, this chapter will provide a narrative of the licensing processes of the early second-generation antidepressants, especially the first one: Prozac. This

will be used to demonstrate that these drugs were originally treated – and continue to be treated – far differently than they would be if all stakeholders were fulfilling their respective mandates objectively and without industry influence.

5) Analysis of Media Reporting on Antidepressants

The fifth chapter will examine the collected primary data using the methodology described in Chapter 2 in order to track the reporting on antidepressants. The data will be used to search for trends and to create an evaluative analysis that looks at whether the reporting on antidepressants reflects the new information regarding them, their place in society, and our current understanding of depression. It will also compare that coverage with specific landmark studies, public policy decisions, and news stories in order to analyze whether the media has been providing sufficient coverage of the controversies surrounding antidepressants that call into question their efficacy and safety and whether it appears to have taken an advocative or bystander role of the situation.

6) Conclusion

The sixth chapter will summarize the problems inherent in Canada's reliance on antidepressant medication to deal with the growing problem of depression and the three theories as to why this has not changed. It will then evaluate the quality and kind of media reporting on the issue and put it into the bigger picture context of what it means for a society to possess a profit-driven pharmaceutical sector.

Chapter Two

Theoretical Perspective and Methodology

In a globalized world, Canadians have access to privately and state owned media organizations from all over the world. These enterprises hope to inform, to make a profit, to entertain, to influence opinion or usually some combination of the four. Although most media companies have an agenda that will influence what they choose or choose not to report, the idea is that financial incentives dictate there will always be some organization or even individual person willing to report on important information that is not being covered elsewhere in order to differentiate themselves from competitors and attract an audience and often its attendant advertising revenue. If the story becomes sufficiently important, other organizations will be forced to cover it even if they did not plan to originally or else risk being seen as biased or irrelevant.

As a democratic capitalist nation, the media plays a significant role in Canadian society. We rely on the news media to inform us about important information that we use to make our decisions both personally and at a societal level. A free media's role as public watchdog is so foundational to our system that it is included in our Canadian Constitution's *Charter of Rights and Freedoms* under the heading of fundamental freedom (Section 2, 1982). What and how the news media reports can influence public opinion to the point of making or breaking careers, businesses, or even governments. For this thesis' purposes, it is sufficient to know that the press and overall media can hugely influence the fate of pharmaceutical products and sometimes the companies that make them. Patients and doctors want to know the drugs they are dealing with

work and are safe while politicians and government regulators do not want to be blamed for the consequences of dangerous or ineffective drugs being on the market.

This is especially the case once sufficient media coverage has caused public opinion to widely turn on a drug as happened with benzodiazepines. In the 1960s, benzodiazepines exploded onto the scene. They were anxiolytic drugs that were referred to as tranquilizers since they reduced anxiety. The best known were Librium and Valium and they were extremely effective in their role and marketed so well that doctors began thinking most health problems were simply bottled-up anxiety. This led to Valium becoming the best selling drug throughout the 1970s. However, there were concerns with the severely additive nature of the drugs and the idea that mass-tranquilizing was weakening society and simply masking problems. By the 1980s, the emergence of "health news" like Oprah and Britain's "That's Life" meant that everyone was aware of the controversies surrounding the dependency issues of the drugs. Despite the medical profession mostly defending their safety, these tranquilizers lost the battle of public opinion and came to be seen as dangerous. Essentially, due to the media coverage, benzodiazepines went from being seen as a cure-all to having its users seen as addicts who were victims of the medico-pharmaceutical establishment (Healy, 2004 p. 22-5).

Considering that the media coverage of negative studies was able to turn public opinion and government regulators against benzodiazepines in order to reduce their usage despite the medical profession still believing in them, it is worth questioning why antidepressants, with all of the issues listed in Chapter 1, continue to be so massively prescribed including to people the data suggests will not benefit. Arguably, the medical profession does not believe in their efficacy to any greater extent. In fact, benzodiazepines are in most ways a much more convincing drug as they become effective – obviously so – within minutes instead of weeks and the way they

produce their desired benefit is better understood. The main clinical advantage of SSRI over benzodiazepines seems to be their overdose/negative interaction profile and the fact they are not addicting in the same way, that is, where a patient craves ever greater amounts to gain the benefit. However, this does not mean SSRIs are not dependence-forming and safe to quit at any time as sudden discontinuation can often trigger severe withdrawal symptoms.

Although the drugs act in very different ways and are sometimes used to treat different conditions, there are similarities between the two types. Both classes are useful for some patients in some situations but have side-effects and are much more limited than many of their proponents originally thought. While the research on benzodiazepines was eventually covered by the media sufficiently to inform the masses of their potential dangers so that the people choosing to use them would be properly informed, the same does not seem to have occurred for antidepressants. This calls into question whether the media has been less diligent in their role of public watchdog this time around or whether media reporting has been sufficient but opinions and policy making have become more resistant to change.

It is worth noting that doctors and the rest of the public generally go to different sources for their medical information. Doctors look at the primary research in medical journals while the public relies on journalism that reports on major medical findings in a more laymen-friendly fashion. This means that even if mainstream journalists are insufficiently doing their job, doctors should be seeing these new medical studies that suggest they are overprescribing antidepressants and changing their prescribing habits accordingly. There are several explanations for the consistent increase in antidepressant usage despite the emerging evidence that they are not actually an effective drug in so many of the cases they are given.

2.1 Placebo Theory

One theory is simply that they seem to work although it is usually misunderstood why. Although the placebo effect is now well known, researchers have only recently been truly interested in finding out how and to what extent. For depression, a highly subjective and multifaceted mental disorder, it appears the placebo effect makes up almost the entire benefit of antidepressants for anyone with depression rated less than severe as it is in the majority of cases (Kirsch et al., 2002; Kahn et al., 2005; Barbui, Furukawa, and Cipriani, 2008; Kirsch et al., 2008; Fournier et al., 2010).

Another study showed that, "Although antidepressants alone and psychotherapy alone did differ significantly from placebo controls, treatment-as-usual and waiting list controls, they did not differ from alternative therapies such as exercise and acupuncture or active treatment control procedures (Kahn et al., 2012)." As active treatment control procedures are just the actions surrounding giving a placebo treatment in order to make it seem real, this appears to suggest any active treatment where a professional is spending time with and actively attempting to help the patient is as effective as antidepressants.

Although we do not actually understand why, the placebo effect has been getting consistently stronger over the last twenty-five years, especially for highly subjective conditions like depression, anxiety, and pain. In fact, the difference between drug effect and placebo effect has shrunk so severely that, "Tests reveal that some well-known drugs for depression and anxiety would struggle to pass their clinical trials if they were re-tested in 2015 (Kremer, 2015)." One possible explanation is that research staff are being too warm and optimistic with the patients in the trials. Dr. Nathaniel Katz, the president of Analgesis Solutions, a consultancy firm that attempts to help pharmaceutical companies avoid trial failures, provides instructions to separate

the placebo effect from the drug effect as much as is possible by not offering hope or being optimistic:

> "Telling the truth" means reminding patients that they are part of a trial for a drug that may not work, and which they may not even be given. "Even if it works," Katz says, "it only works for about a third to a half of patients - that's as good as it gets these days."
>
> His company also trains trial researchers to avoid "inappropriately optimistic body language" like putting an arm around the patient, shaking their hand or looking them in the eye. "These are all the things that enhance expectations," says Katz (Kremer, 2015).

Considering the newer classes of antidepressants – the SSRIs, SNRIs, and NDRIs – have more tolerable side-effect profiles than previous types, it is possible that they are simply being given in order to trigger a beneficial placebo effect in many of the cases they are prescribed. It may take doctors and policy makers quite a while more to fully work through the ethics involved in placebos and to learn to harness them in clinical practice. If the benefit of some of our most commonly prescribed drugs can be almost entirely replicated simply with a placebo and by being a warm and optimistic doctor, it calls into question whether so much money should be spent chasing drugs for mental illness when bedside training for doctors seems to be as important as the drugs being given. Anne Harrington's *The Placebo Effect* (1999) discusses the power of the placebo effect while Irving Kirsch's *Emperor's New Drugs* (2009) and studies like *The Functional Neuroanatomy of the Placebo Effect* (Mayberg et al., 2002) are the primary literature covering this ground in relation to the effects of antidepressants specifically.

2.2 Psychiatry-Driven Theory

Another explanation, explored in greater detail in Chapter 3, is that it has primarily been the well-intentioned and self-guided evolution of the psychiatric profession and its unfortunately

rigid and homogenizing diagnostic manual that has led to such heavy prescribing and an inability to move away from drug-based medicine. Due to a desire to be akin to better understood areas of medicine that rely purely on biological indicators and a need to compensate for natural limitations in the discipline which renders its diagnosing highly subjective by necessity, checklist psychiatry has replaced a nuanced understanding of the individual patient's causes of depression in many cases. This results in formulaic diagnosing that has trouble incorporating the unique specifics of an individual patient into their own treatment, resulting in homogenized treatments centered heavily around antidepressants which have been thought to work without needing to deal with non-biological causes of depression such as relationship stress or socioeconomic status. This notion has been most thoroughly explored in Allan Horwitz and Jerome Wakefield's work, *The Loss of Sadness: How Psychiatry Transformed Normal Sorrow into Depressive Disorder* (2007) as well as Allen Frances' *Saving Normal: An Insider's Revolt Against Out-of-Control Psychiatric Diagnosis, DSM-5, Big Pharma, and the Medicalization of Ordinary Life* (2013).

2.3 Political Economy Theory

Finally, there is another, more promising area in which to seek an explanation: the political economy perspective. Political economy studies the multi-disciplinary interplay between politics, economics, law and public policy to determine how, contrary to their stated objectives and rationales, public policies are often determined by the dynamics of wealth and power. Such an approach would suggest, broadly speaking, that continued mass antidepressant prescribing in the face of so much evidence that it is not beneficial to most consumers is primarily driven by the influence of the self-interested businesses, particularly the large

corporations, that profit from the sales of antidepressants in our capitalist system and the structures of society and politics that permit, and even facilitate, this.

In the textbook account of a competitive market economy, things are relatively simple since the products bought are of no concern to the state. There will be competition between firms to maximize their own sales and profits. Market forces will distribute profits and allow consumers to purchase whatever they like best at whatever prices they are willing to pay. At most the state may involve itself and develop regulations to meet certain social goals such as creating minimum wage and age requirements for workers or ensuring minimum environmental or health standards are met by the businesses involved while businesses may lobby government in protest of these or for preferential treatment. Overall though, there is a general acceptance by the public and the state that the economy can self-regulate via market forces with minimal risk.

However, most markets are more complex, featuring the power of large corporations to skew market as well as regulatory outcomes in their favour. This is a considerably complicated issue in regards to medicine. As our individual survival and the productiveness/security of a nation is based on healthy, functioning human bodies, industry related to the health of people is considerably more important to both the state and the individual than most industries. Due to its importance and the complicated nature of medicine, few people are capable of effectively acting as informed consumers and democracies have traditionally demanded much greater democratic and regulatory oversight of health-related industries.

Humans may have always suffered illness and sought to treat them in various ways but in a capitalist system, selling these medicines for profit has become just another way to make money. The commodification of medicine has taken different forms in different phases of

capitalism. Its form today derives from the corporate phase of capitalism which differs from the previous monopoly phase. While both are dominated by large monopoly corporations, prior to regulatory changes in the 1950s and 1960s, these corporations made their higher profits in competition with other firms in the market on the basis of superior technique and productivity (in addition to some collaborative price-fixing) while following these changes, the large corporations primarily earn their higher profits by using their economic and political clout to alter and control the priorities of the state and other stakeholder groups (Healy 2012, p. 8-9, 28-9). This is done to accomplish two main objectives:

1) The expansion of the international sole-ownership patent regime.

Under the World Trade Organization's (WTO) Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement, developed in 1994, WTO member countries are required to extend twenty year copyrights to companies when they discover a new drug that meets patent requirements (Healy 2012, p. 28-9). Under this regime, every new drug is internationally owned by a single company until its patent ends and drug companies are not required to compete on price unless there is a different competing drug for the same illness. In order to avoid price competition, the largest companies work collectively to expand intellectual property (IP) rights on different drugs, none of which has an exact competitor. The high prices they can then charge for them are justified as necessary for expensive trials. However, they still leave big pharmaceutical corporations with exceptionally high returns until the patent ends. This results in a relatively unified and oligopolistic non-generic pharmaceutical sector whose driving motive is selling as many drugs as possible at the highest price the market will allow. Considering this is hope-giving and sometimes life-saving medicine, the market will generally allow very high prices before patents expire at which point competing generic drugs enter the market whose

prices may be as much as 85 percent lower (Gilchrist, 2016 p. 1). This makes increasing patent lengths the easiest way to increase profits.

This is perhaps most blatant in the lobbying for the Trans-Pacific Partnership (TPP), a trade agreement being negotiated between twelve Pacific Rim countries including Canada and the US. According to the humanitarian organization Doctors Without Borders, these IP protection provisions within the TPP would increase drug prices and make medicine less affordable to poor people in developing countries. They would do this by, for example, allowing the extension of patent protection if there were regulatory approval delays and by allowing companies to "evergreen" their patents, that is, alter them in minute ways that would allow them to extend their patent protection (Blackwell, 2015). Considering the benefits seen in the TPP to the non-generic drug industry as a whole, it is not surprising to note that in 2009, years before the TPP debate had become mainstream, lobbying reports in the US showed twenty-eight organizations had filed fifty-nine lobbying reports that mentioned the TPP with almost half of these being pharmaceutical companies or pharmaceutical associations (Drutman, 2014).

2) Controlling the accepted facts and narrative around health conditions and treatments so as to create demand for drugs.

Despite the largest pharmaceutical companies being unified in their support for expanding the patent regime and not required to compete on cost for the same products, some competition does remain. This is chiefly because companies try to get out their own patented version of a treatment for a specific disorder and because generic producers are ready to pounce upon drug lines whose patent protection has expired. However, evidence suggests this competition is not as beneficial for consumers as free-market advocates usually suggest since the competition appears to be one of marketing more than substance. That pursing newer, more

effective drugs has become secondary to marketing and creating drug demand is suggested by the fact that in 2015, nine out of ten of the largest pharmaceutical companies spent more on marketing than research and development with Johnson and Johnson actually spending twice as much. Of the top ten largest companies, only Roche would spend more on R&D. The majority of this marketing budget would be spent influencing health care professionals directly, the people responsible for educating and acting as gatekeepers for consumers entering the medical marketplace (Swanson, 2015). As both very effective drugs and drugs that target illnesses without existing treatments tend to sell themselves, this suggests significant effort is being made at brand differentiation of the type seen with cars and colas. This is a major issues as drugs are not like cars or colas where the preferred choice depends on subjective preferences. There often is a superior drug for any given situation and the one selected by the doctor should not be dependent on which company ran the most successful marketing campaign.

Significant marketing resources are also going towards disease-mongering, the selling of the illnesses themselves in order to create demand for treatments. Investigated by Lynn Payer in her 1992 book, *Disease-Mongers: How Doctors, Drug Companies, and Insurers are Making You Feel Sick*, this takes the form of informing people of existing ones, overstating risks, creating unjustified fear and pushing for the creation/legitimization of new illnesses to be covered by insurance and diagnosed by medical specialists. Basic aspects of life like aging and being unhappy when bad things happen are medicalized and treated as illnesses that require the purchasing of drugs. This is especially the case for mental health disorders which are almost all multi-faceted and subjective in nature (Wolinsky, 2005).

Many things once considered simply as personality traits that may require a bit of willpower or therapy to control have been added to the DSM, the guidebook of official

psychiatric disorders, sometimes referred to as the "bible of psychiatry (Horwitz and Wakefield, 2007 p. 21)." Amongst other additions to the newest DSM, eating too much has become Binge Eating Disorder and excessive temper tantrums in kids has become Dysruption Mood Dysregulation Disorder, both now positioned as mental illnesses that insurance companies must take seriously and that are now fair to treat with drugs (Frances, 2012). As the pharmaceutical industry logically wants to medicalize as much of normal life as possible – since healthy people do not need to buy their drugs – it is likely efforts would be made to influence the doctors creating the DSM disorder guidelines in favour of widening the scope of what is considered disordered. How much and how directly is difficult to know but researchers found 57 percent of the DSM-IV task force had industry connections and 72 percent of the DSM-5 task force had industry connections (Cosgrove and Krimsky, 2012).

There are also very valid concerns with the quality of data being presented to legitimize the volume of drug prescribing that is occurring. The dominant neoliberal economic paradigm, with its goals of downsizing government, deregulating business, and privatizing services previously provided by the state, has resulted in government downloading the running of drug safety trials to the companies themselves with about 90 percent of published clinical trials now sponsored directly by the pharmaceutical industry (Fisher, 2007; LaMattina, 2013). Profit-seeking private drug companies now demonstrate the safety and efficacy of their products by paying profit-seeking private research companies – and the cash-starved universities who must compete with them for contacts – to run trials (Angell, 2005 p. 101). Considering the research companies rely on the drug companies for their profits and desire repeat business, it must be noted there is a much stronger incentive by the research companies for the clinical trials that they are running to be favourable to the drug company employing them than there used to be for

academics who were paid primarily by the state via their institution. This is an issue as there is a significant number of large-scale studies showing that industry-funded research is considerably more likely to show a drug positively than government or privately-funded research (Bekelman, Li, and Gross, 2003; Lexchin et al., 2003; Kelly et al., 2006; Bourgeois, Murthy, and Mandl, 2010).

The data is also then owned solely by the company paying for the research and nobody has any right to access it outside of drug regulators who are generally very reluctant to release any proprietary drug data – even when doing so would better inform doctors and benefit patients – unless health concerns become overwhelming. Even more worrying is that the public often does not know trials exist at all because there is little incentive or requirement for drug companies to show data putting their drugs in a negative light. This means negative tests are often just buried, a tendency that hugely warps the public's perceptions of drug safety and efficacy. This happens despite volunteer patients in these trials usually being informed that society will benefit from the untested treatment they are receiving by adding to the public knowledge base (Wolford, 2014). One study suggests that as many as half of all clinical trials are left unpublished and there is no incentive on the part of the pharmaceutical industry for any of these to be trials that would make people view their products favourably (Riveros et al., 2013).

The capitalist production and marketing of pharmaceuticals is dominated by large corporations which exist and operate in an environment in specific relations with other actors. Molecules are discovered by private pharmaceutical and biotechnology companies as well as academic institutions and other non-profits that are often using public funds provided to them by government organizations like the US' National Institute of Health (NIH) and Canada's Canadian Institutes of Health Research (CIHR). Promising molecules discovered by universities, non-

profits or biotechnology companies are then usually licensed to pharmaceutical companies who take them, in addition to molecules discovered internally, and use their greater resources to refine them, pay to put them through the expensive regulatory trials, market, and ultimately sell them (Goulding and Marden, 2009).

The pharmaceutical companies tend to play it fiscally safe, focusing on creating less risky and less innovative molecules whose mechanisms of action are already understood while purchasing the most promising discoveries from small biotechnology companies and academic institutions that do not usually have the same fiduciary responsibilities to shareholders and can afford greater risk in their research choices. The US would have the greatest percentage of innovative drugs coming from their large pharmaceutical corporations with approximately only half of the scientifically innovative FDA-approved drugs being discovered by biotechnology companies and academic institutions between 1998 and 2007. Outside of the US, the larger pharmaceutical companies tend to focus their efforts on low-risk drugs who already have established mechanisms of action to an even greater degree (Kneller, 2010). Also relevant in the sales chain are the generic companies that wait for drugs to go off patent and then manufacture and market their own versions as well as the pharmacies, the ground level stores that receive drugs from the manufacturers and actually sell them directly to the public.

Due to the complicated nature of human biology and medicine, there are numerous stakeholder groups involved who are not strictly commerce related and who are designed to work as checks and balanced in order to maximize the quality of medical outcomes. Doctors are the informed patient advocates and points of entry into the medical system who must provide prescriptions in order for patients to purchase most drugs. Government-run regulatory agencies such as Health Canada and the US' Food and Drug Administration have been created by

politicians in order to ensure the safety and efficacy of the drugs by data collected by the pharmaceutical-industry hired researchers that run trials which must show sufficient safety and efficacy before a company is allowed to enter a drug into the market. These researchers recruit doctors and patients to be in the trials. There are also medical journals to ensure doctors have the best and most current information in which to provide treatment for patients while journalists and patient advocacy groups help to inform the general population on medical matters and increase the likelihood governments and companies will act in accordance with the best interests of patients. If all of these stakeholders were fulfilling their mandates objectively and without outside influence then the system should be fairly successful. You would get the innovation and efficiency that can result from the incentive of capitalist profit-seeking while the other stakeholders would maintain their credibility, legitimacy and reputations as defenders of patients by ensuring that the public remains informed and that industry incentives promote the general health of society.

However, this perfect scenario relies on stakeholder groups following their mandates faithfully, remaining free from bias. This is difficult as an inherent conflict of interest exists between the drug industry and the rest of the mentioned stakeholders. Most of the stakeholders logically want drugs prescribed in a way that balances the twin goals of minimizing costs and maximizing treatment quality. However, the drug industry naturally wants drugs prescribed in a way that maximizes profits by maximizing costs for stakeholders who pay for their drugs. Jurgen Drews, former head of research at pharmaceutical giant Roche, would state in 2003 that, “the ethics of successful business have replaced those of medicine. The supreme loyalty of today's companies is not primarily directed at patients and their physicians but at shareholders.

Consequently, the most influential figures in today's pharmaceutical companies are no longer the heads of R&D but the heads of marketing and finance (Jurgen, 2003 p. 411)."

Of course, maximizing drug efficacy and keeping their drug costs low often helps maximize profits since it can give their drugs a market advantage over the drugs of their competitors. However, for individual companies and for the industry as a whole, maximizing profits remains paramount within the capitalist system. This means drug companies are driven by an internal logic that prefers patients receive drug treatments over non-drug treatments, expensive drugs over cheaper ones, and perpetual treatments over cures. This last point is demonstrated by the fact that blockbuster drugs – those with over $1 billion in sales annually – are essentially never cures that are taken and then stopped. Instead they are treatments for conditions that need to be taken regularly and often indefinitely. This change in orientation towards perpetual consumers has meant blockbuster drugs have increased from six percent of total drug sales in 1991 to 45 percent in 2006 (Healy, 2012 p. 10).

In addition, most of the stakeholders mentioned above also rely on maintaining a reputation for credibility which means they may be required to discuss drugs negatively in a way that could hurt drug company sales. In these cases, they have opposing priorities from the drug companies who would naturally prefer the coverage of their drugs by other stakeholders be positive in order to drive sales, regardless of accuracy.

In order to maximize profits, the drug industry will naturally want to influence the behaviour of the other stakeholders so that everyone's priorities and interests align as closely as possible with their agenda. This is not surprising. Humans as individuals and groups often attempt to convince or force others to recalibrate their priorities and objectives to more closely

align with their own. Just think of the character of the same name in Mark Twain's book *The Adventures of Tom Sawyer*. When tasked with whitewashing a fence – a tedious chore – Tom immediately went about convincing the other neighbourhood boys that painting the fence with him was fun and in their own interest despite knowing it was not. Convincing others to favour our end goals is completely natural and can often be healthy when it results in a transfer of knowledge and the building of empathy that can come when people are made to see each other's viewpoints. However, the pharmaceutical companies are different in their attempts to influence the other stakeholders who may try to influence them in both theirs means and ends.

There is certainly a large difference in the means to influence of the different stakeholders. The general evolution of traditional pluralism theory, as developed by Robert Dahl, into neo-pluralism provides an enlightening narrative for this asymmetrical competition as it studies opposing forces within a democracy and how it is decided who government is responsive to. Traditional pluralism theory, or pluralism I, argued that the American power structure was made up of competing groups with none being dominant. Political and economic power was not evenly divided but everyone has some power and no single asset confers power sufficient to dominate. Other things like charisma or popular support also had significance and could compete with money. The competing of the different groups in the power system promoted "polyarchy," Robert Dahl and Charles Lindblom's term for a system supposedly operating under democratic rules. It was supposed that under this system, power would be tamed and conflicts would be resolved to a mutually beneficial conclusion for most of those involved. The idea was that the means of the different competing interests was relatively equal and in some kind of democratic equilibrium if only because there could be coalitions formed to counter those becoming dominant. Groups could make up for less money by having wide-spread public support or

exceptionally skilled or charismatic politicians on their side (Manley, 1983 p. 368-70). This appeared likely to be true through the 1950s and the 1960s as one of the main mechanisms of turning money into government influence – lobbying – was found to be barely surviving as an industry in 1963 (Drutman, 2015).

However, this theory had little predictive power when applied to major events and it was eventually understood that competing groups simply did not have equal power to influence events. Coming at the end of the 1960s, pluralism II, or neo-pluralism, would have to concede a special spot for corporate interests in controlling the political agenda (Manley, 1983 p. 370-1). This privileged position would result from two factors: 1) The fact that the government needs the economy to be successful and this requires business optimism and inducements given to business which usually requires business representatives be present for the discussion; and 2) In a market system, decisions made solely by businesses often result in that decision being taken off the government agenda and never made accessible to popular control (Smith, 1990 p. 316).

In addition to the power it wielded simply by virtue of its role in the economy, there would be a wide-spread change in how corporations interacted with the state in the early 1970s in response to the increased influence seen by other societal stakeholders:

> Congress had gone on a regulatory binge in the 1960s—spurred on by a new wave of public-interest groups. Large corporations had largely sat by idly, unsure of what to do.
>
> In 1972, against the backdrop of growing compliance costs, slowing economic growth and rising wages, a community of leading CEOs formed the Business Roundtable, an organization devoted explicitly to cultivating political influence. Alcoa CEO John Harper, one of the Roundtable's founders, said at the time, "I think we all recognize that the time has come when we must stop talking about it, and get busy and do something about it."
>
> This sense of an existential threat motivated the leading corporations to engage in serious political activity. Many began by hiring their first lobbyists. And they started winning. They killed a major labour law reform, rolled back regulation, lowered their taxes, and

helped to move public opinion in favour of less government intervention in the economy (Drutman, 2015).

By 1976, pluralism's evolution into neo-pluralism would be solidified with the acknowledgment by Dahl and Lindblom that, "Businessmen play a distinctive role in polyarchal politics that is qualitatively different from that of any other interest group. It is also much more powerful than an interest-group role (Dahl, 1976 p. xxxvi)."

Perhaps equally important, neo-pluralism would see the state less as an impartial mediator between different groups and more as a collective of often autonomously acting departments and individuals that balance looking after organizational interests and career interests of their own (Smith, 1990 p. 320). Looking from this perspective, elements within the state can be seen as far more open to cooperating with organizations that have the resources to influence them, whether this be through campaign donations for politicians or the offering of well-paying jobs to bureaucrats within agencies tasked with regulating their industry. Indeed, from this neo-pluralist perspective, the acknowledgment that business can be seen as a uniquely dominating force in regards to getting what it wants from government leads to the logical conclusion that its superior resources means it can get desired concessions from other stakeholders as well, even without making use of its influence within the state.

This is important because although industry and the other stakeholders may wish to alter the behaviour of the other groups they interact with, they have decidedly different desired ends. Stakeholders such as patient groups, doctors, regulators, and politicians may desire drug companies to adjust behaviour to be fully honest about their products and to work more in the public interest. This might mean they want the companies to present them with all of the negative data available about their products and to spend more on research and less on

marketing. However, their objective is not to fundamentally alter the purposes of these companies, to stop them from being profit-motivated entities. They want the companies to succeed in making useful products and they need to make a profit to do so. The other stakeholders generally just want the industry to channel that profit motivation down channels that allow for the greatest benefit to society. However, pharmaceutical companies *do* wish to alter the motives of other stakeholders fundamentally. While the industry does not want to make the other stakeholders so transparently unwilling or unable to fulfill their original mandates that public opinion forces politicians to take drastic steps to remedy matters, their ideal situation – and arguably the one that exists – is one where other stakeholders tasked with restricting their profit-maximization in the name of safety, efficacy, or controlling costs have been effectively neutered without it appearing so (Healy, 2012 p. 247).

For this thesis' purposes, the assumption will be made that well-regulated and non-monopolistic free-market enterprise produces the greatest drug innovation. This is certainly debatable for pharmaceuticals considering Czechoslovakia would produce more drugs per capita during the 1950s and 1960s than any other country despite being in the Soviet bloc and even today we see much of the significant innovation coming from the public and non-profit sectors (Healy, 2012 p. 18). However, considering the contemporary economic and political climate, a comparison of the existing system to the idealized version that is often used to justify it is practical.

In an ideal situation for patients – under our existing system – biotech companies, universities, and non-profits would discover interesting molecules that they would license to larger pharmaceutical companies in addition to whatever the pharmaceutical companies themselves developed. The larger companies would experiment with and refine the molecule

before paying reputable researchers to run it through trials designed and executed according to best scientific practices. If the trials show the drug as sufficiently safe and effective for unbiased regulators, the drug would be approved and become available in pharmacies. If not, the studies would still be made available to the public to increase overall knowledge and to prevent other companies from subjecting more test patients to an already failed drug concept. Doctors would read credible medical journals discussing the drugs so that they could make informed judgments about whether it makes sense to prescribe the drug to their patients. Academic researchers would do long-term studies on the drug and if problems were found the study results would appear in medical journals and be reported by regulatory agencies to doctors who would adjust their prescribing habits to best fit the data. Throughout the process, the media would be informing the public of developments while independent patient groups would be lobbying companies, insurers, and governments so that the most effective treatments were available and affordable to the people they represented. If necessary, the informed public may pressure politicians to get involved and create legislation that changes the rules for any involved stakeholders in a way that should hopefully lead to better future outcomes. Any malfeasance by any of the groups would be suitably punished by the legal system or the fully informed purchasing habits of consumers in order to sufficiently disincentivize future reoccurrences. In the end, all stakeholders would be as close to equally informed regarding any drug as possible and would make their decisions solely in line with their mandate which should lead to optimal outcomes and efficiency maximization in the medical system.

Chapter 4 will explore at length why this ideal situation is far from the reality but it is worth providing some examples at the outset of places where the stakeholders who are supposed to provide balance to the agenda of the pharmaceutical industry are possibly compromised in

doing so by relationships with said industry that have at least the appearance of conflicts of interest:

> 1) Between 1998 and 2011, the pharmaceutical industry and healthcare products industry spent $2.1 billion dollars lobbying the US federal government. The top four lobbyists were three pharmaceutical producers and their industry association (Chernomas and Hudson, 2013 p. 148). In 2015, the pharmaceutical industry would spend more lobbying the US government than any other industry and a full 50 percent more than the second largest spender: insurance (Weissman, 2016).
>
> 2) In November of 2014, the Ontario Health Ministry conducted eight drug reviews where thirteen patient advocacy groups spoke. All thirteen declared receiving industry funding, usually from manufacturers of drug treatments for the diseases the advocacy group covered (Goomansingh, 2014).
>
> 3) In Canada, Dr. Joel Lexchin, Associate Professor with the Department of Family & Community Medicine at the University of Toronto, estimated that pharmaceutical companies were spending $1.7 billion per year to promote their products to doctors through drug reps (Square, 2003).

This industry money spent influencing and funding these three difference groups calls into question the objectivity of the government officials, patient groups, and doctors involved since there is no reason to believe profit-maximizing companies would spend money like this without expecting a return on investment. A return on investment necessarily requires a deviation in behaviour away from what the other stakeholders would have naturally done in pursuit of their own mandates. Although the industry may argue their investment into influencing doctors

through a technique like employing drug representatives is benefiting everyone by making the other stakeholders more educated on the disorders and treatments they work with, industry motives have to be seen as inherently at odds with the groups they are claiming to assist. Even pharmaceutical company GlaxoSmithKline's CEO, Sir Andrew Witty, would acknowledge this conflict of interest when the company moved away from sales-based drug rep pay and he stated: "We recognize that we have an important role to play in providing doctors with information about our medicines, but this must be done clearly, transparently and without any perception of conflict of interest (Archer, 2013)."

Regardless of the occasional gesture of good will from a company when faced with sufficient criticism, the logic of capitalism demands efforts be made to bypass, negate, or co-opt any group that can place restrictions on profit-maximization and, unsurprisingly, there are efforts to do so with every group involved. Direct lobbying, gifts, or financial contributions are only the most blatant forms of influencing but even seemingly innocent things such as purchasing advertising within a medical journal or from a media source creates a financial relationship that can alter behaviour and create dependence on the funding of the pharmaceutical company. For instance, one study found that medical journals who received paid advertising from the pharmaceutical industry were less likely to print articles that were positive about dietary supplements (Kemper and Hood, 2008).

There is a large amount of literature already exploring this perspective, much of which covers the same ground. Some of the most important ones are Marica Angell's *The Truth about the Drug Companies* (2005), Ray Moynihan and Alan Cassels' *Selling Sickness: How the World's Biggest Pharmaceutical Companies are Turning Us All Into Patients* (2005), Ben Goldacre's *Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients* (2012), and

David Healy's *Let them Eat Prozac: The Unhealthy Relationship Between the Pharmaceutical Industry and Depression* (2006) and *Pharmageddon* (2013).

In a way, the situation where the self-interested policies of a health-related industry end up limiting the overall quality of health outcomes within a society has been studied and politically dealt with before; the result in most of the developed world was the introduction and expansion of publically-funded healthcare systems to the point that the USA stands alone as an industrialized nation without some form of universal healthcare (Chernomas and Hudson, 2013 p. 2). This state involvement was mostly a result of market failures of the kinds that can be understood through traditional economic theory:

> *efficiency*—since significant market failure exists in the health sector (information asymmetries; public goods; positive and negative externalities; distorting or monopolistic market power of many providers and producers; absence of functioning markets in some areas; and frequent occurrence of high transaction costs)
>
> *equity*—since individuals and families often fail to protect themselves adequately against the risks of illness and disability on a voluntary basis due to short-sightedness (free-riding) and characteristic shortcomings of private health insurance (moral hazard and adverse selection) (Preker and Harding, 2000).

However, even with the similarities between the cases, there has not yet been sufficient democratic pressure to alter the status quo and demand the government take a larger role in ensuring positive health outcomes when it comes to pharmaceuticals in most countries. Despite the differing emphasis between Canada and the US on using government funds to pay for universal healthcare, the two countries remain very similar in their attitude of leaving the pharmaceutical drug discovery and distribution system primarily in the hands of companies that have a fiduciary responsibility to their shareholders to prioritize profits over the health of its customers.

Overall, although misunderstanding the placebo effect and the subjective nature of psychiatry have likely had significant influence on our society's tendency to rely almost solely on antidepressants in the treatment of depression, it is very unlikely that things would have gotten to where they are if there was not so much money to be made by a wealthy and well-connected industry. This aspect will be covered in much greater depth in Chapter 4 in order to build credibility for the overall argument that doctors would not be prescribing these substances at the rate they are now if the role of doctors and the government regulators had not been compromised by the influence of the self-interested pharmaceutical industry.

However, the point of this paper is not to try and break down the respective causes of overprescribing and assign each a percentage of the blame. Nor will it be capable of resolving absolutely the reasons why Japan, Australia, the UK, and the Netherlands are actively moving away from antidepressant treatment while Canada is not. Instead, this paper intends to focus solely on measuring the role of English-speaking Canada's media in informing their readers about the changing views on antidepressant medication that have led the above countries to attempt to change their prescribing rates.

2.4 Methodology

While Chapter 3 and 4 will rely on secondary sources to build a case that antidepressants are overprescribed, Chapter 5 will use primary data to explore the effectiveness of Canada's media in alerting people to this fact. Essentially, it will analyze and code every article from Canada's *The Globe and Mail* newspaper written between 2000 and 2015 that contains the word antidepressant. Each article containing the word will be categorized depending on its content in

order to establish trends in the media's reporting about antidepressants. *The Globe and Mail* will stand as a proxy for Canada's media because it is, by far, Canada's oldest existing national, English-speaking newspaper and is considered Canada's "newspaper of record"[2] (Buchanan, 2009 p. 70).

That range of years was chosen in order to ensure that the focus is not just on the period when significant concerns regarding the safety of the newer and more heavily prescribed classes of antidepressants began to emerge in the scholarly literature but also a sufficiently long period before it so that we can understand how and when exactly these concerns emerged in the media. Prior to 2001, the vast majority of the media coverage surrounding antidepressants had been positive. Since then, studies, and stories have trickled out leading to the doubts that caused the various other mentioned countries to change their tactics in dealing with depression. If Canada's media, represented in this case by *The Globe and Mail*, has been doing its job in informing the politicians, policy makers, and public as a whole and has taken an active advocacy role in transforming the issues it discusses into action then there should be an increase in articles referring to them negatively over time as journalists and columnists refer to previous findings with spikes during years when especially meaningful cases and studies emerged.

The Globe and Mail articles will be drawn from several sources in order to ensure that every relevant article available is included as none of the available sources individually possessed every relevant article. The articles were drawn from three sources in this order so as to guarantee original versions were given priority:

[2] French-speaking Canada has different media and the English *Globe and Mail* will likely carry less significance there. From this point on when referring to Canada in relation to media coverage, English-speaking Canada is what is meant.

1. The ProQuest Historical Newspaper database accessed through the University of Manitoba.

-This database provides PDFs of the original print newspaper. PDFs saved into an electronic thesis database, outlined in Appendix A. Only covers 2000-2012 and missing some articles.

2. The ProQuest Canadian Newsstand Major Dailies database accessed through the University of Manitoba.

-This database provides a text version of the original newspaper print that was typed up by employees of the database after the newspaper was made available. Includes some minor typos. Text copied into MS Word documents which were saved to an electronic thesis database, outlined in Appendix A. Covers from 2000-2015 and missing some articles.

3. *The Globe and Mail* website (www.theglobeandmail.com).

-The newspaper's own archive located on their website. This website provides text versions of the most current versions of the articles which means small alterations may have been made since their original printing in the newspaper. This means there may be small differences in how readers view this version of the story versus the original newspaper print. Will also include articles that were never printed in the newspaper. This becomes increasingly important as a greater number of relevant articles are left out of the typed newspaper in recent years as greater emphasis became placed on on-line news. Text copied into MS Word documents which were saved into an electronic thesis database, outlined in Appendix A. Covers from 2000-2015 and missing some articles.

The search terms are 'antidepressant(s)' and 'anti-depressant(s).' Any articles found with these words in the text or title will be included with the exceptions of paid-for ads since these do not reflect the paper's stance, table of contents since these are only referencing the real articles, and TV guides since these are not actually articles at all.

These articles will then be organized under subheadings in order to find trends. As older, first generation antidepressants have been mostly replaced in Canadian medical practice by those of the second and third generation, with a few exceptions, the focus will be on the newer antidepressants due to contemporary relevance. This means that articles that specify they are

referring to only the earlier antidepressants will not be included in antidepressant reporting trends. Reporting on antidepressants that were widely in use after the year 2000 but whose popularity collapsed after troubling findings, such as Nefazadone, will be included until the date they were officially discredited by Canadian health authorities. This ensures the trends are not warped by negative reporting about irrelevant antidepressants that are generally only used in cases where treatment options have been exhausted since these are not the drugs being argued to be overprescribed. As these articles are all written since the second and third generation of antidepressants took over and mostly replaced the older types in most medical practice, articles that simply use the generalized term antidepressant or anti-depressant will be assumed to be referring to the newer and more frequently used contemporary antidepressants (Symphony Health Solutions, 2015).

Table 2.1 Relevant Antidepressants

Type of Commonly Prescribed Antidepressants	Scientific Name	Trade Names	Creator
Selective Serotonin Reuptake Inhibitor (SSRI)	Fluoxetine	Prozac, Sarafem, many others	Eli Lilly
SSRI	Sertraline	Zoloft, Lustral, many others	Pfizer
SSRI	Paroxetine	Paxil, Seroxat, many others	SmithKline Beecham, now GlaxoSmithKline
SSRI	Citalopram	Celexa, Cipramil, many others	Lundbeck
SSRI	Fluvoxamine	Luvox, Floxyfral, Fevarin	Kali-Duphar, part of what is now Abbott Laboratories
SSRI	Escitalopram	Lexapro, Cipralex,	Lundbeck, Forest Labratories
Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)	Desvenlafaxine	Pristiq	Wyeth, now part of Pfizer
SNRI	Duloxetine	Cymbalta, Ariclaim,	Eli Lilly
SNRI	Milnacipran	Ixel, Toledomin	Laboratoires Pierre Fabre

SNRI	Venlafaxine	Effexor, Efexor	Wyeth, now part of Pfizer
Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)	Mirtazapine	Remeron, Avanza, Mirtazon	Organon International
Serotonin Antagonist and Reuptake Inhibitor (SARI)	Trazodone	Desyrel, Molipaxin, Oleptro, Trialodine,	Angelini Research Laboratories
Norepinephrine-Dopamine Reuptake Inhibitor (NDRI)	Bupropion	Wellbutrin, Zyban	Burroughs Wellcome, now part of GlaxoSmithKline
Serotonergic Antidepressant	Vilazodone	Viibryd	Merck KGaA
Atypical	Nefazodone	Serzone, Dutonin, Nefader	Bristol-Myers Squibb (Discontinued in Canada in Nov 2003)

Not included in the analysis will be the less commonly-prescribed earlier antidepressants and the newer ones that are not often prescribed for depression. This includes norepinephrine reuptake inhibitors (NRI/NERI), tricyclic antidepressants (TCA), tetracyclic antidepressants (TeCA), monoamine oxidase inhibitors (MAOI), lithium, or any others not on the previous list.

There will also be several other codes that any of the articles can possess in order to establish other significant or interesting trends in the reporting on the newer and more commonly prescribed antidepressants. These include:

1. Suicidal Thoughts and Actions - This code will be attached to any article that contains the implication that antidepressants can increase the risk of suicidal thoughts and/or actions.

2. Violence/Crime - This code will be attached to any article that contains the implication that antidepressants can increase the risk people will engage in crime or behave violently towards others.

3. Side-Effects - This code will be attached to any article that discusses negative side-effects of antidepressants. The code will further specify if the side-effects end after treatment is

discontinued or if they are enduring with the subcategories: 'During Treatment' and 'After Discontinuation.'

4. Efficacy - One of these three codes will be attached to every article in order to indicate how the article is attempting to make the read feel about the efficacy of antidepressants:

Positive - Articles will be coded as 'Positive' if the article's tone and content suggests that the antidepressant(s) being discussed are an effective treatment for depression. The article may mention side-effects or risk of the drugs and still be coded as 'Positive' if the article suggests that they are effective in most cases. The exception is if the side-effect(s) mentioned include a significant increase in the chance of suicide since this is the worst possible consequence of depression. Essentially, these articles are trying to increase or would inadvertently increase expectations of drug efficacy.

Neutral - Articles will be coded as 'Neutral' if they are not intended to influence opinion regarding the mentioned drug(s) efficacy in treating depression. This includes financial articles discussing the share-prices of pharmaceutical companies that do not actually discuss the drugs, articles where someone is prescribed an antidepressant to treat something other than depression, and articles that mention someone being prescribed an antidepressant but without discussing its efficacy. Also included are articles discussing antidepressants not on the inclusion list above. Essentially, these articles are not written in a way that would influence expectations of drug efficacy.

Negative - Articles will be coded as 'Negative' if the article's tone and content suggest that the antidepressant(s) being discussed are ineffective or less effective in treating depression than someone who believes them to be effective in most cases would expect. Essentially, these articles are trying to decrease or will inadvertently decrease expectations of drug efficacy.

5. Overprescribed - This code will be attached to any article that contains the implication that antidepressants are being overprescribed.

6. Drug System Failures or Potential Failures - This code will be attached to any article that makes a case for pharmaceutical companies using their wealth and resources to create conflicts of interest in other healthcare stakeholders or to cause other healthcare stakeholders to take actions they would not have if they remained free of pro-industry bias. Examples of this include industry influencing the findings/reporting of researchers who are running their antidepressant trials, industry threatening funding to universities in order to stifle criticism regarding their antidepressants, industry influencing the make-up or role of drug regulators to benefit themselves, industry providing gifts to doctors in order to influence them to prescribe their antidepressants, and any other situations where an antidepressant-producing company is providing money, threatening unjustified legal action, or taking action that would lead to another party's ability to follow their original mandate being seen as compromised.

It also includes articles suggesting pharmaceutical companies engaged in illegal/unethical behaviour in regards to their antidepressant products. These may include concealing relevant information that could lead to patient harm, advertising them for disorders they are not licensed for, and knowingly selling adulterated/unsafe products.

This category will not include articles about unethical behaviour by pharmaceutical companies that are strictly related to financial matters, non-antidepressant drugs, or antidepressant drugs that are not relevant to this thesis.

7. Alternative Treatments - This code will be attached to any article that mentions alternative forms of treatment being equal or superior to antidepressants for treating depression and will specify which alternative(s) is being discussed:

Diet - Any article discussing the alteration of non-drug consumptive habits as a method of treating depression.

Electrical Therapy - Any article discussing the use of electricity as a treatment for depression. Includes Electroconvulsive Therapy (ECT), Transcrainial Direct Current Stimulation (tDCS), Deep Brain Stimulation (DBS) and Electrical-Current Therapy.

Exercise - Any article discussing the use of physical exertion as a treatment for depression.

Light Therapy - Any article discussing the use of artificially-produced therapeutic lighting as a treatment for depression.

Meditation - Any article discussing the use of meditation or the self-directed controlling of one's own thoughts as a treatment for depression.

Nature - Any article discussing the use of being outdoors as a treatment for depression.

Social Interaction - Any article discussing the use of social interaction with non-therapists as a treatment for depression.

St. John's Wort - Any article discussing the use of the herb St. John's Wort as a treatment for depression.

Talk Therapy - Any article discussing the use of conversation with a trained therapist in a professional setting as a treatment for depression.

Other - Any article discussing a treatment for depression that is too rarely mentioned to have its own separate heading (Less than three articles). This includes: Magnetic therapy, negative ion therapy, therapeutic animals, acupuncture, aromatherapy, music/art therapy, humour, and illicit drugs such as marijuana, LSD or ketamine.

Each of these codes will include qualifiers in Appendix A when relevant facts are provided in the article in order to differentiate the severity of depression being treated since antidepressants have often been seen as being more effective for those with severe depression. This means some articles will be coded 'Moderate' if referring to treating someone with moderate or milder depression and 'Severe' if the article is referring to treating someone whose depression is more severe than that. Additional subcategories will consist of 'Youth (< 25)', 'Elderly (> 64)', 'Pregnant', 'Male' and 'Female' if the article specifies that only this group is being discussed. As an example, an article could potentially have the code 'Positive (Moderate, Youth), Negative (Severe)' if it suggested antidepressants are an effective treatment for a youth with mild or moderate depression but was ineffective for people with severe depression. As antidepressants are used across every segment of society, any positive or negative coverage is significant in that it could apply to and arguably affect the consuming habits of a large number of people. Due to this and for simplicity's sake, these qualifiers will be present in Appendix A but will only be discussed in the body thesis analysis if a significant portion of the total relevant reporting.

After applying the applicable codes to all 892 articles in Appendix A, the data will be compared with a body of important landmark studies, policy decisions, and news stories located in Appendix B. Appendix B will constitute important facts surrounding the efficacy and safety of the relevant antidepressants that will be compared with the coverage of antidepressants by *The Globe and Mail*. The media coverage of antidepressants will be scrutinized in several key areas: The reporting on their links to suicide/violence, their side-effects, their efficacy, opinion on their prescribing trends, their political economy/quality of scientific support, their relationship to drug regulators, and their comparison to alternative treatments for depression. This will help deduce whether antidepressant prescribing remains so high in Canada – with only very minimal steps to reduce it compared to some other developed countries – because Canadians were insufficiently informed of important developments regarding these drugs.

Academic studies provide the most important data for the public to be made aware of. In order to qualify for Appendix B, they must provide evidence that is peer-reviewed and within a journal that ranked as first quartile quality by SCImago Journal Rank (SCImago, 2007). If the trials are valuable for demonstrating something precise like antidepressant benefit over placebo then they also must be meta-analyses of multiple trials or individual trials large enough that their margin of error is under the traditionally acceptable 5 percent (500+ participants). In regards to studies showing antidepressant side-effects, some are expected and generally acceptable during a drug-treatment. This means that to qualify, a study must show side-effects that are applicable to humans, significant, continue after ending treatment or be capable of causing harm to the user that is permanent.

Also important are government warnings and policy decisions since these are cases where health regulators have given their own endorsement of scientific data as particularly credible and

noteworthy. In cases where government regulatory bodies of different countries release a similar warning about antidepressants as tends to happen, only the government warnings by the health regulators of whichever English-speaking OECD nation released it chronologically earliest and those made by Health Canada will be included as these are the most essential warnings for the Canadian public to be made aware of. The requirement they be English-speaking OECD nations is because these nations have cultural, economic, and political similarities and linguistic connections to Canada that make the actions being taken in them arguably more relevant to Canadians.

Also included are news stories from non-*Globe and Mail* media sources demonstrating notable conflicts of interest or corruption anywhere within the system responsible for discovering, researching, regulating, manufacturing or prescribing antidepressants that substantially call into question the credibility of claims their safety or efficacy.

Chapter Three

Historical Chapter: The Evolution of Psychiatry in Regards to the Origins, Understanding and Treatment of Depression

In their 2007 work, *The Loss of Sadness,* Allan Horwitz and Jerome Wakefield explain that until recently, there have been two separate conditions that manifested depressive symptoms and that these were sharply differentiated by mental health professionals so that only treatments beneficial to the specific condition would be given. The first was normal sadness or "sadness with cause." This was considered a normal human reaction to any significant loss of loved ones, social status, physical well-being, or material possessions and an obvious link between the cause and the symptoms was generally observable. Traditional treatment of this was simply the comforting of the individual by friends and family so that they could overcome the sadness and move on with their life. No medical intervention was required as this was not considered an illness or disorder. The second type has traditionally been known as melancholia, depression or "sadness without cause." This was considered a disorder relative to normal sadness in that it caused depressive symptoms without having any observable external trigger. Although relatively rare, these symptoms tended to be long-lasting and to recur in those prone to them. These were the standard symptoms that were associated with intense bouts of normal sadness such as insomnia or excessive sleep, social withdrawal, lack of interest in usual activities, loss of appetite, etc. That they occurred without cause or as a disproportionate response to any loss experienced meant they were assumed to stem from some internal dysfunction (Horwitz and Wakefield, 2007 p. 20).

Taken for granted is the notion that sadness is an evolutionarily beneficial response to loss since traits unhelpful to our survival rarely survive natural selection and certainly none so totally debilitating as intense bouts of sadness can be. Although by no means totally confirmed, there are several benefits suspected of normal sadness in humans.

The first, put forward by Australian psychiatrist Aubrey Lewis, is that it is used as an instinctively recognized "cry for help" that draws attention to someone who needs social support. This is supported by the fact that post-partum depression tends to emerge in times of low social support and poor child health. It effectively coerces assistance from those around the mother under the threat that she will be unable to function and care for the child without increased assistance from her community.

A second theory is that depression evolved to benefit children who had just lost their guardians which would usually be their parents. The sadness of losing their protectors results in a "quiet despair" that would be beneficial for not alerting predators now that they are unguarded.

A third theory, suggested by John Bowlby, is that the prospect of the painfulness of depressive feelings following a loss or separation from loved ones led people to more vigorously attempt to maintain their social cohesion. During our evolution, temporary separation from others would have been fairly routine. Becoming depressed about these separations, if they were prolonged, provides an incentive to find each other and maintain our social relationships which would, in turn, increase a community's chances of survival.

A fourth theory is presented by British psychiatrist, John Price. Depression is linked to reduced testosterone, elevated cortisol, and retardation in behaviour and is deeply rooted in the reptilian brain possessed by most vertebrates and all mammals. These changes in body chemistry that make up depression might be the result of the acceptance of defeat in the intraspecies fights

for social status and mating rights so common in the animal kingdom. Price suggested that the negative behaviour, mood and thoughts surrounding depression are adaptive responses to a defeat in a battle for social status because they demonstrate subordination to the victor. Depression is thus part of an involuntary subordinate strategy (ISS) that causes nervousness, anxiety, withdrawal, and lack of self-assertion. Essentially, when an animal judges itself to be weaker than its opponent, its body will automatically ensure that this is actually true and will make this obvious to its competitor. The dominant creature will then usually recognize that the submitting creature has stopped competing and is no longer a threat. This makes the dominant creature more likely to allow the weaker to survive where it may get to reproduce later.

This theory is supported by the fact that lower-status primates are found to be more prone to depression. This also seems to apply to humans who are lower on the socio-economic hierarchy and to people in enduring states of subordination, both of whom have greater risk of depression. Human women are disproportionately affected as they are more likely than men to be in subordinate positions. In addition, it supports the studies which show sadness is a normal response to a reduction in social status.

The fifth theory is that the sadness response prevents rash actions. As it usually emerges following a life crisis where people are forced to reconsider their plans and expectations of their future, the slowing down of their responses may allow them the time necessary to fully evaluate their options and to make the most rational, realistic decisions. Referring to this, psychiatrist Randolph Nesse said, "In this situation, pessimism, lack of energy, and fearfulness can prevent calamity even when they perpetuate misery (Horwitz and Wakefield, 2007 p. 68)."

The sixth is that normal sadness can be a useful trait in causing people to give up on unobtainable goals. The period of reduced activity that normally accompanies sadness can allow

the mental faculties' time to reconsider and recalibrate desired life objectives. The depression often ends when a more realistic plan emerges and new hope for situational improvement is restored (Horwitz and Wakefield, 2007 p. 66-9).

Regardless of which of these theories or combination thereof is accurate for explaining the existence of sadness, they generally indicate that we evolved sadness as a coping response to loss and other setbacks. It is not sadness as such but disordered sadness that needs to be treated and that requires understanding how and why normal sadness becomes disordered and how to prevent and treat it. As the significance of a loss is completely subjective to the individual experiencing it, this disordered sadness is often not the result of physiological issues in our "hardware," that is, our physical brains and bodies. Each person's unique psychological "software" is the result of their upbringing, circumstances, and experience. This means that people put differing value on different things and will respond differently to loss. It also means that people will view the world differently and may experience sadness episodes based on a distorted cognitive perception of the world, themselves, and the future. Due to this, it is difficult to know if a loss response is disproportionate to a loss and if a person actually suffers from a disorder.

Horwitz and Wakefield suggest that the harmful dysfunction (HD) criteria get around this issue by accounting for social norms. They conclude that an individual suffering from a collection of sadness symptoms is actually disordered if a loss response mechanism is unable to perform its biologically designed function and if the resulting dysfunction is harmful according to social norms. This means that if an episode of sadness does not fit into the framework of any of the theories listed above and is judged by your society to be harmful, it can be considered a harmful dysfunction.

Since harmful dysfunctions can be the result of both our physiological and psychological make-ups, "Loss responses can emerge in situations for which they are not designed, they can be of disproportionate intensity and duration to the situations that evoke them, and in extreme cases that can occur spontaneously, with no trigger at all (Horwitz and Wakefield, 2007 p. 33)." They can also begin as a normal, healthy response to loss but become disconnected from their cause to become disordered (Horwitz and Wakefield, 2007 p. 32-3). This wide variety of potential origins for depression makes it difficult for medical professionals to diagnose whether someone's depression is normal or disordered since it is not always obvious if their sadness is fulfilling a biologically designed function.

3.1 A New Understanding of Depression

Depression as a major health concern for society is a relatively new phenomenon. Until roughly 1980, depression was considered very rare. Most nervous states were considered anxiety disorders and only fifty to one hundred people per million were considered to suffer from what was then known as melancholia. This is currently at roughly one hundred thousand per million - a thousand fold increase - despite, or perhaps because of, all of the supposed cures we have developed.

Obviously, there is nothing wrong with correctly differentiating depression from anxiety in order to provide the correct treatment as, until recently, they were treated the same. Generally referred to as “nerves” and “nervous breakdowns,” these issues were to be treated with drugs or talk therapy, a legacy resulting from the success of Freud’s psychoanalytic theories. These nervous issues were treated with alcohol and opiates through the nineteenth century and bromides and barbiturates in the first half of the twentieth century with the addition of stimulants

in the 1930s for people with chronic fatigue. By the 1950s, Dexamyl was in use, a mixed stimulant/sedative that was the original "Mother's Little Helper" and the 1960s and 1970s saw the rise and fall of the tranquilizing benzodiazepines as mentioned above. Stimulants and benzodiazepines would both lose their mainstream status as a panacea due to side-effects, especially addiction issues (Healy 2004, p. 20-4).

Partially responsible for the change in public opinion that led to the fall of the tranquilizers were competing drug companies Mead Johnson in America and Bristol-Myers Squibb in Britain. Both were working on serotonin drugs that would hopefully replace Valium by not being dependence forming. To do this, they sponsored conferences and papers to outline the risk of benzodiazepines. However, their own drugs failed to be capable of replacing them, leaving a vacuum in effective drug treatments for nerves (Sheahan, 2000 p. 479-504). Although unsuccessful following their original unfocused emergence and unable to compete against the market-dominating benzodiazepines, antidepressants would eventually come to fill this role.

The original two antidepressants were both discovered in 1957. The first tricyclic antidepressant (TCA), imipramine, was discovered by Roland Kuhn and the first monoamine oxidase inhibitor (MAOI), iproniazid, was discovered by Nathan Kline. The respective companies working with them, Geigy and Roche, had no interest in marketing them for depression at the time as it was considered so rare. However, when drug company Merk launched their antidepressant amitriptyline in 1961, they decided to market depression as well as their drug. Merk purchased fifty thousand copies of Frank Ayd's 1961 book, *Recognizing the Depressed Patient*, and sent them out to general practitioners free of charge. The book discussed the antidepressant properties of amitriptyline and Merk would give the book to doctors and

psychiatrists wherever amitriptyline was being marketed. However, the drug still did not sell well compared to the reigning benzodiazepines.

In the 1960s and 1970s, several senior biological psychiatrists would begin arguing that many of these patients being seen as anxious were actually depressed meaning they required antidepressants instead of tranquilizers. This lead physician Paul Kielholz in Switzerland, supported by pharmaceutical company Ciba-Geigy, to set up the first meeting of the Committee for the Prevention and Treatment of Depression in 1972 whose mandate was improving the recognition and treatment of depression. Paul Wender and Don Klein would set up the comparable National Foundation for Depressive Illness in the United States in 1983 (Healy, 2004 p. 26-7).

New research backing the newer understanding of depression would come from social psychiatrists. Michael Shepherd in London would suggest in 1996 that it was primary-care physicians actually encountering the majority of nervous problems instead of psychiatrists and that a large percentage of them were likely depression (Shepherd et al., 1966). This would lead to numerous studies in the 1980s where the general population was surveyed for depression and these studies would form the basis of SSRI marketing. Shepherd was unhappy with his research being used as a marketing tool by the pharmaceutical companies, comparing it to the sorcerer's apprentice taking advantage of his master's absence to create havoc within the workshop (Shepherd, 1998).

Another major development occurred in the world of psychiatric drugs in the late 1960s, the rise of the antipsychiatry movement which questioned the legitimacy of psychiatric practices and diagnoses as a whole. This movement was primarily a result of the Rosenhan Experiment

where psychologist David Rosenhan had eight healthy associates get themselves admitted to psychiatric hospitals under the guise of hearing auditory hallucinations which they would immediately say were gone upon after being admitted. In almost no cases were the staff able or willing to recognize these people as non-disordered even though the other patients quickly detected the fraud. The second part of the experiment had a hospital challenge Rosenhan to try and sneak in patients without real symptoms so that the hospital staff could prove they were able to detect them. The hospital would name 41 out of 193 new patients as possibly being the fake patients when, in reality, Rosenhan did not send in anyone. This experiment demonstrated the troubling lack of consistency in the diagnosing criteria shared by the psychiatric profession. There was criticism that psychiatry was inherently unreliable since different psychiatrists would not necessarily diagnose patients who possessed the same symptoms in a similar fashion (Rosenhan, 1973).

This criticism led in 1980 to the creation of the third volume of the Diagnostic and Statistics Manual of Mental Disorders (DSM). The DSM, sometimes referred to as the "bible of psychiatry (Horwitz and Wakefield, 2007 p. 21)," would move beyond its traditional role of outlining known psychiatric disorders to listing the specific symptoms that made up the disorder. The DSM-III would provide operational criteria for psychiatric disorders that would provide practitioners with a checklist of symptoms to look for when diagnosing. It would also see the anxiety disorders broken down into several different disorders while the forms of depression would be collapsed into the single large category - major depressive disorder (Healy, 2004 p. 27-8).

In order to understand how depression suddenly became so common in the 1980s and the ever increasing usage of antidepressants to treat it, it is necessary to understand how this

accusation of unreliability and the new DSM altered psychiatry. The discipline of psychiatry has traditionally suffered from an inferiority complex in the same way political science and economics have. While scholars of these social sciences have historically desired for their disciplines to be considered akin to natural sciences with empirically-proven laws, psychiatry has always desired to be like the other medical disciplines in their methods for diagnosing illness. Psychiatry is the only medical discipline where there are not objective diagnostic tests or demonstrable causes for the vast majority of illnesses it studies. Instead, to diagnose patients, psychiatrists have been forced to rely on checklists of subjective symptoms and their own professional opinion complete with their own personal biases. While any competent doctor looking at your blood tests and seeing sickle-shaped red blood cells will diagnose you with sickle-cell anemia regardless of their opinion on anything else, psychiatry does not have this luxury and diagnoses will necessarily vary.

Even the term illness can be considered inappropriate in the psychiatric context since it is not the case of discovering a new illness by locating actual organic pathologies within a body that cause harmful symptoms like in the rest of medicine. Instead, new illnesses are voted into being by those psychiatrists who are on the team involved in the publication of each subsequent DSM, now on its fifth version. The psychiatrists involved think of habits, behaviours, and mental states which they consider negative or problematic and then design a disorder based around them. After that, anyone that fulfills a subjective checklist of behavioural criteria is considered to have an illness simply because the DSM says they do, not because there is anything demonstrably wrong with the person's physiology. The DSM-listed disorder relevant to this paper, major depressive disorder, falls under this category of non-demonstrable "illness."

Unlike diseases in other medical disciplines, the subjective and non-verifiable nature of mental illnesses means there is virtually unlimited room to expand the number of disorders and the range of people who fall under the category of mentally ill. Every time psychiatrists get together to design a new DSM, the number of disorders increases as each member of the panel gets to add their own pet disorders based around their own research and personal experiences. This phenomenon has been referred to as "diagnostic inflation." Dr. Allen Frances, a professor of psychiatry and the chair of the committee that designed the DSM-IV, said that, "Before DSM-III, there were too few diagnoses - now, because of diagnosis inflation, there are far too many (Frances, 2013 p. 36)."

At the heart of modern pharmaceutical psychiatry is the assumption that somewhere, currently hidden from scientists, there is a chemical imbalance in the brain that causes the negative behaviours labeled as mental illness. For depression, it was believed to be a lack of the neurotransmitter serotonin since Scottish psychiatrist, George Ashcroft, had found lowered levels of the chemical in the spinal fluid of depressed patients and the cadavers of suicides. However, he rescinded his theory when further investigation found that this was not actually a causal relationship (Ashcroft, 2000 p. 189-200). Essentially, it was noted that although genetic factors and stress do affect the brain's physical structure and people with depression did often have reduced serotonin, there was no evidence that this reduced serotonin actively caused the depression. At least as likely was the idea that stressful circumstances and/or genetics led to the depression and that being depressed would cause a reduction in serotonin (Leo and Lacasse, 2008 p. 36).

Despite Ashcroft rescinding the theory and it not being supported by the evidence, the theory appealed to many. It appealed to patients and patient-groups because it fought some of the

stigma surrounding mental health issues. If it is just chemicals in your brain being imbalanced that is causing the issue then there is no room to blame the disorder on some character defect. Who would believe it is possible for a patient to control chemical levels in their brain any more than someone with leukemia can control the number of white blood cells in their body?

Many psychiatrists also desired the theory to be true because it would make them more like other medical practitioners who could diagnose with objective criteria: "For the psychiatry profession, the theory was a major driving force behind the rise of biological psychiatrists within the profession, and moved the profession from one involved in talking to patients about everyday problems, to a profession that was treating their patients' organic diseases—just as the internists were treating diabetics suffering from insulin shortages, the psychiatrists were now treating depressed patients suffering from serotonin shortages (Leo and Lacasse, 2008 p. 36)."

The chemical imbalance theory also appealed to the pharmaceutical industry because a chemical imbalance would likely require the type of chemical treatments that they sold. After all, how could something like simply talking to a therapist rebalance brain chemicals? However, the companies needed to suggest that their drugs "fixed" a chemical level in the brain without stating that the chemical level had actually been the cause of the depression since they had no proof that this was true.

It was clear that they understood this tenuous connection needed to be implied as causal – but never actually so stated in fear of legal reprisal – as early as 1989 in order to sell the drugs. That year, a memorandum from Pfizer's French headquarters suggested when designing the packaging label on their SSRI Sertraline (Zoloft) that: "Considering the fact that the monoaminergic hypothesis of depression is not unique and that some authors have even stated a hyperfunctioning of the monoaminergic pathway, it seems therefore preferable not to write

anything about etiopathogeny of depression, and to describe only the *actions* [sic] of Sertraline (Leo and Lacasse, 2008 p. 37)." They are essentially stating that they do not actually know the cause of depression so they must market the drug based on it reversing one symptom while implying that the one symptom is actually the root cause. One early SSRI advertisement would state, "When serotonin is in short supply, you may suffer from depression (Leo and Lacasse, 2008 p. 37)." Another for the SSRI Lexapro would state, "In people with depression and anxiety, there is an imbalance of serotonin (Leo and Lacasse, 2008 p. 38)." These statements seem to be trying to suggest that adding additional serotonin would remedy things without specifically saying a lack of it was the cause of the depression.

With the majority of patient groups, psychiatrists, and the pharmaceutical industry all generally in favour of this theory for their own reasons and the research seemingly showing that the drugs were effective, the media would generally endorse and accept the chemical imbalance theory as settled science. However, Jonathan Leo and Jeffrey Lacasse would contact twelve media publications that had reported the theory as objectively true in 2006 and 2007 in order to ask for their citations. Several would not reply and several would simply say they definitely existed or that they should look for the relevant articles themselves. Those who provided actual citations would provide articles simply stating the correlation between low serotonin and depression; none would reference a paper arguing the causal relation that they had been reporting (Leo and Lacasse, 2008 p. 38-40).

"This optimism [for the existence a locatable brain-chemical imbalance to explain mental illness] was shared by most biological psychiatrists until about fifteen years ago but, except for a few diehards, is now rapidly fading away. Billions of research dollars have failed to produce convincing evidence that any mental disorder is a discrete disease entity with a unitary cause

(Frances, 2013 p. 31)." Regardless of the science, with the invention of the first SSRIs, pharmaceutical companies brought it back as a convenient and laymen-friendly slogan to drive drug sales. The use of the slogan was successful enough that it is common now for patients to inform their doctors that they are suffering from a self-diagnosed “chemical imbalance" (Kramer, 2002). It also seems likely that people who believe they are suffering from a chemical imbalance would be more likely to request a chemical treatment over something like talk therapy.

This chemical-imbalance theory becomes even less useful when the evidence shows that both drugs that increase serotonin levels in the brain, like SSRIs, and drugs that reduce the level of serotonin in the brain, like reserprine, have been linked to a reduction in depressive symptoms. In addition, if the chemical-imbalance theory of depression were correct, other drugs that rapidly reduce the neurotransmitters serotonin, norepinephrine, and dopamine in the brain should trigger depression yet do not (Kirsch, 2009 p. 63-6). Of course, there are some mental health disorders that are directly linked to observable physical abnormalities or damage within the brain and body. However, these are a small fraction of the huge number of people diagnosed with mental illnesses for which no cause is discerned.

The DSM-III-R, a revised version of the third edition, would emerge in 1987 just prior to two major national depression awareness campaigns that were launched in early 1988 and based upon the groundwork of Kielholz’s Committee for the Prevention and Treatment of Depression. These campaigns were the Depression-Awareness, Recognition, and Treatment (DART) program in the United States and Defeat Depression in the United Kingdom. Both campaigns would be supported by drug company Eli Lilly which had just won FDA approval for its antidepressant Prozac in December, 1987 (Healy, 2004 p. 26-7). The National Institute of Mental Health (NIMH) turned DART into a "private and public effort" to inform people about mood

disorders and the American Psychiatric Association (APA) would create, with pharmaceutical company support, training sessions for physicians and mental health care providers with particular emphasis placed on "biological and pharmacological treatments (Whitaker and Cosgrove, 2015 p. 75-6)." In DART's case, Eli Lilly would also provide two hundred thousand posters and eight million brochures titled *Depression: What you Need to Know*, to be distributed to doctors and anyone who would contact a DART hotline. These brochures also emphasized pharmaceutical treatments.

On one hand, these public-awareness health campaigns were providing useful information that many sufferers would likely benefit from and would likely reduce feelings of social stigma as they became aware of how common the condition was. On the other hand, there seems to be a conflict of interest considering the information regarding the disorder was coming directly from the people who make the profits for the sales of the drugs used to treat it. Even if the conflict of interest does not result in unethical behavior, the perception is still very strong. That Eli Lilly had so much control of the narrative of DART would make one think that they may overemphasize the prevalence of depression and push the biological causation narrative of depression at the expense of other potential causes that may not require pills to fix such as socioeconomic status. This seems possible considering a 1986 poll found that only 12 percent of Americans said they would take an antidepressant; 78 percent said they would just wait until it went away naturally. After DART, *Sixty Minutes* would explain that most doctors now believed depression was caused by a chemical imbalance and that depression could be treated rapidly and effectively with Prozac 70 percent of the time and that this jumped to 90 percent if a second round of treatment was required (Whitaker and Cosgrove, 2015 p. 76). With such a supposedly

effective drug available and a narrative that explained depression was a chemical imbalance that needed drugs, this public reluctance to taking antidepressants would evaporate.

The depression campaigns had two main objectives. The first was to alert physicians and third-party health care payers regarding the huge economic burdens of untreated depression. Considering credible parties now believe depression to be the second or even leading cause of disability world-wide, this appears to have been successful. Whether the primarily recommended treatments actually relieve this economic burden is another matter considering that the frequency of depression has jumped a thousandfold since the introduction of antidepressants (Healy, 2004 p. 27-9). As Dr. Frances states, "A persistent, pervasive, and well-financed "disease awareness" campaign can create disease where none existed before (Frances, 2013 p. 39)."

The second part of the campaign was to shame doctors with the knowledge they were likely missing many instances of depression and by pointing out suicide cases where the person could likely have been saved with better recognition (Healy, 2004 p. 29). This pressure on the doctors has almost definitely shifted the issue from a problem of underdiagnosis to one of over-diagnosis since “there is no evidence that mass detection and treatment of depression has lowered national suicide or disability rates (Healy, 2004 p. 29).”

Healy points out the very real issue that the campaigns were basing their messages on trials that studied people with depression severe enough to be hospitalized for it. This fits with much of the new research suggesting only the most severely-depressed people benefit from antidepressants at all. The drugs need to be taken for weeks before they take effect and patients were told they may feel worse until they do. During this time, there is evidence suggesting the risk of suicide is higher. For long-term sufferers of depression, this long-term treatment with an emphasis on avoiding recurrences makes sense. However, into the 1990s, the drugs were

increasingly given to people outside this category. They were given to people suffering stress reactions during adjustment periods in their lives and to adolescents suffering what was once considered typical teenage turmoil. In both cases, the average depressive episode was less than the time it usually took for the drugs to start working. The expected economic benefits and the predictions regarding reduced disability/suicide rates were developed with the severely-depressed, long-term patient in mind who were just a small fraction of those given the drugs. This meant that the espoused benefits would not emerge on a greater scale when given to the wider society as had been suggested by the campaigns (Healy, 2004 p. 29-30).

The way the new SSRIs were believed to work meant that getting off of them during treatment was never an option recommended by the drug manufacturer. A prolonged period of doing worse on the drugs than before was expected. Patients, doctors, and emergency responders responding to suicide attempts were all informed that feeling terrible and trying to kill yourself were not irregular side-effects of the drugs but instead meant the drug was working. No matter how bad you were doing on them, the pamphlet Eli Lilly provided Prozac-using patients in the UK, titled *Day by Day*, simply said to keep using it with slogans like: "Day 5 - Keep going! No matter how bad you are feeling now, you should feel better in a few weeks (Healy, 2004 p. 192)." This was even a view commonly held by members of Britain's postmarketing surveillance system. A suicide attempt would be treated as the drug beginning to work and taking the patient off the drug would not usually be considered. This essentially implied that the drug would work for everyone and nobody has legitimate reasons to want to quit treatment early. It left no room for the idea that the drug is not working or is making things worse (Healy, 2004 p. 190-2).

Following this 1980s transition towards symptom checklist diagnosing, the number of Canadians receiving prescriptions for antidepressants has climbed from 3.2 million in 1981 to

42.6 million in 2012 (Kirkey, 2014; Hemels, Koren, and Einarson, 2002). This includes children despite no antidepressants having been licensed for adolescents in Canada and despite the US FDA stating they believe the evidence demonstrates that antidepressants increase the risk of suicide in this age group (FDA, 2007). This also includes pregnant women despite the evidence suggesting that they double the risks of birth defects and miscarriages (Healy, Mangin, and Mintzes, 2010).

Unfortunately, a few factors essentially guarantee that this ever-increasing rate of antidepressant prescribing will continue. One is that prescribing drugs is a more profitable route for psychiatrists to take than doing traditional talk therapy, primarily because of what health insurance companies are willing to cover. Psychiatrists providing psychotherapy along with drug prescriptions in forty-five minute outpatient visits have been shown to earn 41 percent less than psychiatrists who choose to simply provide three fifteen-minute psychiatric drug management sessions (Harris, 2011). This has resulted in the number of US-based psychiatrists who provide psychotherapy dropping from 44 percent in 1996-7 to only 29 percent in 2004-5 (West et al., 2003; Mojtabai and Olfson, 2008).

This is unfortunate because psychotherapy has been shown to be as effective as drugs, especially for the mild to moderately depressed, but with no side-effects (Otto et al., 2000; Roshanaei-Moghaddam et al., 2011; Spielsmans, Berman, and Usitalo, 2011). Considering there is a study that suggests as many as 71 percent of people currently receiving antidepressants would fall in this category where psychotherapy would work at least equally well, it seems a lot of people are suffering drug side-effects when it is not necessary (Zimmerman, Posternak and Chelminski, 2002). Although it costs more upfront and takes longer to work, people who recover through psychotherapy do not face the substantial side-effects of the drugs and have been shown

to be half as likely to go into remission as those who recover on the drugs (Andrews et al., 2012). This lower rate of relapse through talk therapy is possible because, as Frances argues, "Taking a pill is passive. In contrast, psychotherapy puts the patient in charge by instilling new coping skills and attitudes towards life (Frances, 2013 p. 103)."

The newer DSMs have also guaranteed that this trend of diagnostic inflation will continue, both as they have tended to lessen symptom requirements for diagnosing and because drug manufacturers leap on them as marketing opportunities. Frances chaired the Task Force that created the DSM-IV which was published in 1994. Under Frances, the committee had attempted to make the new manual as "careful and conservative" as possible, incorporating the lessons learned from the worrying diagnostic inflation that had occurred with the release of the DSM-III. Unfortunately, despite their belief they had managed to limit any negative side-effects of their manual, the new DSM was again used by the pharmaceutical industry to push illnesses for which they could sell their drugs. Following its release was a massive increase in the diagnosing rates of attention deficit disorder, autism, and adult bipolar disorder. Diagnoses' for childhood attention deficit hyperactivity disorder (ADHD) would triple, autism by twentyfold, and childhood bipolar disorder (CBD) would increased by fortyfold. Learning from this experience, Frances makes it clear that it is the dominant interpretation that matters, not the words in the manual themselves. This seems to apply to everything, from theological subjects like the Bible to legal subjects like the Supreme Court's view of the Constitution. It certainly also applies to medicine when one party has a financial interest in having words interpreted in a way that increases product sales. After the committee had released the manual, it became a free-for-all to control the interpretation between patient advocacy groups, physicians, the courts, the schools, the media, drug companies, and other interested parties (Frances, 2013 p. 124-31).

The DSMs have had trouble with major depression disorder despite the definition remaining essentially unchanged since the DSM-III. This is because the definition of major depressive disorder has had to encompass both mild and extremely severe depression and because there is really no way to accurately differentiate the cases of the "normal" and healthy type of sadness from the paradoxically-named mild major depressive disorder. This issue with accurately differentiating between the two has led to expensive, often harmful medication being given to millions of people whose depression is not severe enough to warrant pharmaceutical treatment and who would do just as well with talk therapy or even a placebo (Frances, 2013 p. 136-8).

The new DSM-5 that came out in 2013 will unfortunately make the dividing line between regular sadness and mental disorder even harder to locate. In the earlier editions was something called the "Bereavement Exclusion." Removed in the current edition, this exclusion stated that anybody who had suffered the loss of a loved one within the last two months would require a higher threshold of symptoms to be diagnosed with major depressive disorder since sadness that is intense enough to qualify for MDD after a loss is normal and considered healthy. Essentially the point of the clause was to give the physician two simple options so that they would not say somebody has MDD if it could be better accounted for by normal bereavement (Mario, 2012). The science supported this exclusion clause as a study showed that in the US, 29-58 percent of people would qualify for MDD a year after a loss and roughly 50 percent of widowers would meet criteria for MDD at some point during the first year following the loss (Zisook et al., 1997). Even with the exclusion, they could still be diagnosed with depression but it would require "a longer duration, a more substantial functional impairment, or the presence of specific symptoms

(morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation) (Mario, 2012 p. 1)."

The reason for the removal of the clause as stated on the official DSM-5 website was that there is no real scientific difference between losing a loved one and other stressors that may contribute to MDD. Bereavement loss, like other losses, can trigger a real depressive episode, morph into real depression, or happen parallel to disordered depression and no one should be prevented from being diagnosed in way that allows potentially necessary treatment just because they have lost someone (APA, 2013).

Although Jerome Wakefield and Michael First would agree that loss sadness can become genuine MDD, they argued against removing the exclusionary clause. They note that there are two important aspects of MDD that are generally lacking in bereavement cases which makes them scientifically different. The first is that MDD is generally a chronic disorder where the diagnosis acknowledges that additional depressive episodes will likely occur in the future after the current one has resolved. This is rarely the case for people depressed following a loss. The second is that bereavement sadness is much less likely to have the more concerning depressive symptoms such as a morbid preoccupation with worthlessness, suicidal ideation, marked functional impairment, psychomotor retardation, or psychotic symptoms (Wakefield and First, 2013 p. 3-5).

These differences in the types of symptoms and rates of recurrence make a strong case that bereavement is simply not the same as MDD. By removing the bereavement exclusion, somebody who is showing five depressive symptoms such as depressed mood, fatigue, loss of appetite, loss of enjoyment in normal activities, and trouble sleeping for just two weeks after the death of a child or spouse would qualify for having a mental disorder (APA, 2013). This will

have some troubling side-effects as many grieving people are suddenly added to the ranks of the mentally disordered. First, it will likely lead to expensive and potentially harmful medication for some who will not benefit from it and that might actually become disordered when trying to come off of it. Second, it will distort the depression statistics used by groups such as governments to form policy. Third, insurance companies and potential employers for certain jobs take mental health history into account and may discriminate based on this diagnosis. Fourth, there still remains a social stigma for those suffering mental illness which will be needlessly inflicted on grieving people. As Frances notes, "It is bad enough that stigma is so often associated with having a mental disorder. But the stigma that comes from being mislabeled with a fake diagnosis is a dead loss with absolutely no redeeming features (Frances, 2013 p.104)."

The politics behind the wording of the DSM are extremely important as its influence is so vast. It will affect the diagnosing and prescribing trends of doctors, the demands of patient advocacy groups, and the coverage and reimbursement policies of private and public healthcare treatment and insurance providers. This is concerning as there are some who believe the DSM-5 has been influenced by the pharmaceutical industry even more than its predecessors. The pharmaceutical industry has a large incentive to increase the number of disorders available to doctors and to lower the symptom thresholds required for a diagnosis that may lead to profitable drug sales. Due to conflict of interest disclosure requirements for the DSM-5, 69 percent of the task force members who created it reported having ties to the pharmaceutical industry. This is 21 percent more than the 57 percent that had industry ties who created the DSM-IV. In addition, the disclosure criteria did not require members to report paid-speaking gigs for companies or unrestricted research grants from companies meaning that the number of people with some industry ties may actually be higher. The connections were especially likely in areas where drug

treatment is emphasized (Cosgrove and Krimsky, 2012). This puts everyone who relies on this manual in the tough spot of having to estimate whether these conflicts of interest are benign or not. Simply disclosing the conflict does not guarantee that they did not bias the end product.

This trend towards pharmaceutical-only psychiatry based around ever-expanding subjective diagnosing criteria that appears influenced by the industry which sells the pharmaceuticals is troubling. It allows for the idea of being mentally ill to eventually expand to everybody as the range of behaviours considered acceptable and healthy shrinks and an ever increasing number of historically normal behaviours become labeled as mental disorders that require drug treatments. All this all begs the question, is it actually beneficial to refer to somebody as mentally ill or disordered when their illness cannot be proven to actually exist? The Division of Clinical Psychology (DCP), a subgroup of the renowned British Psychological Society that represents over 10,000 practitioners, believes that it is not. In 2013, they issued a statement calling for the end of psychiatric diagnosis and the abandonment of terms like "illness" and "disorder," arguing instead for a "paradigm shift" away from a biological understanding of mental illness (Doward, 2013). Dr. Lucy Johnstone, a consultant clinical psychologist with the DCP, would say it is not helpful to see mental health problems as illnesses that have biological causes and that, “On the contrary, there is now overwhelming evidence that people break down as a result of a complex mix of social and psychological circumstances – bereavement and loss, poverty and discrimination, trauma and abuse (Doward, 2013)."

Essentially, the DCP wants to acknowledge the fact that the negative or problematic behaviours, habits, and emotions that are currently labeled as illnesses are not the result of abnormalities with our organic "hardware" but are instead a result of our psychological programming, our "software," and how it responds to our environment. In turn, this should lead

towards a holistic approach to mental health and away from a reliance on psychiatric drugs that are designed to alter our biological make-up and fix the ever-elusive "chemical imbalance."

Now, this is in no way to suggest that anything labeled as a mental illness is not real and does not have real-world implications nor are they definitely without a physiological basis just because one cannot yet be found. Although not demonstrable like physical diseases, the consequences of the negative behaviours, emotions, and habits of what are labeled mental illnesses are extremely real and terrible for many people. For anyone who has ever suffered a prolonged period of severe depression, the fact that a psychiatrist cannot objectively prove that you are disordered is of little relief. Continuing the computer analogy, a software issue like a computer virus or the deletion of key operating system files can be as problematic for the proper functioning of your computer as damage to the hardware. However, although both are debilitating and require treatment, the kind of treatment needed must depend on the cause, the severity of symptoms, and on whether the sadness is a biologically healthy response or whether it is disordered.

Considering the large number of people being given antidepressants who either would not qualify as having a mental illness that would benefit from them or whose depression would be insufficiently severe to benefit, it seems the logical conclusion is that we are overprescribing them. Allen Frances, looking at a study of men informed they were HIV-positive at a time when HIV was an assumed death sentence, noted that it was unsurprising that those who were diagnosed as positive gained some depressive symptoms and those diagnosed as negative became happier. More surprising was that almost everyone in both groups had returned to their baseline happiness levels within six weeks. For Frances, "The lesson is clear—we have far too much faith in pills, far too little trust in resilience, time, and homeostasis (Frances, 2013 p. 43)."

Chapter Four

The Political Economy of Prescriptions: The Role of Big Pharma

The role of the pharmaceutical industry in shaping healthcare policy regarding depression must be considered in trying to understand why certain treatments are prioritized over others and why our medical culture has been slow to recognize the limits of antidepressant medication.

Like many western countries, Canada allows its physicians extensive freedom in their drug prescribing decisions. After a medication makes it through Canada's drug regulatory body, Health Canada, doctors are allowed to prescribe it to their patients if they believe it will help. This includes 'off-label' prescribing where the drug being prescribed is not licensed for the issue being treated but the doctor believes it will be of benefit regardless. This freedom to act makes the personal knowledge and experience of individual doctors very important. Although there are general drug and treatment guidelines that doctors can potentially get in trouble for veering too far from, as a rule, governments acknowledge that they are not supposed to interfere with whatever treatment a doctor feels is best for their patient.

Canada has a publicly-funded universal healthcare system in the form of Medicare that provides funding to the provinces and territories so that their healthcare systems can cover the majority of medical costs for citizens in a way that meets national standards. However, Medicare does not require that the provinces and territories cover medication outside of hospitals. This must be paid for either through privately-purchased insurance, an employee benefit plan, out of pocket, or by a provincial pharmacare plan if available. This means the federal government and the provincial governments that provide minimal pharmaceutical coverage have less incentive to attempt to reduce the rates of drug prescribing or ensure maximum efficacy of the drugs prescribed compared with governments that completely fund outpatient medication. This also

means that Health Canada will allow the patenting and use of almost any new drug that appears better in randomized-control trials than placebo, even if it is shown to be less effective and/or more expensive than existing drugs. The idea is that it is the doctor who should be worrying about efficacy and cost-effectiveness, not the regulators who should not be limiting the options of doctors. Due to this hands-off approach by the federal government and lack of nationally consistent healthcare policy, there is a lot of room for pharmaceutical companies to step in and build the narrative surrounding both illnesses and their treatments.

Even more importantly, due to Canada's close relationship with the United States, there is a tendency for US healthcare policies to get imported to Canada and for Health Canada to take cues from the FDA. In addition, due to the interconnectedness of the two nations, Canada's culture surrounding drugs is heavily shaped by the US media including direct-to-consumer advertising (DTCA) that is limited in Canada but still seen by many Canadians who watch US television. This means special care must be paid to the role of pharmaceutical companies and their relationship with the US government in order to understand how they have come to have so much influence over Canadian mental healthcare policy.

To understand this, it is first useful to understand the three major shifts in the relationship between the pharmaceutical industry and the provision of healthcare in general since WWII. These are: 1. The medical profession's changing attitude toward drug patents and the development of an international drug patenting system; 2. A shift to many drugs being prescription only; and 3. A transition to health regulators requiring drugs to target a specific disorder and to be proven effective for it in randomized-control trials.

4.1 A New Drug Patent Regime

The change in medicine's attitude towards patents under neoliberal administrations and the formation of the international patenting system were likely the most important factors in turning the pharmaceutical industry into one of the top three most profitable industries within the forty-seven industries listed in the Fortune 500. In fact, from the early 1980s onwards, it was number one by a large margin before being bumped down to third place in 2003 when some of its most profitable patents expired (Angell, 2005 p. 3-4).

"In the 1970s and 1980s, profitability of Fortune 500 medicine merchants (measured by return on revenues) was two times greater than the median for all industries in the Fortune 500. In the 1990s, when intellectual property protections of the landmark *Hatch-Waxman Act* kicked in, the drug industry's profitability grew to almost four times greater than the median for all industries in the Fortune 500 (Public Citizen, 2002 p. 2)." Considering the sale price of a drug will often fall by as much as 80 percent following the end of a patent and that this occurring to a handful of drugs knocked the industry down two places in the industrial profitability ranking, it is not surprising that the industry takes patents extremely seriously (Angell, 2005 p. 9).

At the end of WWII, only Britain and the US allowed for the patenting of medical products while other countries like Germany and France only allowed patents for the process used to make a medical product. Either way, all of these patent monopolies were only national in scope meaning different companies would often own the rights in different countries. For example, a substance like amitriptyline, the best-selling antidepressant in the 1960s, would be patented by Roche in Switzerland, Merck in the US, and Lundbeck in Denmark. This meant there was no reason for a company to invest too heavily into a single drug since, outside Britain and the US, other companies could simply make the drug as well with a different method.

However, this began shifting when France switched to product patenting in 1960 and Germany in 1967. Companies began applying for product patents in all of the major countries simultaneously in order to prevent competitors from making their own version in a different nation and cutting into profits. This trend would continue and the 1980s would see the foundations laid for international drug patent protection which would be put into practice via the World Trade Organization's Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement in 1994. This agreement would give a corporation a worldwide twenty year monopoly on a product and would make it for them be profitable by focusing on and intensely marketing a single drug worldwide such as Liptor, Nexium or Prozac (Healy, 2012 p. 28-9).

This has had troubling consequences. Patents have traditionally only been given if the product creator was able to prove the drug had clear benefit and was novel, that is, substantially different from other molecules on the market. Of course, drug companies tend to argue that their products are novel and of benefit even when they are not since the monopoly rights granted by active patents allows them to sell their products for substantially more money with competitors prohibited from selling generic versions. Traditionally, countries would grant patents to promote innovation but voters and government healthcare systems were the ones on the hook for the higher costs, meaning they had reasons to disallow frivolous or fraudulent patents such as the American patent on Depakote. This patent was taken out in 1991 on a French anticonvulsant known as sodium valproate that was first produced in 1962. By the mid-1960s, the sedating effects of sodium valproate were known to be useful in treating mania. Abbott would file a patent on semi-sodium valproate in 1991 that was based on making it novel by reducing a small amount of the sodium within the compound, something that was totally irrelevant to its efficacy. Abbott then ran a trial proving its efficacy for mania, a foregone conclusion.

Essentially, the company took an old drug that was already known to be effective for a secondary condition and then changed it in a meaningless way to make it novel even though it was understood to already be effective for said condition in its current cheap, generic form. This would not historically have been granted a patent because nothing was actually contributed. However, after TRIPS went into effect and drug sales became increasingly international, countries attempting to build up their own pharmaceutical industry suddenly had an incentive to give patents to their own companies despite lack of novelty or benefit since foreigners were also paying the higher costs and providing tax revenue. Countries would become committed to backing national companies in the international market and the US had incentive to back Depakote which went on to become a blockbuster – a drug with over a billion dollars in sales – thanks to skilled marketing only made possible by a patent that prevented replication of the molecule (Healy 2012, p. 30-1).

This marks a major shift away from the traditional belief in medicine that creating and providing drugs important for clinical care is neither a commercial nor industrial calling and they therefore should not be patented. This is exemplified by the likes of Ernst Chain and Howard Florey who did not patent their method for producing penicillin in the 1940s and by Jonas Salk who refused to patent his polio vaccine in the 1950s.

Much of the change in how the medical profession saw patents was likely the result of the vast public investment in medical research during WWII. This funding forged partnerships between pharmaceutical companies, scientists and universities, leading in the 1940s and 1950s to the development of the "knowledge economy" and the creation of some of the most novel and effective drugs ever created: antibiotics, antihypertensives, psychotropics, diuretics, hypoglycemics, cortisone, and the first cancer fighting techniques. Truly a golden age for

pharmaceutical innovation where it seemed private and public participants played their role to the benefit of all (Healy, 2012 p. 28-30).

However, it was not to last as industry began to dominate the relationship and drug discovery and manufacturing firmly became considered a commercial enterprise with the quest for corporate profits being the main driver. The neoliberal Ronald Reagan administration in the US would mark this transition and lead to an explosion in profitability for the industry. Before the Reagan period, there was a strong sentiment among intellectuals and academics that there was something unsavoury about getting too close to business and its higher pay, a notion that you could choose to do good or you could choose to do well but it was difficult to do both. This would change under Reagan's rhetoric and the wealth gap that had been narrowing since WWII began expanding again as the stigma of getting rich faded, becoming seen as something more akin to a virtue. The negative notion of "selling out" to industry was replaced by a more positive-sounding one of "partnering" with them.

This change in thinking would also affect people in the field of medicine and it was in this new culture that government initiatives would lead to the hugely increased profitability and influence of the pharmaceutical industry. The biggest was the "technology transfer," the creation of a series of new laws designed to more rapidly turn state-supported research into new products. This was supposed to benefit both citizens, who gained faster access to consumer products based on research they had funded, and also high-tech US corporations whom would be in a stronger position in world markets. The 1980 *Bayh-Dole Act* was the most important of these and it enabled small businesses and universities to patent discoveries coming from research sponsored through the National Institutes of Health (NIH). The NIH was the primary distributor of government funding for medical research.

Before Bayh-Dole, anything discovered via taxpayer funding was in the public domain and free for everybody to use. Now, the small businesses and universities would use their patents to grant the large drug companies exclusive license so that they could use their extensive manufacturing and marketing capabilities to sell the drugs. This would be hugely profitable for the companies and universities but would provide minimum benefit to the taxpayers who funded the research in the first place and who were often unable to afford the new treatments discovered when the drug companies chose to charge too much for the patented drugs. Also important was a group of legislation that started in 1984 with the passing of the *Hatch-Waxman Act*. Originally created to assist the failing US generic drug industry by reducing FDA requirements for bringing generic drugs to markets, the law also provided drug company lawyers a loophole that has been abused to greatly extend the length of their monopoly rights for brand-name drugs (Angell, 2005 p. 6-9).

With a chemical compound now being patented by a single company and having the rest of the world honour that patent, it was possible to have drugs regularly become blockbusters. Essentially by definition, none of these blockbusters drugs would be "cures" in any traditional sense, instead being lifestyle or risk management drugs that would need to be purchased and taken indefinitely. This would also ensure that companies became extremely invested in individual drugs since they would be worth billions over the course of their patent duration. This means companies will defend their blockbusters no matter what because any fines they are required to pay if they are caught breaking laws surrounding their knowledge of drug dangers or lack of efficacy will be only a fraction of what they lose if their drug is removed from the market.

This difference can be seen in the different treatments received by reserprine and the antidepressant Prozac. Back in the early 1950s, the drug reserprine, an early antihypertensive and tranquilizer, was found to be linked to suicidal ideation. It was also owned around the globe by 26 different companies due to the existing patent regime which meant nobody was invested in it enough to really defend it, allowing it to fall into disfavour amongst doctors. In the 1990s, Prozac would also be linked to suicides but Eli Lilly, the sole owner, would suffer hugely if this link became accepted by doctors (Healy, 2012 p. 52-3).

Leigh Thompson, Lilly's chief scientific officer at the time, would state in an internal email regarding a UK drug regulator's concerns about Prozac causing suicidal ideation, "I hope Patrick realizes that Lilly can go down the tubes if we lose Prozac and just one event in the UK can cost us that (Healy, 2012 p. 53)." Another internal memo by Lilly regarding their next blockbuster, Zyprexa, would state, "The company is betting the farm on Zyprexa. The ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve world class commercialization of Zyprexa (Healy, 2012 p. 53)."

The ability to make billions on a single successful drug if the marketing is properly done means there is also a huge incentive in protecting said drug from any bad publicity. This can mean saturation marketing, threatening critics with legal or financial repercussions, or even using financial donations as a way to get institutions to self-censor such as likely happened to Dr. Healy himself. In 2000, after accepting a position at the University of Toronto as a professor of psychiatry in the Mood and Anxiety Disorders Program at the Center for Addiction and Mental Health (CAMH), Healy would give a talk about his concerns that the available data showed Prozac increased the chance of suicide and violence. Although his talk was highly praised by

those viewing it, the job offer was promptly withdrawn without any explanation except that Healy's "approach" was suddenly incompatible with the center. What was likely the real reason was fear for funding they were in negotiation with from Prozac's manufacturer considering Eli Lilly had recently cancelled a $25,000 donation to the Hastings Center, a think tank in New York specializing in ethics, following them publishing an article that was similar in content to Healy's talk (Healy, 2004 p. 235-7).

There have been other similar situations where the industry would target doctors being critical of their products and would get assistance from groups that should be defending the critics. One of the best known examples is the Nancy Olivieri case. In 1996, internationally acclaimed expert on blood disorders, Dr. Nancy Olivieri, was working with deferiprone, a hopeful treatment for genetic disorder thalassaemia major which causes severe anemia in children with it. Her randomized control trial first found it seemed to be ineffective then would come to suggest that it was actually toxic and led to liver fibrosis in some patients. She would suggest this to Apotex Inc., the Canadian generic drug company that was funding her research. They would dispute the drug's risk and argue there was no need to inform patients of the possibility in their consent forms and that doing so would violate the confidentiality she had signed. Dr. Olivieri would tell her concerns to the Research Ethics Board (REB) for the hospital doing the studies, the Hospital for Sick Children (HSC). The REB would tell her to report her findings to Health Canada and to revise the consent forms for her test patients so that their consent to continue the trial would be fully informed. After receiving a draft of the updated consent forms, Apotex would end the part of the trial she was involved in and threatened legal action if Dr. Olivieri informed her patients of the new-found dangers (Thompson, Baird, and Downie, 2001 p. 4-5).

Ideally in this case, the HSC and its affiliated university, the University of Toronto, would have fought to protect her academic freedom so as to ensure that researchers would have the informed consent of their trial patients. Instead, internationally acclaimed blood researchers Dr. Nathan and Dr. Weatherfall would write: "Although the Hospital for Sick Children and University of Toronto knew that [Olivieri's academic] freedom was under attack, Olivieri received harassment instead of support from the hospital and ineffectual support from the university in her legal stand against Apotex (Baylis, 2004 p. 45)."

Just like in the Healy case, the behaviour of the university and hospital appeared to be influenced by drug company money. The official report would state: "Since the early 1990s the University of Toronto and Apotex had been engaged in discussions for a multimillion-dollar donation, intended to allow a new biomedical research centre to be built that would benefit the University and its affiliated health care institutions. In the spring of 1998, agreement in principle was reached on what then would have been the largest donation the University had ever received. It was to have been matched by other sources to provide the approximately $92 million needed for the new biomedical research center. Later in 1998, after the controversy became public, the University and Apotex decided to suspend discussions until the dispute involving Dr. Olivieri and Apotex was resolved (Thompson, Baird, and Downie, 2001 p. 5)." Although not definitive, this conflict of interest makes the company-friendly actions taken by the academic and medical institutions in this case disturbing.

These changes in policy that would essentially turn government and many academic institutions into pharmaceutical industry partners lead it to becoming the most profitable industry until 2003. From 1960-1980, prescription drug sales stayed basically static as a percent of US GDP. From 1980-2000, they would triple as a percent of US GDP (Angell, 2005 p. 3). From

1990 to 2000, the top ten drug companies had profits of nearly 25 percent of sales except for a brief dip around the time of Bill Clinton's healthcare reform proposal. In 2001, the top ten US drug companies in the Fortune 500 were still managing an average net return of 18.5 percent of sales compared to the median return for the other Fortune 500 industries of 3.3 percent. In 2002, the profits from the top ten Fortune 500 drug companies were $2.2 billion higher than the profits from the other 490 Fortune 500 companies *combined* (Angell, 2005 p. 11).

It is impossible to estimate, or likely overstate, exactly how much political clout the pharmaceutical industry gained in this period with access to these kinds of funds. However, it seems likely that it was this influence that convinced Congress to pass the *Prescription Drug User Fee Act* in 1992. This act authorized the pharmaceutical companies to pay fees to their regulator, the FDA, in order to expedite the approval of their drugs. The fee was initially about $310,000 per drug, small change for the companies, and quickly came to make up approximately half of the FDA's budget at around $260 million per year in 2004. This essentially made the FDA dependent on the industry they are supposed to regulate (Angell, 2005 p. 208). It also made the FDA, on average, the fastest approver of drugs in the developed world (Angell 2005, p. 35).

Although it seems like a blessing for taxpayers – getting the pharmaceutical industry to pay for government regulators to safety-check their products with their own money – it has not been a positive experience and seems to have resulted in 'regulatory capture,' that is, having the regulators promote the interests of the industry they are supposed to be policing. The extra funding from the industry has been set aside almost solely to ensure the drugs are approved quickly, not to guarantee they are safe (Angell, 2005 p. 208). This is an issue as the more rapidly a drug gets approved, the less time available to catch any dangers. A point made clear considering that in the decade following the enacting of the *Prescription Drug User Fee Act*, "a

record thirteen prescription drugs have had to be withdrawn from the market - after they caused hundreds of deaths (Angell, 2005 p. 209)."

Considering the lobbying money the industry brings to Washington, the FDA has its work cut out for it in remaining independent, especially considering that the FDA leadership is politically appointed. In the 2002 election cycle, according to the Center for Responsive Politics, the pharmaceutical industry gave 72 percent of the $10 million it donated to campaigns to Republicans. When the well-respected Dr. Alastair Wood was nominated for FDA commissioner in 2002, there was concern that he favoured regulatory action by the FDA too much (Kranish, 2002). Senator Frist, a friend of Dr. Wood and medical advisor to the Bush administration, would be quoted as saying, "There was a great deal of concern that he [Wood] put too much emphasis on [drug] safety (Kranish, 2002)." The Bush administration would predictably veto his nomination. Another candidate for the position who did not make it, Dr. Raymond Woosley, would state, "It is pretty clear that anyone who has said anything that industry doesn't like isn't going to make it (Kranish, 2002)." It was essentially the case that the nomination process for the head of the regulatory agency was in fact regulated by the industry that was supposed to be regulated.

The FDA commissioner eventually chosen by the White House was Dr. Mark McClellan, the brother of White House press secretary Scott McClellan. In a speech in Mexico in 2003, the new commissioner would argue that the US should not reduce its drug prices to be in line with the rest of the world but that the rest of the world should increase theirs to be in line with the US. McClellan would also argue that other wealthy developed nations were essentially violating patents by using price controls to keep their drug costs down (Angell, 2005 p. 212).

This commissioner would be working essentially in tandem with the Bush administration and the Republican-dominated Congress that passed the 2003 *Medicare Prescription Drug, Improvement and Modernization Act*. The bill was seen by many as a gift to the pharmaceutical industry as the funding to provide a prescription drug benefit to seniors was tied to the government's Medicare Part D program not being allowed to use its sizable buying power as leverage to negotiate lower drug prices from the drug companies. Essentially, the bill allowed the Medicare Part D program to spend $400 billion dollars of tax-payer money on drug industry products for seniors over the next decade – although that number was estimated to rise to as much as $534 billion – on the condition that Medicare could not negotiate to ensure they got good value for the money (Oliver, Lee, and Lipton, 2004). Whether the Republican administration and Congress would have been so favourable to the industry without the donations is hard to know but the appearance of such a conflict of interest is jarring.

These political appointees then politicize decisions in the FDA that should be based on science. A 2006 survey by the Union of Concerned Scientists surveyed one thousand scientists working for the FDA and found 61 percent said they were aware of cases where 'Department of Health and Human Services or FDA political appointees have inappropriately injected themselves into FDA determinations or actions.' 18.4 percent say they have personally have been asked, for non-scientific reasons, to inappropriately exclude or alter technical information, or conclusions based on that data, in a FDA scientific document.' Only 47 percent believed the FDA 'routinely provides complete and accurate information to the public' (Fromer, 2006) A US Department of Health and Human Services (HHS) Office of Inspector General had also conducted a survey in 2002 that found two-thirds of FDA scientists did not believe that the FDA adequately monitored prescription drugs and that eighteen percent of those surveyed had been

pressured to grant approval to a drug despite their reservations about safety and/or efficacy. Despite these survey results, the HHS released parts of the survey in 2003 and reported that the FDA scientists had confidence in their decisions (Schmit, 2004).

The FDA also has conflict of interest issues in the eighteen advisory committees that decide whether to approve drugs. These committees consist of outside experts who review the drug applications and make recommendations to the FDA that the regulator will almost always take. There are rules to disallow experts who have conflicts of interest but these are often waived on the grounds that their advice is indispensable (Angell, 2005 p. 210). *USA Today* would examine the committee records in 2000 and find that 92 percent of the committee meetings had at least one member with a conflict of interest and that 55 percent of meetings had half or more of the members with a conflict of interest (Cauchon, 2000 p. 1A).

There would be other issues with the FDA in relation to antidepressants and it is difficult to know how much had to do inherent conflicts of interest between the organization and the industry it was supposed to regulate. Duloxetine, a very commonly used SNRI antidepressant, would undergo a trial asking whether it was suitable for incontinence. During this trial, there would be several suicides which seems like very important information considering these were not depressed patients and were thus not expected to be suicidal (Lenzer and Brownlee, 2008). However, since it was never licensed for incontinence, this trial data was never made available to anyone outside the FDA despite it being very relevant to doctors treating depressed patients until it was leaked (Wood, 2009).

Another part of the problem is the close relationship between regulators and those within industry. People within these two kinds of organizations are involved in the same area of expertise, discuss the same issues, and see each other regularly. Although they are supposed to

be on opposing sides, this contact leads to empathetic relationships which can potentially make regulators more sympathetic to the priorities of industry than they would otherwise be. Humans find it far more difficult to make decisions that will hurt someone's interests if they know the people being hurt personally (Goldacre 2013, p. 123).

These relationships often can also lead to good jobs being offered to regulators within the industry. Although it is not hard to see how regulator's would make good employees for a drug industry – after all, they know the ins-and-outs of the drug approval process from the other side – it is a bit disconcerting knowing that a regulator was making decisions that could harm or benefit a drug company right before getting paid for doing services for that same company. Whether taken or not, the opportunity for this job being used as a bribe in exchange for a desired decision seems to clearly exist. The European Medicines Agency (EMA) especially seems to have difficulty with this and in December 2010 would actually have its executive director Thomas Lonngren step down and begin working as a private consultant for the pharmaceutical industry four days later without the EMA even asking what type of work he would be doing (Goldacre, 2013 p. 125).

Canada's *Accountability Act* currently maintains a five-year ban on lobbying from sufficiently high-ranking government officials but you can still become advisers or public affairs officials immediately after leaving. Although full of loopholes according to critics, this ban makes it more difficult for high-level officials to use their personal connections to lobby the regulatory agency for preferential treatment. However, the opportunity still exists for a company to provide a good job in exchange for favourable treatment from the person while they still work in the Canadian government and also means lower-ranking members of the regulatory agencies can become industry lobbyists immediately after leaving (Maher, 2015).

Although it is hard to know the extent that the pharmaceutical industry's financial and political clout has had on Canadian governing and regulating institutions, the fact Health Canada takes so many of its cues from the larger FDA is troubling and likely means that Health Canada would have pro-industry bias in its decision making even without being directly lobbied. However, Health Canada also accepts money from the pharmaceutical industry in the form of user fees to pay for the approval process which might explain why their decision making is even more secretive in a way that favours industry than the FDA. While the FDA releases the studies it bases it drug approval decisions on, Health Canada keeps them secret so as to protect the industry's commercial interests (Weeks, 2015). Considering the FDA releases their data, there really is no reason Health Canada could not as well.

However, there are examples of more direct industry influence. For instance, the University of British Columbia has an organization known as the Therapeutic Initiative (TI). Set up in 1994 by the Minister of Health before being taken over by the university in 2013, the program is an internationally acclaimed independent drug policy watchdog that provides evidence-based advice to healthcare workers about drug therapies and studies the safety, efficacy, and cost-efficiency of drugs to determine which ones should be offered through BC's Pharmacare. Primarily thanks to the TI, BC had the lowest prescription drug rates in the country amounting to a saving of $700 million a year. In addition, the warnings the TI sent out regarding dangerous drugs have saved many lives with the delays they caused. Slowing the release of the anti-inflammatory drug Vioxx accounts for an estimated 500 by itself.

Despite the success of the program, the BC Liberal Party would reduce its funding from $1 million to $550,000 in September of 2010 and then suspend funding completely in September of 2012, citing a breach of security within the Ministry of Health involving patient's data.

However, no members of the TI were at fault in the incident (Culbert, 2013). Liberal Premier Christy Clark would even justify the cut at one point during the campaign by saying it was to "respect the private sector (Culbert, 2013)," a response that contained more questions than answers. For their part, TI argued that the pharmaceutical industry had been trying to get rid of them for some time and had finally gotten the Liberals to use the breach as an opportunity to do so. Pharmaceutical companies and pharmacies have donated nearly $600,000 to the BC Liberals over the last eight years, roughly fourteen times what they gave to the NDP, their main political rival in the province. The Liberals went on to form a panel, stacked heavily with industry insiders, to reconsider the drug-review process in BC. Predictably, the panel chose to restrict the role of the TI and enlarge that of pharmaceutical companies and patient advocacy groups, most of which receive large donations from pharmaceutical companies (Culbert, 2013). Due to pressure on the government, the TI's funding has been partially restored to its 2010 level of $550,000 (Harnett, 2013).

For this thesis' purposes, it is also worth noting that the TI produced one of their summary letters on the use of antidepressants in youth. They explained that due to misrepresentations of the data by the pharmaceutical industry which inflated the apparent efficacy and safety of the drugs, "The published literature on this topic is an incomplete and inaccurate representation of the totality of evidence. The profession has had a difficult time coming to terms with this fact (Therapeutics Letter, 2004)."

4.2 A Transition to Prescription-Only Drug Sales

Another major in shift in the pharmaceutical drug culture was the 1951 adoption of prescription-only drug laws. Before this, people could purchase essentially any drug at the pharmacy except for the very addictive narcotics like cocaine and opiates which had been switched to prescription-only earlier. However, due to the disingenuous pushing of supposed "cure-alls" by unscrupulous manufacturers and salesmen, laws were passed so that doctors had to write a prescription in order for patients to buy many types of drugs. The idea was that the medically-trained doctors would be able to protect their patients from do-nothing or harmful drugs. Unpredicted at the time, however, was that this change tended to make doctors less objective than before as they were the one writing the note that decided what drug the patient should take. It emotionally invested the prescribing doctor in the treatment and it is human nature to see one's own actions as good. This meant an increased likelihood that doctors would often attribute any improvement in the patient to the drug they were prescribing and any worsening of the patient's condition to the illness being fought. It would also make it more difficult for the patient to decide to get off of a treatment since their doctor had decided this was the best drug for them and a prescription from them would be necessary to start a new one (Healy, 2012 p. 52). This was even more of an issue for something like antidepressants when feeling and doing worse on the drugs for a relatively long-time is supposed to be part of how they work. It could essentially trap you in a treatment you did not want since either doing worse or doing better on it would both be interpreted as the drug working.

Even more worrying, this switch to prescription-only drugs made doctors the main target for the majority of the drug industry’s marketing since they were the gatekeepers to consumer's wallets. This targeting of doctors has taken several forms. As discussed in Chapter 3, there was

extensive campaigning around depression during the release of the first SSRI antidepressants with much of it intended to guilt doctors into imagining all the suicides they could have prevented if they had been actively looking for depression and prescribing these new products. It has also included marketing their drugs to doctors for uses that they have not been approved for, something that is illegal and has resulted in prosecutions in the US that lead to GlaxoSmithKline being fined $3 billion and Johnson and Johnson being fined $2.2 billion (Blackwell, 2014).

Another way has been through pharmaceutical representatives and the influence they have on doctors. In Canada, Dr. Joel Lexchin estimated that pharmaceutical companies were spending $1.7 billion per year to promote their products to doctors through drug reps (Square, 2003). As a doctor should desire the best balance of treatment cost and efficacy and the drug reps desire the use of their own company's most expensive drugs, it is clear they are not working towards the same goal. This means any influence by the representatives can be seen as compromising the objectivity of the doctors, especially when gifts are given. Dr. Arnold Relman, the former editor of the *New England Journal of Medicine*, argued doctors should not be able to gain from any part of the healthcare system besides directly from their own services so as not to bring self-interest into their medical decisions (Chernomas and Hudson, 2013 p. 157-8)

Considering the problematic nature of this, there has been considerable push back by the medical profession and the problem is not what it once was. However, the crackdown will likely be insufficient. For instance, the Ontario College of Physicians and Surgeons are proposing rules that would bar Ontario doctors from accepting most gifts but would still allow them to accept free lunches, drug samples, speaking and consulting fees, as well as funding for educational events. Even if they do not think they do, the research shows that doctor's prescribing habits are influenced by the gifts and visits from drug reps and will continue to be even if they are of lesser

value (Blackwell, 2014). For this paper's purposes, it is also worth noting that even these limited gift restrictions were not in effect when antidepressants first became popular. This means many of those currently prescribing them would have been very much on the receiving end of expensive good-will building gifts at the same time the drug reps were explaining how effective their drugs were.

Another conflict of interest comes through continuing medical education (CME). Most professions require their members take some amount of continuing education courses during their career to retain their license and the pharmaceutical industry has used this as a chance to advertise. In the US, private companies that are funded by pharmaceutical companies have been accredited by the Accreditation Council for Continuing Medical Education (ACCME) to give educational seminars to doctors that allow them to retain their licenses. Industry would pay for 60 percent of this education in 2006 and this share has only risen since (Hébert, 2008). One of the accredited private companies would express its value to the pharmaceutical companies that fund it by stating, "Medical education is a powerful tool that can deliver your message to key audiences, and get those audiences to take action that benefits your product (Angell, 2005 p. 139)." Even Eli Lilly itself is accredited and allowed to educate doctors (Angell, 2004 p. 140). A 2011 survey of doctors would find that 88 percent of the 770 responding doctors believed that industry sponsorship introduced bias to educational events (Tabas et al., 2011).

As a rule, it is rare that businesses spend large sums of money on anything that will not increase their profits so it seems safe to assume that they are getting a return on investment via the prescribing habits of doctors that they have influenced through their educational programs. This merging of education and marketing is troubling due to the basic conflict between the goals of industry and medical professionals. Doctors are supposed to prescribe the most effective

treatment that is fiscally reasonable and to side with the cheapest one when all other things are equal. A drug company wants their most expensive treatments used in order to maximize shareholder returns regardless of effectiveness or whether a competitor has a more effective product.

The situation is also problematic in Canada. Dr. Hébert, referring to 60 percent of US-CME funding coming from industry, would state, "Although there are no reliable data in Canada, there is also no evidence that the situation is any different here (Hébert, 2008 p. 805)." There is a difference between the two countries in that Canadian CME programs are typically not created by industry. Instead, industry tends to provide learning grants as gifts so that doctors can attend programs without paying out of pocket. Although this is still troubling as the research shows gifts influence prescribing behavior, even this policy of keeping industry away from educational programming design seems at risk. In 2009, the Canadian Medical Association was faced with criticism over its decision to team up with pharmaceutical company Pfizer Canada Inc. in the creation of an accredited CME program. Pfizer Canada provided $780,000 to fund an accredited online course that would cover twelve subjects. Although Dr. Shortt of the Canadian Medical Association and Pfizer had said the company would have no influence on how the program was developed, two Pfizer staff members sat on the administrative board that was responsible for overseeing the development of the program (Weeks, 2009). This seems to suggest the possibility that Pfizer may have been able to influence the program's design in order to ensure Pfizer products were given preferential treatment or that no information provided to Canadian doctors would hurt Pfizer's commercial interests even if the information was relevant in order to achieve the best medical results.

4.3 The Evidence-Based Drug Era

The next big change in medicine would come with a transition to a complete reliance on trial-based evidence to decide what drugs were effective and safe for what illnesses. There were two reasons for this change. The first was the findings of the Kefauver Committee which had looked at twenty-two pharmaceutical companies and found the costs to the companies of the goods sold were only 32 percent of sales in 1958 and were managing after-tax returns of 21-22 percent, double that of other manufacturing. The committee rejected industry claims that these high profits were needed for research and development and to compensate for drugs that failed, arguing much of the research being done was of little social value, simply manipulating existing molecules to create new patentable products with little to no new benefit (Comanor, 1986 p. 1178-9).

The second reason was a finding in 1961 that mothers who had taken the hypnotic thalidomide were prone to having babies with deformed flipper limbs. Considering thalidomide had been a prescription-only drug, it was clear that prescription-only was not enough protection for consumers against dangerous drugs and something else needed to be done. Thus began the evidence-based era where massive trials needed to be ran before a drug hit the market in order to demonstrate their value. By 1962, drug companies were required to prove to the FDA that their drugs were a safe and effective treatment for a medical condition through well-controlled clinical trials, the gold standard of which is the randomized-control trial (Healy, 2012 p. 47).

This seems promising on the surface but clinical trials are only as reliable as the people doing the studies. Traditionally, drug companies would pay universities to do their research. In 1990, 80 percent of industry research was done at academic institutions which meant these studies were relatively safe from bias as these medical schools and teaching hospitals had

reputations for objectivity to protect. This would drop to only 40 percent a decade later as a for-profit research industry began building up around the now extremely wealthy drug companies. Although the drug-owning companies were not allowed to simply do their own trials as this would be too blatant a conflict of interest, these for-profit Clinical Research Organizations (CRO) would attract company contracts by being increasingly accommodating to the demands of their drug company sponsor (Angell 2005, p. 101). By 2010, these CROs accounted for approximately one-third of the pharmaceutical industry's research and development spending and would run nine thousand trials in 2008 alone. As for-profits, these companies have a reputation to protect in the same way universities do but in the opposite direction. The more accommodating they are to requests from their sponsors in how they should run their drug trials, the more business they will receive (Goldacre, 2012 p. 111).

The 1980s were a troubling time for academic institutions as neoliberal policies and objectives meant they were already suffering from shrinking reimbursement from patient care and reduced government funding for medical education and clinical trials. In the US government's attempt to downsize and transfer its traditional responsibilities onto the private-sector, there seemed to be a decision that since industry was already funding some of its own clinical trials, why not let them fund them all? The academic institutions responded to this shrinking revenue stream by competing for contracts with the for-profit research companies. To do this, they started becoming equally accommodating of requests that insert conflicts of interest into the results (Angell, 2005 p. 101).

CROs and academic institutions have now been known to do things that were traditionally unheard of in running a clinical trial. One example is researchers accepting gag orders that forbid them from publishing or discussing data from trials they have been paid to

conduct without permission from the drug company. One study looking at forty-four trials, 98 percent of them funded by the pharmaceutical industry, found that sixteen of the trials allowed the companies to see the data as it came in and an additional sixteen of the trials allowed the funding company to end them at any time (Gøtzsche et al., 2006). This meant companies could try to interfere if the study was going badly and that they could prematurely end the trial to hide worsening trends or to exaggerate an early and modest benefit. Even if allowed to finish, forty of the forty-four studies put constraints on publishing rights so that only the company could decide if anybody else saw the trial results at all. None of these studies would mention these restrictions or that the company had the opportunity to interfere with the trial. The scientists who completed this important study were then harassed by Lif, the Danish pharmaceutical industry association, who vaguely accused them of serious misconduct before an investigation found they did nothing wrong. Despite the investigation, Lif would send letters accusing them of scientific dishonesty to their employers, the Ministry of Health, Ministry of Science, and the Danish Medical Association in what appeared to be a blatant attempt to intimidate them and any others who would challenge the industry's methods (Goldacre, 2012 p. 39-41).

Another study in 2005 would look at 107 accredited medical schools within the US and ask their administrators about their contracts. Although they were not required to be honest for this study, a concerning 62 percent said they allowed the contract between the industry sponsor and researcher to be confidential so that people reading the study would have no idea how much influence the sponsor had on the results. Half the centers allowed the sponsor company to draft the research paper, half included clauses forbidding the researchers from sharing their data after it was published, and one-quarter allowed the company to insert their own statistical analyses into the manuscript (Mello, Clarridge, and Studdert, 2005). It is very hard to measure how much

bias this intervening by the company introduces into any study but it certainly calls into question the idea that anyone outside of the company – which makes the profits from selling the drugs – actually understands the real data about the drugs.

In many cases, drug companies would use ghostwriters, that is, ask well-known scientists and thought-leaders for permission to include their name on trials written by others whose name is often not included. This allows the company to add legitimacy to work that may have been done by less reputable researchers who may not be as concerned about maintaining reputations for following objective and unbiased scientific protocol. In exchange, the person who lent their name would look like a more prolific researcher, getting credit for work they did not do. Looking at forty-four trials, one study would find evidence of ghost authorship in thirty-three, or 75 percent, of them (Gøtzsche et al., 2007).

This hierarchy change wherein many universities and their researchers essentially became partners of industry was perhaps exemplified in a *Boston Globe* article. It stated, "Dr. Martin Keller of Newton earned more than $842,000 last year while serving as chief of the psychiatry department at Brown, according to financial records. More than half of his compensation came from the pharmaceutical industry, including companies such as Pfizer Inc., Bristol-Myers Squibb, Wyeth-Ayerst, and Eli Lilly, all of which market antidepressants that Keller lauded in a series of medical research reports (Bass, 1999 p. A1)."

By 2002, the authors of a survey of academic policies on this topic would conclude, “We found that academic institutions rarely ensure that their investigators have full participation in the design of the trials, unimpeded access to trial data, and the right to publish the findings (Schulman et al., 2002 p. 1335).” These trials that the universities sign their names on but have

limited access to the data from are the same trials used by regulators like Health Canada and the FDA to decide if drugs are safe, effective, and should be allowed to market.

The difference in results between industry-funded research and government or independently-funded research is remarkable. One study in 2006 looked at every trial from four academic journals and found that of the 542 trials, industry-sponsored trials were positive 78 percent of the time while independently-funded trials only 48 percent of the time. For competitor's drugs put against the sponsor's own drug, there was only a 28 percent chance of the competitor's being superior (Kelly et al., 2006). Another study in 2010, looking at 500 trials, found that industry-sponsored research was 85 percent likely to be positive while only 50 percent of government-sponsored research was (Bourgeois, Murthy, and Mandl, 2010). In addition, a pair of systematic reviews in 2003 would look at every existing study that examined the relationship between industry funding and results using slightly different criteria. Both would find that industry-sponsored trials were roughly four times more likely to report positively on the drugs (Bekelman, Li, and Gross, 2003; Lexchin et al., 2003). This seems predictable considering a 2009 systematic review looking at surveys from twenty-one studies found two percent of researchers admitted to falsifying or fabricating data at least once and found 14 percent said they had seen this when asked about the behaviour of colleagues. One-third would admit to other questionable research practices and 70 percent would say they had seen them from colleagues (Goldacre, 2012 p. 172-3). This all seems to imply that good science is often taking a backseat to the self-interest of companies and the researchers they pay.

This commercialization of trials has made many doctors so skeptical of industry bias that they are unwilling to supply their own patients for studies which they believe have predetermined results. This is even more problematic as this bias becomes assumed to be in all

studies, even in cases when the study is legitimately more independent as the drug-company providing the funding gets no say in how it is ran (Goldacre, 2012 p. 111-2). Even worse, 84 percent of people are entering these trials are proud of their contribution because they believe that their experience will help other patients by expanding our knowledge. They think this because that is what their consent forms tell them. They are not told the data will only be released to the public if they meet commercial goals and only in a way that benefits commercial interests (Goldacre, 2012 p. 43). It seems likely that many people will be less willing to join these trials when they find out the reality. This means the studies made with these conflicts of interests are also slowing, discrediting, and preventing the creation of unbiased studies.

This industry bias in how studies are run goes hand-in-hand with selective publication bias in order to make it essentially impossible to know if you can trust the published material on a drug. As there are no laws requiring a company to publish all of the trials they have sponsored in trying to get a drug to market and since a drug only needs two trials that show benefit over placebo in order to get it through the FDA, a company can simply keep sponsoring them until chance gives them two that do so. Relevant to this thesis, in 2008, some researchers tried to locate every trial on FDA-approved antidepressants that was reported to the FDA between 1987 and 2004. The researchers found seventy-four trials which had involved a total of 12,564 patients. Thirty-eight of the trials showed the drugs worked and thirty-six said they did not. Thirty-seven of the thirty-eight trials showing they had worked were published in academic journals. Of the thirty-six that showed they did not work, only three were published. Twenty-two of the failed trials simply disappeared and were not published. The other eleven trials that the FDA had concluded showed the drugs had failed were published and written up in a way that made the drugs appear successful. This means that the doctors who rely on these journals to

make their prescribing decisions were led to believe that forty-eight of the studies were positive compared to only three that were not (Turner et al., 2008).

All of these major changes in the relationship between the pharmaceutical industry, the US government, and healthcare culture in general would have a dramatic impact on how SSRI antidepressants would be treated by the medical profession when they came on the scene, including in Canada. Fluoxetine, later branded Prozac, was discovered in 1971 and acquired by drug company Eli Lilly. Alex Coppen, a leading psychopharmacologist who advocated the serotonin hypothesis of depression, would profess hopes it could be used as an antidepressant. This initially appeared unlikely though as Eli Lilly's first trialist, Herbet Meltzer, would find one of his patients getting muscle spasms and another becoming akathisia – a disturbing feeling of inner restlessness – in addition to other symptoms usually associated with antipsychotics. It had little or no effect on depression and other senior clinicians would get the same results with many of the test centers having fluoxetine patients become agitated or akathisia. The stress on the patients seemed severe enough that Lilly monitors recommended that the worst-off patients be also put on benzodiazepines while on fluoxetine. In trying to find what it worked for, it was also provided to patients with atypical psychotic disorder and patients hospitalized with depression. It would actually make the psychotic patients worse and do nothing for the depressives. After being found to be ineffective for obesity, pain syndromes, and several other issues, fluoxetine was about to be shelved. However, it was given one last chance and provided to five patients with milder depression and all would respond. This would lead to Lilly deciding to fully back the drug (Healy, 2004 p. 50-2).

In 1981, former pathologist and psychiatrist Paul Leber would move to a job in the Central Nervous System (CNS) division at the FDA. One of his first acts was to realize that the

current system of comparing new antidepressants to older ones in order to prove efficacy may be a flawed approach since it was possible that neither drug actually worked. Instead, the drugs would require a placebo comparison to prove efficacy. This was worrying for fluoxetine since it had been shown to not work on severe depression and Mianserin, the best-selling antidepressant used in Europe, had failed a US placebo-controlled trial. This possibly meant the test subjects were too mildly depressed, as beating placebos is difficult when dealing with mildly depressed patients, but it also suggested that getting any antidepressants through the regulators would now be more difficult (Healy, 2004 p. 53-4).

There would be three placebo-controlled trials for fluoxetine, now branded as Prozac, in order to gain the necessary two to get through the FDA. The first, Karl Rickels' study in Philadelphia, would find no effect for Prozac. The second was called Protocol 27, a six-centered study that compared Prozac to imipramine and placebo. One of these centers was Jay Cohn from Los Angeles whose study was later discounted by the FDA for being non-credibly favorable to Prozac. In the remaining five studies, Prozac failed to be better than imipramine and was not more effective than placebo in three of them. However, it was more effective enough in the last two that the combined results of Protocol 27 would still be used as a positive study for Prozac. The third study by Louis Fabre would only have eleven patients complete their Prozac treatment over an effective study-period of only four weeks. This very limited study was the second positive required for the drug to pass regulators. If the multi-centered Protocol 27 was broken into pieces then there would be four studies that showed Prozac as more effective than placebo and four that showed it as inferior. A 50 percent success rate at being better than sugar for curing depression does not seem adequate to allow a drug to be titled an antidepressant but it was considered sufficient (Healy 2004, p. 54-5).

Lilly had wanted to launch fluoxetine in Germany in 1984, branded there as Fluctin. German regulators would state: "Considering the benefit and the risk, we think this preparation totally unsuitable for the treatment of depression (Healy, 2004 p. 58)." Despite this set-back, Lilly hoped to launch Prozac in the US in 1986 and the FDA would approve it in late 1987 after much scrutiny regarding serious design flaws in the clinical trials used to get it approved. This was the beginning of an era where less effective antidepressants would begin getting approval and Prozac would launch in Canada and the US in 1988. The FDA's excuse when approving new drugs that would often have maybe two out of six studies showing it to be better than placebo was to simply assume the trials were failures, not the drugs. For Zoloft, there was only one out of the five trials which were done that showed greater efficacy than placebo (Healy, 2004 p. 55). Paul Leber would state, "How do we interpret … two positive results in the context of several more studies that fail to demonstrate that effect. I am not sure I have an answer to that but I am not sure that the law requires me to have an answer to that – fortunately or unfortunately. That would mean, in a sense, that the sponsor could just do studies until the cows come home until he gets two of them that are statistically significant by chance alone, walks them out and says he has met the criteria (Healy, 2004 p. 56-7)."

There was a similar situation when the SSRI citalopram, which goes by the trade names Celexa and Cipramil, received FDA approval to treat MDD in 1998. It was accepted based on the evidence of seven placebo-controlled trials. Of those, two showed small but significant differences while two studies failed to but were considered too small in any case and the other three well-controlled studies failed to show any benefit. Even the two that actually showed benefit only averaged an improvement of two points on the HRSD (Kirsch, 2009. p. 36-7). This is quite a minor benefit considering that people have been shown to improve by as much as six

points on the scale simply by sleeping better even if the person's depressive symptoms do not actually change (Kirsch, 2009 p. 20).

Citalopram would be the only antidepressant case where unsuccessful trials would be publicly acknowledged by the FDA so that prescribing doctors could know they existed and this only happened based on the objections of one man. Paul Leber, the director of the FDA Division of Neuropharmacological Drug Products wrote in a May 4, 1998 internal memo that:

> One aspect of the labeling deserves special mention. The [report] not only describes the clinical trials providing evidence of citalopram's antidepressant effects, but make mention of adequate and well-controlled clinical studies that failed to do so… The Office Director is inclined toward the view that the provision of such information is of no practical value to either the patient or prescriber. I disagree. I believe it is useful for the prescriber, patient, and 3rd-party payer to know, without having to gain access to official FDA review documents, that citalopram's antidepressants effects were not detected in every controlled clinical trial intended to demonstrate those effects. I am aware that clinical studies often fail to document the efficacy of effective drugs, but I doubt that the public, or even the majority of the medical community, is aware of this fact. I am persuaded that they not only have a right to know but that they should know. Moreover, I believe that labeling that selectively describes positive studies and excludes mention of negative ones can be viewed as potentially "false and misleading." (Kirsch, 2014).

However, this man's opinion that doctors and patients should have access to all relevant trials instead of just the positive ones would ultimately change nothing as made clear with the FDA approval in 2011 of the serotornergic antidepressant, vilazodone. Under the trade name Viibryd: "Seven controlled efficacy trials were conducted. The first five failed to show any significant differences on any measure of depression, and the mean drug-placebo difference in these studies was less than ½ point on the HAM-D, and in two of the three trials, the direction of the difference actually favored the placebo. The company ran two more studies and managed to obtain small but significant drug-placebo differences (1.70 points). The mean drug-placebo difference across the seven studies was 1.01 HAM-D points. This was sufficient for the FDA to grant approval, and the information approved by the FDA for informing doctors and patients

reads, “The efficacy of VIIBRYD was established in two eight-week, randomized, double-blind, placebo-controlled trials.” No mention is made of the five failed trials that preceded the two successful ones (Kirsch, 2014)."

Returning to Prozac, soon after reaching market, there would be complaints from prescribing doctors that Prozac was actually causing suicidal ideation and suicide attempts. A paper would be published in the *American Journal of Psychiatry* that looked at several patients whose conditions had deteriorated rapidly upon starting treatment (Teicher, Glod and Cole, 1990). Although the small sample size meant nothing was definitively proven, it was an omen of things to come even though Lilly would write off the findings as flawed. Lilly instead would trumpet the interpretation of a survey of 1017 patients done by researchers at Massachusetts General Hospital which found that Prozac had no greater chance of causing suicidal ideation than MAOIs, tricyclics, lithium or any other antidepressant (Fava and Rosenbaum, 1991).

However, analyzing the same data, David Graham at the FDA, the American College of Neuropsychopharmacology (ACNP) and the researchers Dr. Teicher, Dr. Glod, and Dr. Cole would find that Prozac was actually three times more likely to lead to suicidal ideation than the other drugs (ACNP, 1992; Teicher, Glod and Cole, 1993; Healy, 2004 p. 69). Lilly would not acknowledge these other credible interpretations of the data which showed Prozac as being far riskier than the alternatives.

Lilly would begin their defensive refrain that "It's the disease, not the drug" when treated patients seemed to get worse. It seemed unlikely Lilly actually believed this as during their clinical trials to get Prozac to market, they had put the patients on other medications in addition to Prozac in order to reduce the worrying side-effects (Healy, 2004 p. 64, 72). Dr. Nancy Lord, testifying at a murder case where Prozac was involved, would argue that the drug trial protocols

that got Prozac to market were deeply flawed and that, “In my opinion, this drug has not been approved. It’s been approved with sedatives, but taking fluoxetine all by itself has never been studied (Healy, 2004 p. 90-1).” In any case, Lilly’s blame-the-disease defense would be heavily compromised by a 1991 Yale Child Study Centre study that would find that ten- to seventeen-year-old children being prescribed Prozac for OCD would often become suicidal even though they had no history of depression (King et al., 1991). These feelings would go away when taken off the drug and return when put back on it. They were also dose-dependent with stronger doses causing them while weaker doses did not, a strong indicator of cause and effect (Healy, 2004 p. 72).

By the mid-1990s, Lilly was facing a series of civil suits. 160 of them were consolidated into a Federal Multi-District Legislation (MDL) case and the drug was being cited in a number of crimes. The first of these cases to get to court was the Wesbecker case where Joseph Wesbecker, a man with a history of depression who was on Prozac at the time, walked into his workplace and killed eight people, wounded many others and then killed himself with an AK-47. As the results of this case would set a strong precedent for how the courts treated any criminal cases that involved the drug, its outcome was very important (Healy, 2004 p. 84).

Although the jury eventually decided by the smallest possible margin possible that Prozac and Lilly were not guilty considering Wesbecker's previous history of mental illness, it was discovered after the fact that the plaintiffs had essentially been bribed to make a weaker case then they otherwise would have. Considering it could cost Lilly $150-500 million if they lost plus open themselves up to additional lawsuits that could potentially bankrupt the company, Lilly had offered the plaintiffs a settlement offer in the form of a high/low split. This meant Lilly would be forced to pay out a lot if they lost but that they would also still pay out a quite large

settlement to the plaintiffs even if Lilly won the case in exchange for the prosecutor not opening up questioning on how Lilly conducts its clinical trials (Healy, 2004 p. 94-6).

The man overseeing the trial, Justice John Potter, was incensed. He filed to have the not-guilty verdict replaced with "dismissed with prejudice as settled (Healy, 2004 p. 96)." Potter would later say, "In my opinion, it was not proper because I do not think you should secretly pay money to the other side to have them pull their punches ... I think the public has the right to expect that a trial is a *bona fide* contest and not some sort of show that one side puts on with the consent of the other to influence public opinion. It was done to discourage other plaintiffs and to help settle the pending lawsuits for less money than they might have been settled for otherwise. Between these two parties they got what they wanted but I think a bigger issue is whether the system was somehow corrupted a little bit and I believe it was (Healy, 2004 p. 96)." The Kentucky Supreme Court would receive the case and find that "there may have been deception, bad faith conduct, abuse of the judicial process or perhaps even fraud (Healy, 2004 p. 96)." It seems that when a company is this desperate to hide their methods of running clinical trials that they preemptively hand over large sums of money so that nothing is put on record that there needs to be more regulatory oversight.

There would be other problematic and unethical behavior by pharmaceutical companies that would make questionable the scientific evidence they had put forward to demonstrate the safety and efficacy regarding their antidepressant drugs. For example, international drug company SmithKline Beecham (SKB) – known as GlaxoSmithKline (GSK) since 2000 – was caught with an internal memo advising staff to withhold clinical trial findings in 1998 that indicated their SSRI paroxetine, brand named as Paxil in North America and Seroxat in the UK, had no benefit in treating adolescents. Since the clinical trials were unable to show the drug as

useful in treating pediatric depression in order to get it approved for this purpose, GSK's Central Medical Affairs team (CMAt) recommended the firm "effectively manage the dissemination of these data in order to minimize any potential negative commercial impact (Kondro, 2004)." GSK's Study 329, conducted in the US from 1993-1996, was the largest trial to date on using SSRIs on a pediatric population. It showed no benefit over placebo but CMAt suggested publishing the positive data from the trial in abstract at the European College of Neuropsychopharacology regardless. CMAt also noted, "It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine (Kondro, 2004)."

Bizarrely, the FDA would agree with GSK that the public did not need to be informed about the negative trial results on the drug label and stating: "We agree that ... the results from Studies 329, 377, and 701 failed to demonstrate the efficacy of Paxil in pediatric patients with MDD. Given the fact that negative trials are frequently seen, even for antidepressant drugs that we know are effective, we agree that it would not be useful to describe these negative trials in labeling (Katz, 2002)." It seems difficult to understand what the point of clinical trials are if regulators ignore negative results with the reasoning being that lots of trials do not show the drugs working but we know they do. It seems that the purpose of the trials is supposed to be to show if the drugs work or not in an environment set-up to remove outside variables. Saying we know the drug works so the negative trial results are irrelevant – in this case the largest study on the drug to date – seems to have the whole process backwards.

The trial study was published in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 2001 where it became controversial for downplaying the negative results in addition to being ghostwritten by a public relations firm hired by SmithKline Beecham

(McGoey and Jackson, 2009). Soon after, Britain's Medicines and Healthcare products Regulatory Authority (MHRA) advised doctors against the use of paroxetine in people under 18 as Study 329 showed it was ineffective and increased episodes of suicidal behaviour. France, the US, and Ireland quickly did likewise (Kondro, 2004).

The MHRA would run an investigation into GSK's conduct but would announce in 2008 there would be no charges since it was believed the laws were unclear at the time. Regardless, GSK would settle a lawsuit for withholding data filed by New York State Attorney Eliot Spitzer in 2004 for $2.5 million and would be fined $3 billion by the US Justice Department in 2012 for unlawfully promoting Paxil for people under eighteen, preparing a misleading article on Study 329, withholding information on a diabetes drug, and improperly marketing a half-dozen other drugs. Whether these fines were sufficient to disincentives others is debatable as GSK made $11.6 billion from paroxetine sales alone from 1997-2006. Despite all of this, the study was never retracted because the journal stated the data showing the drug did not work was available for anyone to interpret. This means Study 329's conclusion that "Paroxetine is generally well tolerated and effective for major depression in adolescents" remains in use and widely cited despite getting the company successfully sued for it under the False Claims Act (Thomas and Schmidt, 2012). However, despite never retracting it, it should no longer find much traction with the release of Restoring Study 329, a new study that looked over the same data and concluded "Neither paroxetine nor high-dose imipramine demonstrated efficacy for major depression in adolescents, and there was an increase in harms with both drugs (Le Noury et al., 2015 p. 1)."

In the end, it is almost impossible to get a fair impression of antidepressants based on industry-funded research. Proof of trial-bias within industry-funded studies and of behaviour by regulators that suggests their independence has been compromised calls into question the

credibility of all industry-funded and favouring decisions and evidence. How are patients, doctors, and insurers supposed to make informed judgments about what drugs to take, prescribe, or cover when they cannot trust the data to be unbiased? We are instead forced to rely on independently-funded research that studies the drugs after they are in use by the public but these are few and far between. Although the ones that exist seem to suggest that there is still value in antidepressant medication as a treatment in some cases, they also suggest that the number of people who would benefit from them is significantly less than the number currently being prescribed them.

Chapter Five

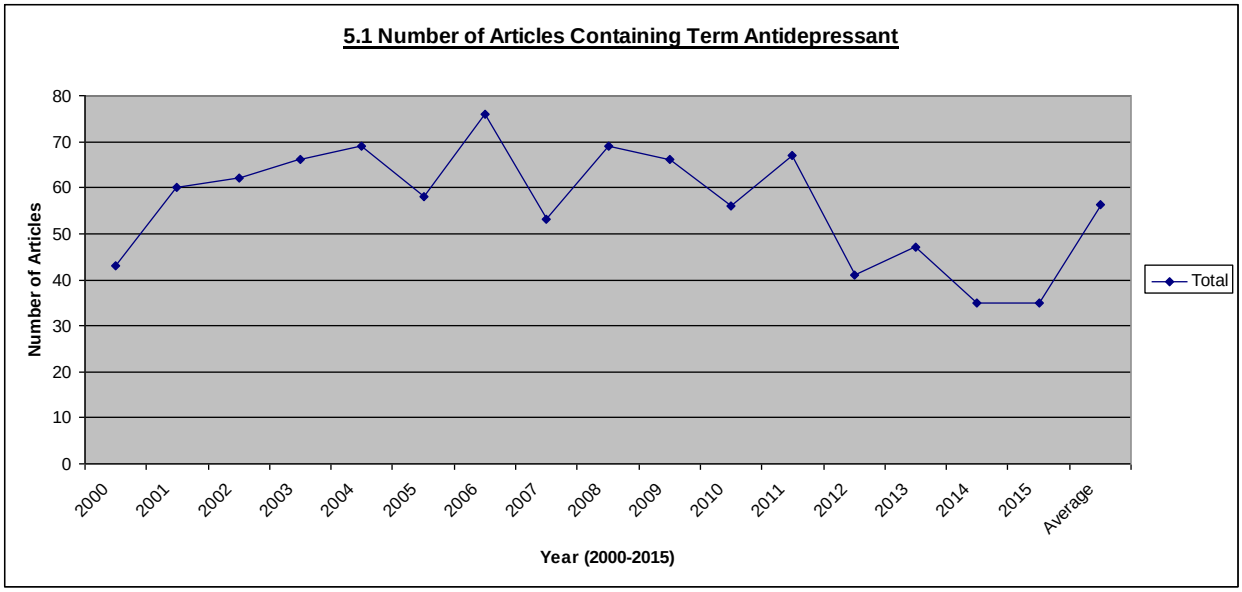
Analysis of Media Reporting on Antidepressants

Whatever your opinion on the efficacy of antidepressants, it seems difficult to argue against the idea that people should be aware of the facts and controversy surrounding them. Doctors are required to make prescribing decisions based on the information available and generally trust that regulators and government legislation will ensure they have the best possible. However, the previous chapter seems to suggest that this is not necessarily true. If people are aware of this controversy then they can weigh the risks of taking antidepressant medication with a greater understanding of the variables that informed their doctor's decision to prescribe them a drug. They can ask their doctors what information they are basing their prescription-writing on and if they believe the information to be compromised, can inquire if a different drug or a non-drug treatment might be preferable for them. In addition, as informed participants in a representative system, they can apply pressure to government to optimize healthcare system outcomes.

There are 892 relevant articles from the years 2000-2015 in Canada's *The Globe and Mail*, our "newspaper of record (Buchanan, 2009 p. 70)," located in Appendix A. These will be used as a proxy for overall media reporting on antidepressants and will be compared against a list of reference points in the form of significant studies, government decisions, and stories from those years that relate to the various facets of the antidepressant situation. These reference points, located in Appendix B, are selected for their significance which meant they should have influenced public opinion regarding the efficacy and/or safety of antidepressants if and when reported on.

As the articles in *The Globe and Mail* are being searched for using keywords that are variations of the term 'antidepressant,' all reference points will have to be related to antidepressants and not simply to the pharmaceutical system as a whole. This comparison of media stories and reference points will allow for the analysis of reporting trends and provide data regarding whether the reporting on antidepressants has been sufficient to alert the public and everyone involved in the healthcare system about the controversy surrounding the presumed benefits of antidepressants.

The overall question to answer in the analysis section is to what degree regarding antidepressants is the media taking a leadership/advocacy role, to what degree is it attempting a purely objective, bystander role, and to what degree is it failing in its duty to inform altogether. If it is embracing an advocacy role then there should be a consistent increase in annual negative reporting on the various troubling aspects of antidepressants and the system that made them the primary method used to deal with depression in an attempt to slow the ever-increasing prescription rates. If it is attempting to simply objectively report facts without attempting to influence society in a specific direction then there should be spikes in years where negative data regarding antidepressants comes to light but no general trend towards greater negative reporting from year to year. If it is failing in its duty then it will be failing to report on major events altogether.



The overall number of articles containing the terms 'antidepressant(s)' and 'anti-depressant(s) has gone in a relatively parabolic arc from 2000-2015 with the last four years being lower than the average and the most recent two years being the lowest of the entire period. This reduction in reporting is despite record high usage levels and is troubling considering that new facts did not stop coming out in 2011.

A 2012 analysis of the existing data would show a combination of antidepressants and therapy as the best treatment but it would also show that although antidepressants were slightly more effective than simply being handed a placebo, placebos given in specific professional way and most alternative treatments were as effective as antidepressants alone (Khan et al., 2012). This seems relatively damning to the medical process Canada is engaging in where vast numbers of people are simply handed antidepressants that possess side-effects and high depression relapse rates without receiving any kind of socialized treatment process that builds resilience. The data was clear now and it seems should have resulted in numerous articles providing a call-to-arms to alter the medical system to reflect that the purely biological theory of depression – which had

designated antidepressant medication as inherently fundamental to treatment – was dead. There was one article explaining this (Appendix A: 17/05/15)

5.1 Suicidal/Violent Thoughts and/or Actions

Antidepressant-linked suicidal and violent behaviour are combined into one category due to their shared characteristics of being, unlike other side-effects, generally sudden, difficult to predict, and psychological in nature.

Timeline:

December 7th, 2000 - Dr. David Healy would have his job offer as Clinical Director of the Mood and Anxiety Disorders program at the University of Toronto revoked after his academic speech on November 30th where he suggested Prozac may cause suicide or violent behaviour in some patients. Eli Lilly, the manufacturer of Prozac, was in deals to provide significant funds to the university (Appendix B:1). There would be significant reporting on the rescinding of Healy's job offer although it would not come until the next year when the facts were made available. With its wider implications regarding academic freedom, there would be nine articles that would discuss the case over the year 2001 (Appendix A:14/04/01, 18/04/01, 21/04/01, 30/04/01, 06/09/01, 07/09/01, 08/09/01, 24/09/01, 29/12/01). This meant there was significant media coverage of the potentially suicide/violence-causing effects of the SSRI Prozac.

June 10th, 2003 - The UK Committee on the Safety of Medicines (CMS) would announce that the risk of self-harm and suicide for people under 18 using the SSRI paroxetine

outweighed any benefits (Appendix B:2). There would be a paragraph on a business news page making mention of this (Appendix A: 11/06/03).

August 22th, 2003 - Wyeth released a warning to doctors about an increased risk of suicide in youth associated with their antidepressant venlafaxine (Appendix B:3). No article would mention this company warning.

December 10th, 2003 - Britain's Medicines and Healthcare products Regulatory Agency (MHRA) would finish their systematic review of SSRIs in paediatric care and release a statement stating no SSRI antidepressants should be used on people under 18, except fluoxetine, due to suicide risks (Appendix B:4). There would be several articles early in 2004 mentioning Britain's efforts to ban most SSRIs in youth but only after Health Canada had released their own warning regarding the drug risks on February 3rd (Appendix A: 04/02/2004, 17/2/04, 20/02/04, 23/03/04, 23/04/04). This meant the dangers were not mentioned by *The Globe and Mail* for almost two months after being formally acknowledged by the UK's health regulators.

December, 2003/2004 - A large-scale literature review would catalogue the available trials and studies demonstrating definitely that adverse drug reactions to SSRIs can cause "mild agitation to manic psychoses, agitated depression, obsessive preoccupations that are alien or uncharacteristic of the individual, and akathisia. Each of these reactions can worsen the individual's mental condition and can result in suicidality, violence, and other forms of extreme abnormal behaviour (Appendix B:5; Breggin 2003/2004)." No article would mention this study although an article would come out ten months later stating definitively the existence of a link between SSRIs and violence, self-harm, and suicide (Appendix A: 20/09/03).

February 3rd, 2004 - Health Canada would advise Canadians under eighteen to consult their doctors to see if staying on their SSRI was worth the increased risk of suicide (Appendix B:6). This would result in a significant spat of articles making mention of Health Canada's warning (Appendix A: 04/02/04, 05/02/04, 17/02/04, 20/02/04, 23/03/04, 23/04/04).

March 22nd, 2004 - The FDA would ask antidepressant manufacturers "to include in their labeling a warning statement that recommends close observation of adult and pediatric patients treated with these agents for worsening depression or the emergence of suicidality (Appendix B:7)." This FDA warning would be mentioned the next day (Appendix A: 23/03/04).

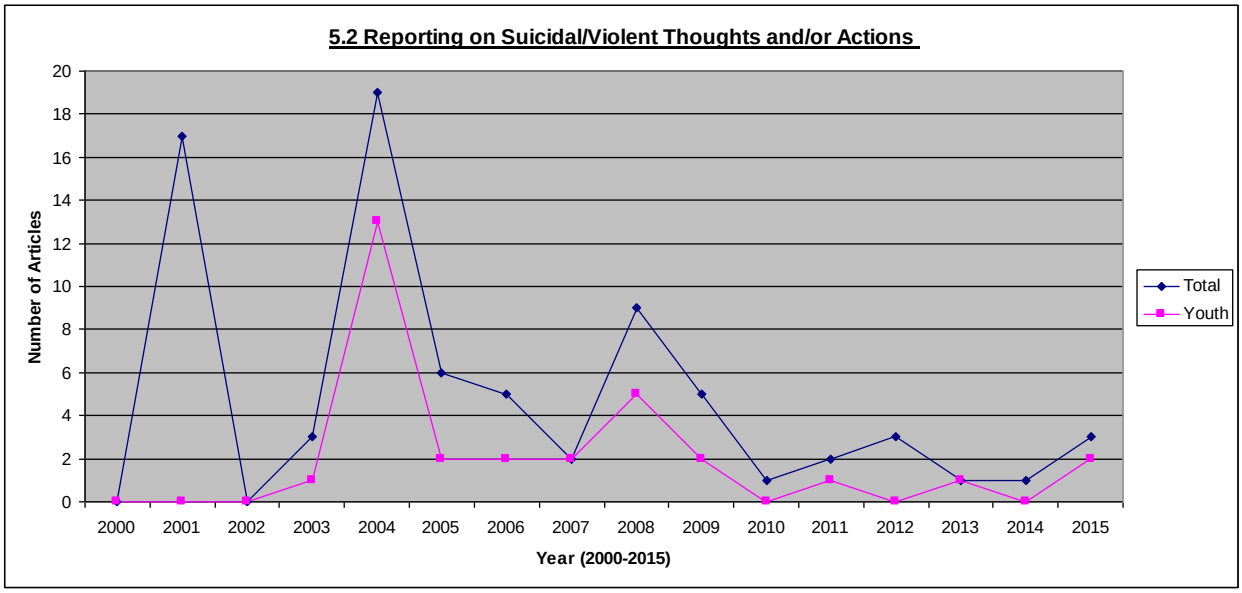
June 3rd, 2004 - Health Canada would ask manufacturers for warnings to be put on SSRIs and other new antidepressants stating "patients of all ages taking these drugs may experience behavioural and/or emotional changes that may put them at increased risk of self-harm or harm to others (Appendix B:8)." This warning would not be mentioned until 2008 when mentioned in an article about a murder investigation (Appendix A: 17/06/2008).

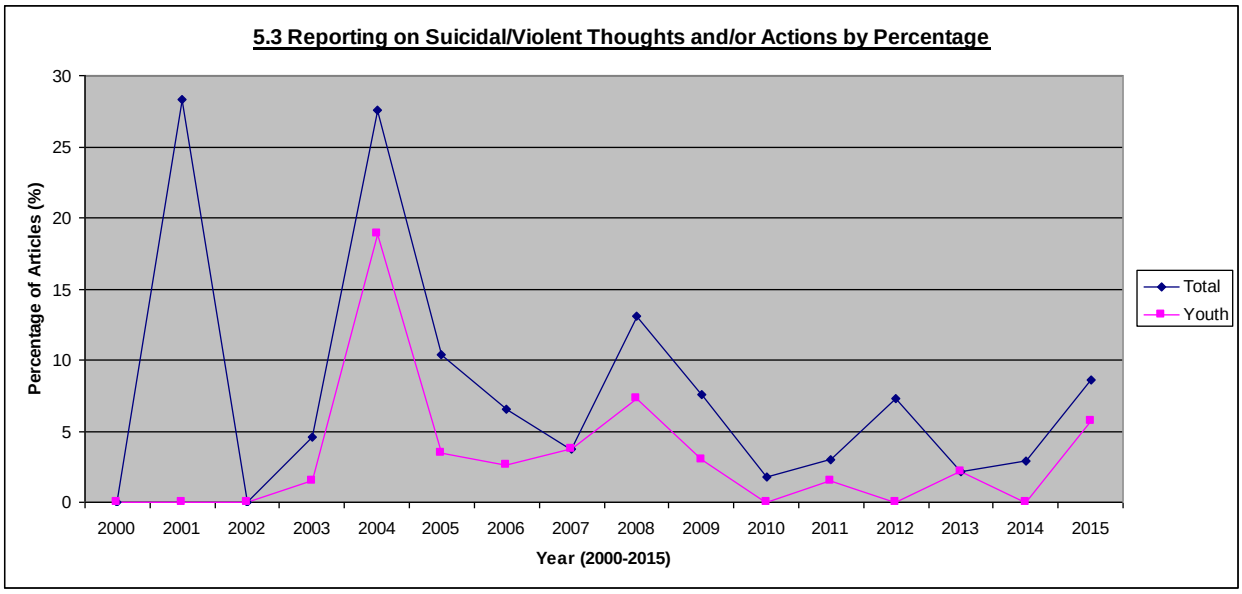
November, 2005 - The FDA gets Wyeth to add the risk of homicidal ideation to their antidepressant venlafaxine's label after a woman using it murders her children (Appendix B:9). No article would mention this warning.

October 15th, 2010 - A study looked at FDA data for serious adverse effects involving "homicide, homicidal ideation, physical assault, physical abuse or violence related symptoms" for any drug with at least two hundred reported cases between 2004 and September 2009. They would find 1527 cases of violence disproportionately reported for the thirty-one qualifying drugs. Eleven antidepressants would make the list including five of the top ten drugs most linked to violence (Appendix B:10; Moore, Glenmullen, and Furberg, 2010). Although no article would

mention this study, there would be an article mentioning a different study with significant findings regarding SSRIs and youth violence five years later (Appendix A: 16/09/15).

Analysis:





There would be major spikes in reporting on the potential for suicidal/violent thoughts and actions during the Healy affair in 2001 and after the warnings in 2004 about the SSRI link to

youth suicides. There would also be a spike in 2008 after the FDA released previously unpublished trials which showed antidepressant efficacy as little better than placebo except in severe cases and comparisons were made to when the drug companies were accused of hiding critical safety data about youth suicide in 2004.

Overall, there was some effective reporting on the link between antidepressants and suicide. This was quantitatively true in 2001 when the public was repeatedly informed of the link between suicide and Prozac during the Healy case and in 2004 when the youth suicide risk of SSRIs in general was being discussed. That said, there was little excuse to not report on drug company Wyeth's suicide risk warning to doctors in 2003, Dr. Breggin's exhaustive 2003 literature review on the agitated and violent mental states SSRIs could cause, or to wait for Health Canada to give a 2004 warning on the SSRI-youth suicide link before producing an article even though Britain's drug regulator had given a warning almost two months prior.

Considering that increased suicide risk when people start new antidepressants or change doses is widely understood now, it is perhaps predictable that reporting on it would have declined to a trickle. Still, considering the potential consequences of ignorance on the topic, the vast numbers of people being prescribed them, and the 38 percent of people taking antidepressants without ever being diagnosed with any DSM mental illness that would benefit from them (Takayangai et al., 2015), it seems preferable this should be mentioned in some manner in most articles where antidepressants are discussed instead of in less than 10 percent of them as over the last seven years.

Also disappointing was the reporting on the relationship between antidepressants and violence against others. Quite a few of the early articles regarding Healy's academic talk focused

entirely on the suicide angle without mentioning the violence (Appendix A: 14/04/2001, 17/04/2001, 18/04/2001, 25/04/2001, 30/04/2001). In addition, the 2004 warning by Health Canada stating the risk of "harm to others" would not be mentioned until 2008, there would be no mention of the FDA getting Wyeth to add "homicidal ideation" to venlafaxine's label in 2005, and the 2010 study showing SSRIs being five of the top ten drugs linked to violence was ignored. There would be a brief mention in 2015 that a new study showed SSRIs were linked to violence in youth (Appendix A: 16/09/15) but overall the link between antidepressants and violence has been getting very little attention despite their ever increasing use. Although minimizing reporting on this might have seemed responsible in order to avoid creating fear and distrust of the mentally ill, increasing public awareness of it might also have motivated people to pressure the government into developing a system capable of delivering alternative treatments.

5.2 Side-Effects

Considering the majority of antidepressants affect major neurotransmitters in the human body that have significance for our various bodily systems, antidepressants tend to have side-effects that go beyond simply altering our psychological processes. These can include temporary side-effects like sexual dysfunction that generally go away once you have quit using them but there are more concerning ones that remain after discontinuation, sometimes permanently.

Timeline:

July 3rd, 2001 - A memo was released to doctors from GlaxoSmithKline in agreement with Health Canada that warned GSK's antidepressant Wellbutrin could cause serious side-

effects including seizures, serum sickness and even death (Appendix B:11). No article would mention this warning.

July 9th, 2001 - Another 2001 Health Canada release would state Bristol-Myers Squibb's antidepressant Serzone could cause jaundice, hepatitis or liver failure with some deaths being reported (Appendix B:12). There would be a brief mention of this (Appendix A:10/07/01).

August, 2003 - Australian drug regulator, the Therapeutic Good's Administration (TGA), would send out a warning stating that maternal use of SSRI during pregnancy or while breastfeeding can cause side-effects in babies such as respiratory disorders and convulsions (Appendix B:13). This would not be mentioned in an article until Health Canada would release similar warnings in 2004 (Appendix A: 10/08/04, 25/11/04, 29/12/04).

December, 2004 - The UK's National Institute for Health and Care Excellence (NICE) would release guidelines recommending "stepped care" where non-drug methods are prioritized for depression less than moderate, in part due to the side-effect profile of the drugs (Appendix B:14). No article would mention these new UK guidelines.

August 9th, 2004 - Health Canada would put warnings on SSRIs and other newer antidepressants saying pregnant women who take them during the third trimester may have babies that experience severe complications such as "feeding and/or breathing difficulties, seizures, muscle rigidity, jitteriness and constant crying (Appendix B:15)." This would be mentioned in an article the next day and other times that year (Appendix A: 10/08/04, 25/11/04, 29/12/04).

September 29th, 2005 - Health Canada would release a warning linking use of GlaxoSmithKline's paroxetine in the first trimester of pregnancy to congenital and cardiovascular

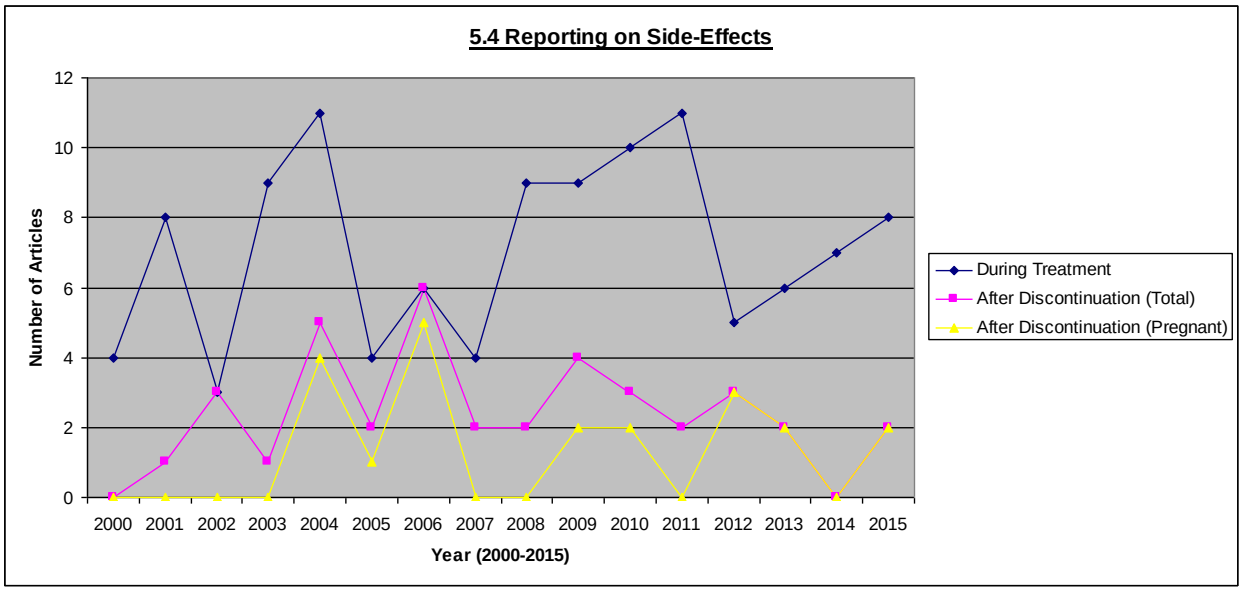
malformations (Appendix B:16). There would be a mention of the warning in a health column a couple weeks later (Appendix A: 14/10/05).

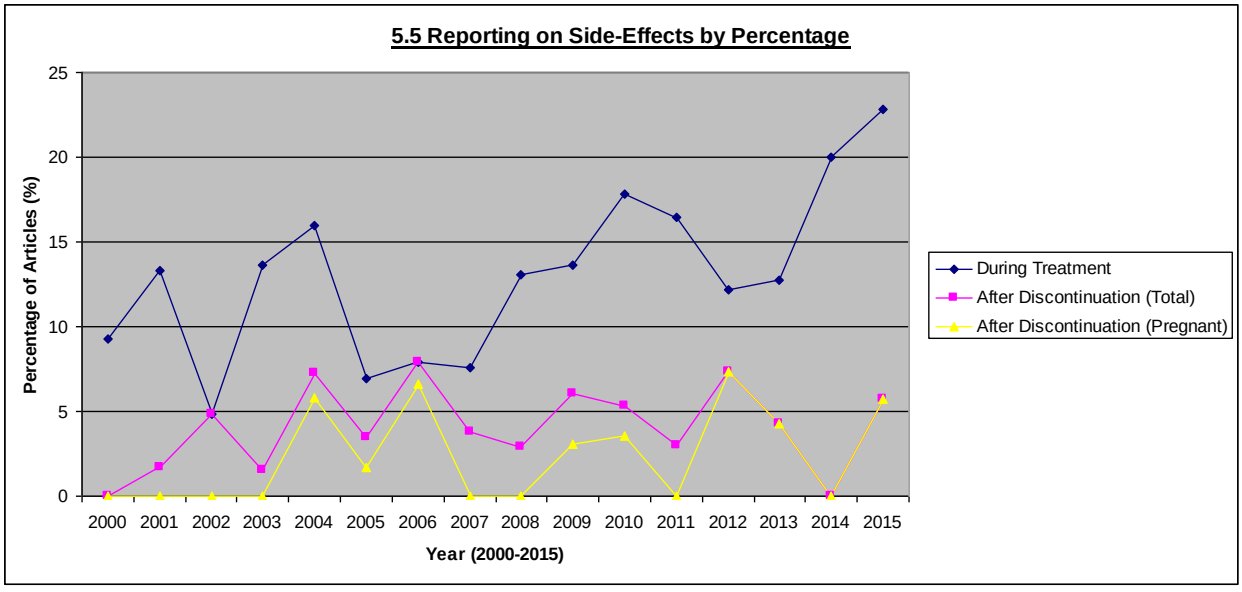
January, 2009 - The FDA had SSRI and SNRI manufacturers add the risk of neuroleptic malignant syndrome, a potentially fatal neurological disorder, to the existing serotonin syndrome warning on their products (Appendix B:17). No article would mention this warning.

April 6th, 2011 - A meta-analysis of sixty-one studies show an 11 percent increase in the chance of breast cancer for women on antidepressants. 43 percent of researchers with no industry ties reported a positive association between the two while zero percent of those with them did (Appendix B:18; Cosgrove et al., 2011). There would be two articles mentioning this over the next two days (Appendix A: 07/04/11, 08/04/11).

May 7th, 2012 - Health Canada would release a warning that Forest Laboratories' antidepressant escitalopram can cause life-threatening heart rhythm abnormalities (Appendix B:19). No article would mention this warning.

Analysis:





The reporting on the non-psychological side-effects of antidepressants has been varied. On one hand, there has been a substantial and increasing percentage of the total articles making mention of side-effects, suggesting an attempt at advocacy as opposed to just reporting facts as they come out. However, outside of the attention paid to the dangers of antidepressants for the

fetuses of pregnant women, which has been fairly consistent and considerable, there has been minimal coverage specifically pointing out that some of the side-effects that antidepressants increase the risk of are potentially permanent – like diabetes or liver damage – or are in some cases even fatal.

A greater public understanding that antidepressants have side-effects, sometimes serious ones, is important to create democratic pressure to provide the funding for alternatives and to create guidelines getting doctors to recommend alternatives. As depression can often be seen as a temporary affair that is corrected by antidepressants, logically there can be a perception that some side-effects while on the drugs is not an issue as they will go away once the patient has recovered. Emphasizing that some of these side-effects are permanent and will continue costing the healthcare system money indefinitely may make the often higher up-front costs of alternative treatments for depression more palatable to voters and politicians.

While not mentioning some of the risks of antidepressants is expected considering *The Globe and Mail* is not a medical journal, it is less understandable to not cover two warnings about potentially fatal side-effects for two widely used drugs from Health Canada and one warning from the FDA for all SSRIs and SNRIs considering that reporting on the actions of government agencies is a critical part of the media's role. They also would not cover the UK's acceptance of the new NICE guidelines that recommended avoiding antidepressants except for those with severe depression, something that could have been critical for altering the antidepressant conversation in Canada. When a serious ally and our historical parent-nation makes a major decision to change course on how they tackle an expensive and ever-growing problem like depression, Canadians need to be made aware of it.

5.3 Efficacy

The efficacy of antidepressants has been called into question over the years with many analyses of the data suggesting they are not much, if at all, better treatments than placebos for people with less depression rated as less than severe. The articles mentioning antidepressants are analyzed to see if they were written in such a way that a reader would feel antidepressants were an effective treatment for depression (Positive), are not effective or less of an effective treatment for depression than someone who believed they usually worked would have expected (Negative), or if the article was not trying to imply anything about their efficacy (Neutral). An article whose central point is the suggestion that antidepressants caused or are causing suicides will be rated as Negative because that is the same as the drug failing to prevent severe depression from causing a suicide. Other than that situation, side-effects do not influence the rating the articles are given.

April 2000 - A study looking at trials for seven drugs and almost 20000 patients provided evidence that antidepressants were not as necessary as previously thought for the prevention of suicide in depressed people by showing that depressed patients given placebo were not more likely to commit suicide than those who were (Appendix B:20; Khan, Warner, and Brown, 2000). No article would mention this study.

February, 2002 - One meta-analysis looking at ninety-six antidepressant trials would find that 52 percent of them saw no difference between antidepressants and placebo. The drug benefit was greater than placebo the more severe the depressive symptoms got with very similar effects between drug and control when the depressive symptoms were mild (Appendix B:21; Khan et al., 2002). There would be one article mentioning this study four months later (Appendix A: 25/06/02).

July, 2002 - A study would look at all data submitted to the FDA for the approval of six of the most prescribed antidepressants – the data used by the FDA to decide whether to approve the drugs – and found that 82 percent of antidepressant benefit was seen in the placebo control which would suggest the drug's affect is of minimal clinical significance (Appendix B:22; Kirsch et al., 2002). No article would mention this study.

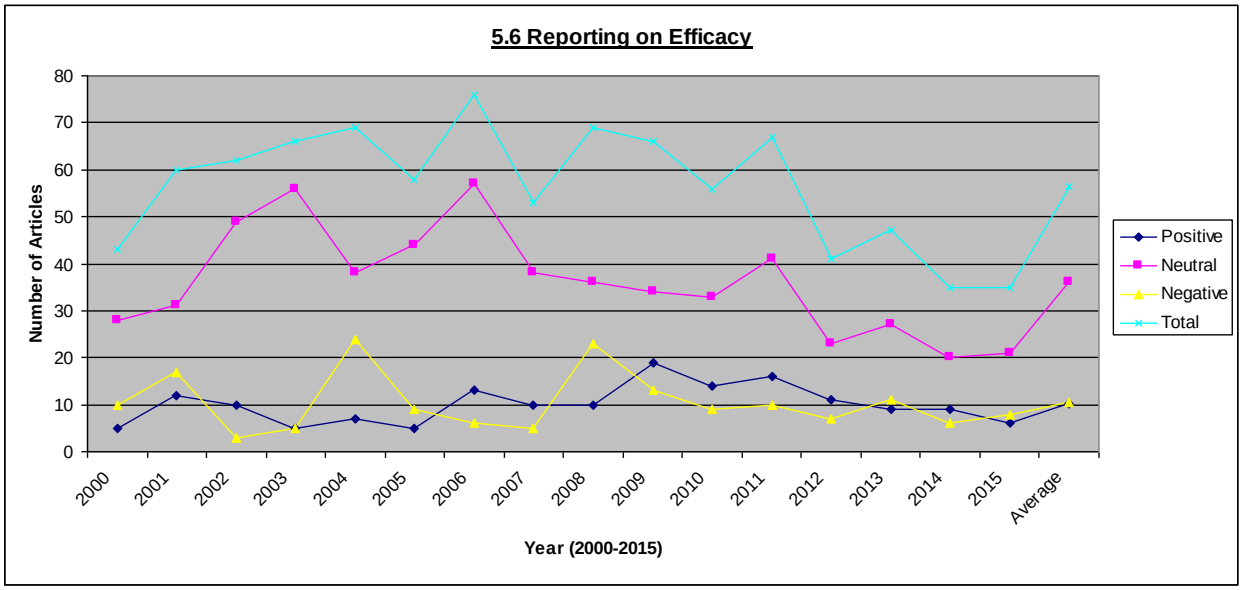
January 29th, 2008 - Using previously unreleased FDA data, a meta-analysis looking twenty-nine published and eleven unpublished trials with a total of 3704 patients receiving paroxetine and 2687 receiving placebo found paroxetine was not more effective than placebo for people with moderate to severe depression as previously believed (Appendix B:23; Barbui, Furukawa, Cipriani, 2008). No article would mention this study.

February 26th, 2008 - Making use of previously unpublished and unavailable antidepressant trials retrieved from the FDA, a meta-analysis looking at forty-seven clinical trials would find fluoxetine, venlafaxine, nefazodone and paroxetine were only slightly better than placebo and less than what the National Institute for Health and Care Excellence (NICE) considered clinically significant (Appendix B:24; Kirsch et al., 2008). There would be an article discussing this the next day (Appendix A: 27/02/08).

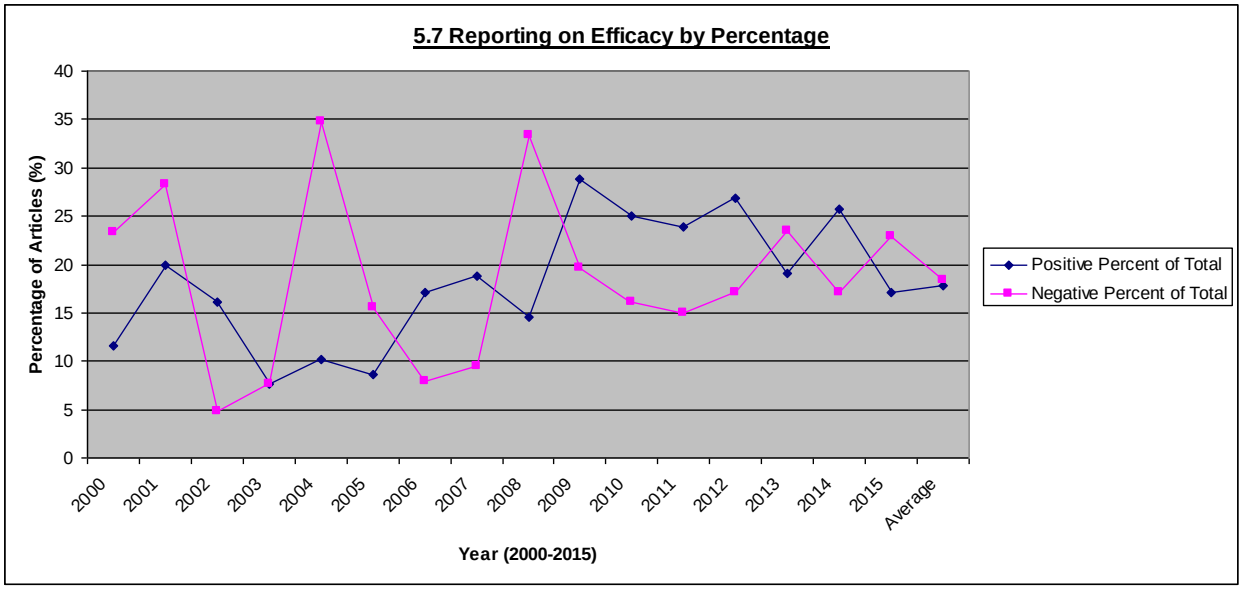
July 7th, 2011 - A meta-analysis of forty-six studies would find that people recovering from depression with the use of antidepressants would relapse in 42 percent of cases while those recovering without them would only relapse in 25 percent of cases. This suggests changes to the brain derived from antidepressants make relapse more likely and can prolong depression. (Appendix B:25; Andrews et al., 2011). No article would mention this study.

July 30th, 2012 - A meta-analysis looking at a total of 177 studies would find that a combination of psychotherapy and antidepressants provided a "slight advantage" over either alone. However, either alone were not "significantly different" from alternative therapies or active intervention controls, that is, the steps taken by medical professionals to make a placebo control appear legitimate. It concluded that, " These data suggest that type of treatment offered is less important than getting depressed patients involved in an active therapeutic program (Appendix B: 26; Khan et al., 2012)." The fact basically any therapy where people are receiving treatment from someone perceived to care about them works as well as antidepressants essentially spells the end of the biological theory of depression. No article would mention this study specifically although one article almost three years later would discuss the success of therapy and the necessity to get people and keep people in active therapeutic programs like those referenced in the study (Appendix A: 22/05/15).

Analysis:



Looking at Figure 5.6, there does not appear to be any consistent increase in the number of negative articles being published regarding antidepressants over the sixteen year period as would be expected due to the increasing evidence demonstrating their shortcomings. 2001 would see a spike with the Dr. David Healy job rescission story, 2004 with the move to warn doctors about the SSRI risk of youth suicide, and in 2008 with the discovery that most of the trials showing antidepressants in a negative light had previously been unpublished and unavailable to researchers who would then reassess the complete data and find the majority of the drugs as not clinically more effective than placebos except in very severe cases. This extremely serious discovery in 2008 would also make it peculiar that 2009-2011 would be the high-water mark for positive antidepressant articles which, including 2012, was four straight years of greater positive reporting than negative.



Looking at Figure 5.7, the reporting in terms of percentages instead of absolute numbers does appear to show an overall steady and gradual increase in negative reporting starting in 2002 if the distorting outliers 2004 and 2008 are removed. Interestingly, positive reporting also appears to be increasing overtime albeit more erratically. From 2008-2015, essentially every year would see both positive and negative reporting at 15 or more percent of total articles while this was only the case 50 percent of the time from 2000-2007. As the three largest controversies – and the coinciding data – had become available to the public and for analysis before the end of 2008 and considering the ever-increasing prescribing rate which suggests they have significant defenders, it is not surprising that opinions on antidepressants would become increasingly more polarized and less neutral as time went on. That their reporting essentially shadows this polarized trend and allows articles both praising and bashing antidepressants suggests *The Globe and Mail* is trying hard to remain neutral in their coverage and are taking no firm editorial stance on being either for or against antidepressants.

This raises the question as to whether the media should simply objectively report facts or whether the people are better served if they possess some kind of pro-majority or pro-consumer

agenda. Should their job be to comfort the afflicted and afflict the comfortable as the misremembered saying about a newspaper's job sometimes goes? The pharmaceutical companies could certainly qualify as comfortable based on their profit margins. Considering the money spent by the pharmaceutical industry to influence the public debate and considering all the troubling interactions between the industry and other healthcare stakeholders described in Chapter 5, should the media be providing a greater service than simply reporting facts as they come out? Should the media simply stand back and assume doctors are providing accurate information and prescribing correctly to patients when the industry's efforts to influence doctors into prioritizing their drugs is well-known and evidence suggests current prescribing rates are not supported by evidence?

Either way, *The Globe and Mail* has been forward, if inconsistent, on reporting the facts on antidepressant efficacy. As mentioned in the timeline, many important studies regarding efficacy were mentioned but there were other large-scale studies demonstrating a disturbing lack of efficacy for antidepressant drugs that were simply ignored, allowing momentum to build behind prescribing drugs that are very difficult to get off of and ultimately may make the depression worse (Khan, Warner, and Brown, 2000; Kirsch et al., 2002, Barbui, Furukawa, Cipriani, 2008; Andrews et al., 2011; Khan et al., 2012). Judging by the reporting trends, they have not emphasized building a case against the drugs but neither have they shied away from releasing negative articles about them. This makes the quality of their reporting on this issue dependent on whether you believe the media should take an advocacy role or not.

5.4 Overprescribed

The increasing prescribing rates combined with the research demonstrating minimal efficacy and often severe side-effects creates the concern that antidepressants are being overprescribed and given to many people who do not benefit from them or even may be made worse off.

Timeline:

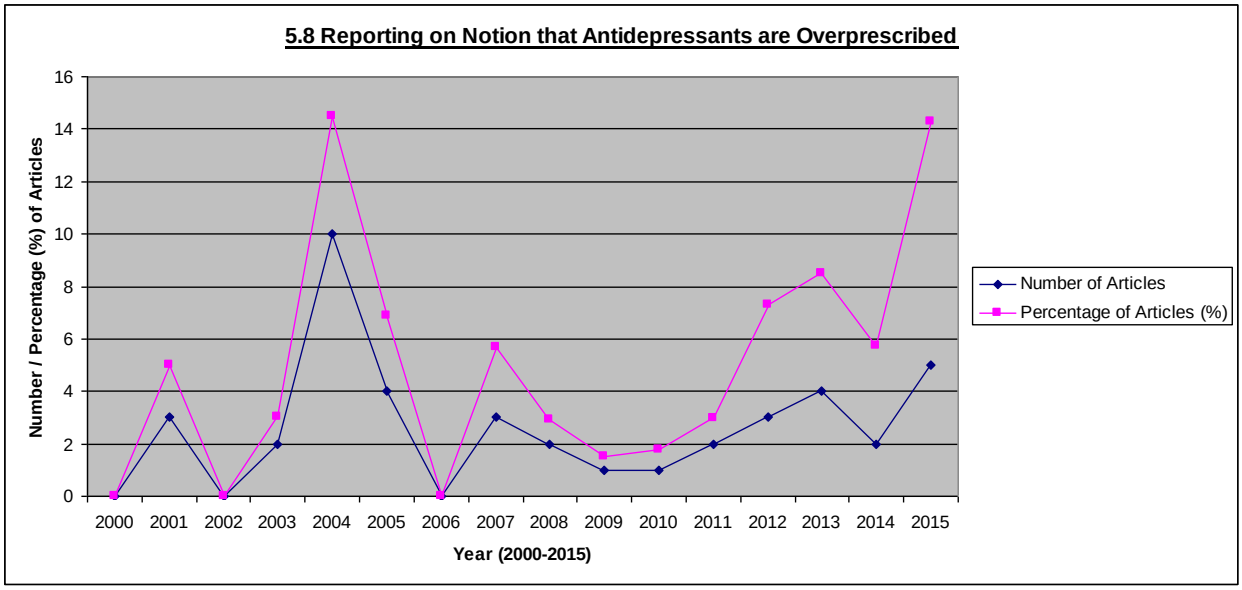
December, 2002 - Antidepressant studies traditionally remove people with too low a depressive rating since it is argued it is unfairly difficult in these cases to show drug superiority over placebo. A study looking at thirty-nine antidepressant efficacy trials would argue this provides a distorted picture of drug efficacy in the real world because many people using them are not severely depressed. The study would find that likely almost 50 percent and possibly as many as 71 percent of people being given antidepressants would not have depression the evidence suggests is severe enough to benefit from the drugs (Appendix B:27; Zimmerman, Posternak, and Chelminski, 2002). No article would mention this study.

March, 2007 - A study looking at data for 5.5 million privately-insured US employees for the year 2002 would find 11 percent of those covered received an antidepressant that year. It would also find that 42 percent of users were "not associated with any clearly identified mental health or "off-label" indication," essentially stating these people were being given them without being diagnosed with a mental disorder or any other medical justification for using pills (Appendix B:28; Larson, Miller, and Fleming, 2007). No article would mention this study.

September, 2009 - A study looking at over two-hundred thousand prescriptions for antidepressants in the US would find that only 21 percent of them were written by mental health

specialists, the individuals most capable of evaluating if a patient would benefit from them (Appendix B:29; Mark, Levit, and Buck, 2009). No article would mention this study.

Analysis:



2001's Healy case and 2004's suicide-risk scare would both see increases in concerns that antidepressants were being overprescribed. 2007 would see an increase while interestingly 2008 would not despite the findings that publication bias had been overstating their benefits. 2010 onwards would see more reporting on the issue while 2012 to the present would see much larger percentages of their articles make mention of the threat of antidepressant overprescribing. In this case, *The Globe and Mail* seems to be primarily reporting on the inferred concept of over-prescription instead of directly on the studies that provided the evidence for the concerns. Although the percentages of articles that mention this issue remain fairly low even with the sizable increase in 2015, it is possible to see the relatively steady increase as demonstrating a willingness to take a stance on the issue that places greater emphasis on advocating for the public good instead of purely engaging in the reporting of new objective facts.

5.5 Drug System Failures or Potential Failures

Based on the points made in Chapter 5, the strange combination of minimal drug efficacy and dangerous side-effects for many users combined with ever-increasing prescribing rates is primarily a result of the interplay between the drug industry and all the other stakeholders in the system. This section looks at areas where policy related to the drug system has been or has the appearance of being corrupted and relationships between stakeholders have or have the appearance of possessing conflicts of interest in a way that will bring about negative health outcomes. Essentially, this is the area where changes in policy can result in better outcomes for patients. The reporting on this section is inevitably the most important because the data and facts that create the narrative surrounding antidepressants are only as good as the system that creates them.

Timeline:

December 7th, 2000 - Dr. David Healy would have his job offer as Clinical Director of the Mood and Anxiety Disorders program at the University of Toronto revoked after his academic speech on November 30th where he suggested Prozac may cause suicide or violent behaviour. Eli Lilly, the manufacturer of Prozac, was in deals to provide significant funds to the university (Appendix B:1). There would be significant reporting on the rescinding of Healy's job offer although it would not come until the next year when the facts were made available. With its wider implications regarding academic freedom, there would be nine articles that would discuss the case over the year 2001 (Appendix A:14/04/01, 18/04/01, 21/04/01, 30/04/01, 06/09/01, 07/09/01, 08/09/01, 24/09/01, 29/12/01). This meant there was much attention drawn to the dangers of having academic institutions receiving money from private interests like

pharmaceutical companies when much of their value to society traditionally comes from their freedom to provide objective, unbiased information regarding the target of study, even if it hurts commercial interests.

May 31st, 2003 - A study would compare the forty-two SSRI trials actually given to Swedish drug regulators with those published and find significant publication bias. Negative results were hidden and data that was published was done so in a way as to make it appear far more positive than it really was. This meant "that any attempt to recommend a specific selective serotonin reuptake inhibitor from the publicly available data only is likely to be based on biased evidence (Appendix B:30; Melander et al., 2003)." There would be no article mentioning this study although articles would begin pointing out this issue nine months later (Appendix A: 17/02/04, 09/04/04, 23/04/04).

March 2nd, 2004 - A full account would be released of the controversy behind a 2001 journal article that had reported the trial results for pharmaceutical company GlaxoSmithKline's Study 329 and Study 377. These studies had been done on their drug paroxetine in an attempt to get it licensed for pediatric depression. However, both trials failed to show the drug as superior to placebo with Study 377 showing it as actually less effective. The company declared in an internal memo that, "It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine." It was discovered the company hired a PR firm to ghostwrite the medical journal article that played up the results as positive, stating the drug was effective and safe for youth when the data showed it was not effective and was linked to much higher rates of suicide than were placebos (Appendix B:31; Kondro, 2004). There would be no article specifically mentioning this evidence of company employees acknowledging that the profit-motive meant they would to mislead doctors and

patients until Eliot Spitzer launched a lawsuit against GlaxoSmithKline in June (Appendix A: 03/06/04). However, there would be earlier articles mentioning studies that suggested companies were engaging in this behaviour and intentionally being misleading about their what their trial results actually demonstrated (Appendix A: 09/04/04, 23/04/04).

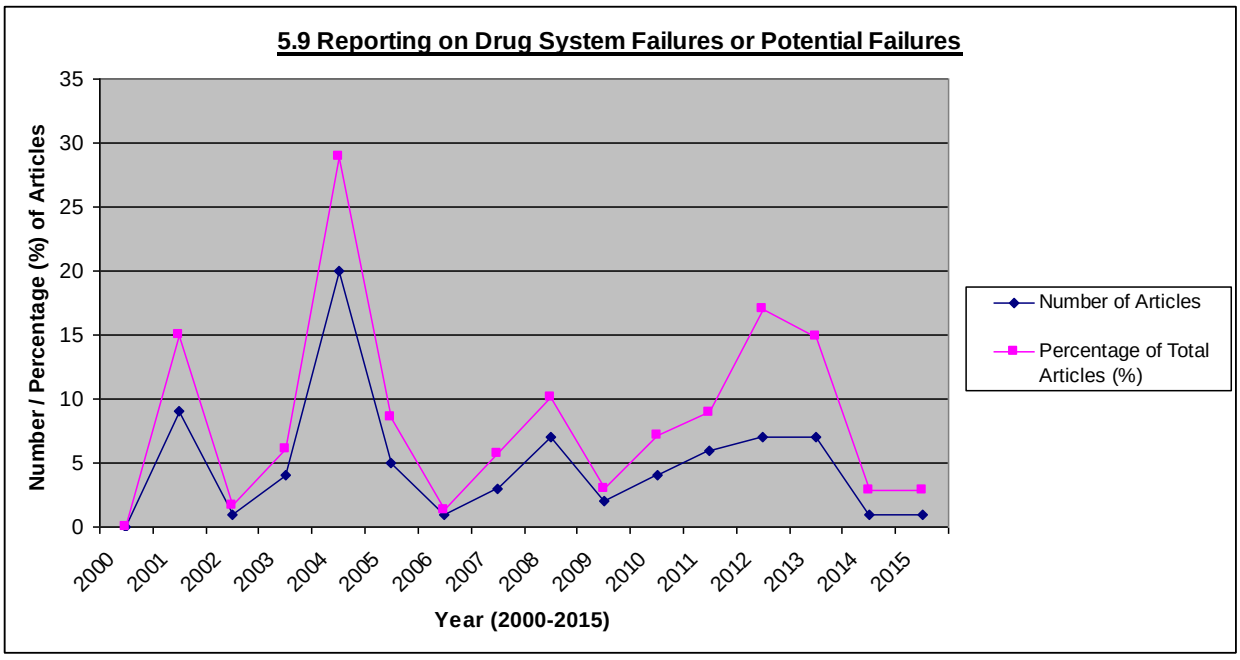
November 8th, 2005 - A study would analyze US advertising for SSRI antidepressants and find it was extremely common for them to refer to depression as a chemical imbalance and state that SSRIs corrected this balance by increasing serotonin. This was illegal as you are not allowed to make scientific claims not supported by scientific evidence but the FDA would never discipline those doing. Although it is difficult to know to exactly what extend it did, this appeared to warp people's understanding of what depression was and what was necessary to treat it (Appendix B:32; Lacasse and Leo, 2005). This study would not be reported on and the notion that the drug companies were fraudulently claiming to understand depression in order to claim they had a cure would not be reported on until 2010 (Appendix A: 18/06/10).

July 11th, 2006 - A study from the February 2006 issue of the *Journal of the American Medical Association* argued that the hormonal changes previously believed to protect expectant mothers against depression did not do so and that some mothers should likely stay on the medication while pregnant. This was following various warnings about severe birth defects in the babies of pregnant mothers using SSRI antidepressants. However, "the study, and resulting television and newspaper reports of the research, failed to note that most of the thirteen authors are paid as consultants or lecturers by the makers of antidepressants ... In total, the authors failed to disclose more than sixty different financial relationships with drug companies (Appendix B:33; Armstrong, 2006)." The lack of transparency about this conflict of interest calls into

question the validity of the study and raises questions about how common this is. It would be almost five years before this would be reported on (Appendix A: 07/04/11).

January 17th, 2008 - A study looking at the FDA data of 12,564 patients and looking at twelve antidepressants would find severe publication bias. Out of seventy-four FDA-registered trials, thirty-seven of thirty-eight studies seen as being positive by the FDA were published while out of thirty-six negative trials, twenty-two were not published and eleven were published in a way that made them look like they had positive outcomes. This meant that doctors reading the available material would believe that 94 percent of trials were positive when it was roughly 50 percent (Appendix B:34; Turner et al., 2008). An article would be published on this study the same day it was released and several other times that year (Appendix A: 17/01/08, 26/04/08, 17/10/08).

Analysis:



There would be substantial reporting on the compromising of the drug system in 2001 with the Healy affair causing concerns about academic freedom, 2004 when it was understood youth suicide risks had been hidden, and in 2008 when the level of publication bias surrounding antidepressant prescribing was made clear. Although it decreased after 2008, there would then be a steady and almost consistent increase in reporting from 2009-2013 although there appears to be no single event acting as the locus for the journalism done on the failures within the drug system during this time as there had been previously. This suggests the compromised political economy of the drug system had become more widely understood and that people had become less shocked by apparent malfeasance by this point in time. This meant a wider array of topics as more facets were understood enough to write about and there would be less emphasis on any specific angle, especially considering the largest scandals around antidepressants had become public knowledge by 2009.

It is harder to understand the major drop-off in reporting on the topic in 2014 and 2015. As mentioned ad nauseum, the issue has not gone away and prescribing rates continue increasing. Interestingly, the year 2015 would see *The Globe and Mail* produce a series of long and detailed articles trumpeting that the data shows a need for greater access to therapy and structured care as it is shown to be as or more effective than antidepressants but with more lasting benefits and less side-effects. These articles would also discuss the steps being taken by the UK and Australia to do the same thing (Appendix A: 23/05/2015, 24/05/2015, 26/05/2015). However, of the three articles, none bother discussing what was wrong with the drug system for it to take almost twenty-five years since Prozac to know that there were better treatments for depression than the chemical ones that most people wound up receiving. A series this late into the antidepressant over-diagnosis crisis suggesting that governments should pay to replace

antidepressants with superior talk therapy when possible is not the same as a media source having done its duty along the way to ensure its audience understood the relevant context and why things were unfolding the way they were.

This recent series is also not proposing a solution as much as a temporary band-aid. Antidepressants are simply one of the latest iterations of the problem with the political economy of the existing drug system. Like the benzodiazepines before them and the second-generation antipsychotics beginning to replace them, antidepressants are simply the drugs du jour that are on patent and thus the most profitable to push as the main treatment for people with mental illness, regardless of efficacy. In imitation of the life-cycle that SSRI antidepressants went through, advertising would increase for second-generation antipsychotics from $1.3 billion in 2007 to $2.4 billion in 2010 and despite their very serious side-effects, they would begin being prescribed for things they were not designed or recommended for like mild depression, insomnia, and even sometimes for mild emotional discomfort. Prescriptions would increase from 28 million in 2001 to 54 million in 2011 (Friedman, 2012).

It is positive that *The Globe and Mail* has covered so many of the serious concerns about the quality of the drug system that the pharmaceutical companies were shaping, even if sometimes belatedly. However, this serious drop-off in reporting on it in the last two years is a problem when the situation continues to get worse and the credibility of many of the players related to the pharmaceutical process are collapsing. Instead of mentioning that antipsychotics seem to be going the same over-prescribed, industry-pushed route that SSRIs have gone, *The Globe and Mail*'s only coverage in 2015 that mentions the two drugs together simply consists of mentioning that a study shows they probably are safe for fetuses in pregnant mothers unless they are taking antipsychotics and antidepressants (Appendix A: 13/05/15). It is not that

antipsychotics may not prove ultimately safe for pregnant mothers but it seems desirable for a media source to provide context and point out the fact that SSRIs were also presumed safe for mothers until sufficient evidence mounted they were not and even then, there was competing evidence saying they actually were safe that came from industry-influenced researchers.

Overall, this is likely the section where advocacy in favour of the general good by the media is most necessary due to its effects on the other aspects and because the complexity of the subject means most people will not have a clear understanding of the situation. People can understand efficacy and side-effects easily enough but understanding how economic and political forces shape the development and interpretation of that data requires a deep desire by the media to provide necessary context and background. Unfortunately it is also an area where *The Globe and Mail* seems uninterested, at least recently, in playing that active role in regards to antidepressants.

5.6 Alternative Treatments

There are various other treatments for depression that evidence shows can be as or more effective than antidepressants, often with less side-effects and more sustainable benefits. The four with no negative side-effects that possess the most convincing evidence for replacing antidepressants in people with the most commonly occurring types of depression are talk therapy, light therapy, exercise, and meditation. There is also St. John's Wort that does possess some side-effects but retains antidepressant medication's low treatment cost and ease of use as well as various electricity-based treatments like electroconvulsive therapy (ECT) that generally

possess potentially more serious side-effects and cost but are effective for severe types of depression.

March, 2003 - A Meta-analysis looking at eighteen trials would find electroconvulsive therapy (ECT) was "significantly more effective than pharmacotherapy (Appendix B:35; UK ECT Review Group, 2003)." No article would mention this study.

December, 2004 - Britain's National Institute for Health and Care Excellence (NICE) would release guidelines recommending "stepped care" where non-drug methods are prioritized for depression less than moderate due to non-drug treatment superiority for mild depression (Appendix B:14). No article would mention this.

January, 2005 - A meta-analysis of thirty-seven trials showed the herb St. John's Wort as having similar effects to antidepressants for mild to moderate depression but with fewer side-effects (Appendix B:36; Linde et al., 2005). No article would mention this but an article from the same month would describe a smaller study where St. John's Wort would prove more effective than paroxetine for even severe depression, again with less side-effects (Appendix A: 11/02/05).

April, 2005 - A meta-analysis looking at sixteen trials "suggests that bright light treatment and dawn simulation for seasonal affective disorder and bright light for nonseasonal depression are efficacious, with effect sizes equivalent to those in most antidepressant pharmacotherapy trials" but with none of the side-effects (Appendix B:37; Golden et al., 2005). This study would not be mentioned although there had been previous and would continue to be studies referring to light therapy as being as effective as antidepressants for seasonal depression (Appendix A: 14/10/02, 05/05/06).

September 11th, 2008 - A study reviewing the literature on cognitive therapy and antidepressant medication would conclude that, "The evidence shows that CT [cognitive therapy] is as efficacious as ADM [antidepressant medication], and that its effects are more enduring (Appendix B:38; DeRubeis, Siegle, and Hollon, 2008)." Only one article six years later would specifically mention this (Appendix A: 22/05/15) although articles would begin coming in a month later suggesting therapy is an equally effective or even better alternative soon after (Appendix A: 22/11/08, 24/10/09).

October, 2008 - A meta-analysis of twenty-nine trials found St. John's Wort as not only effective for mild depression but instead are "similarly effective as standard antidepressants ... and have fewer side effects than standard antidepressants (Appendix B:39; Linde, Berner, and Kriston, 2008)." No article would mention this.

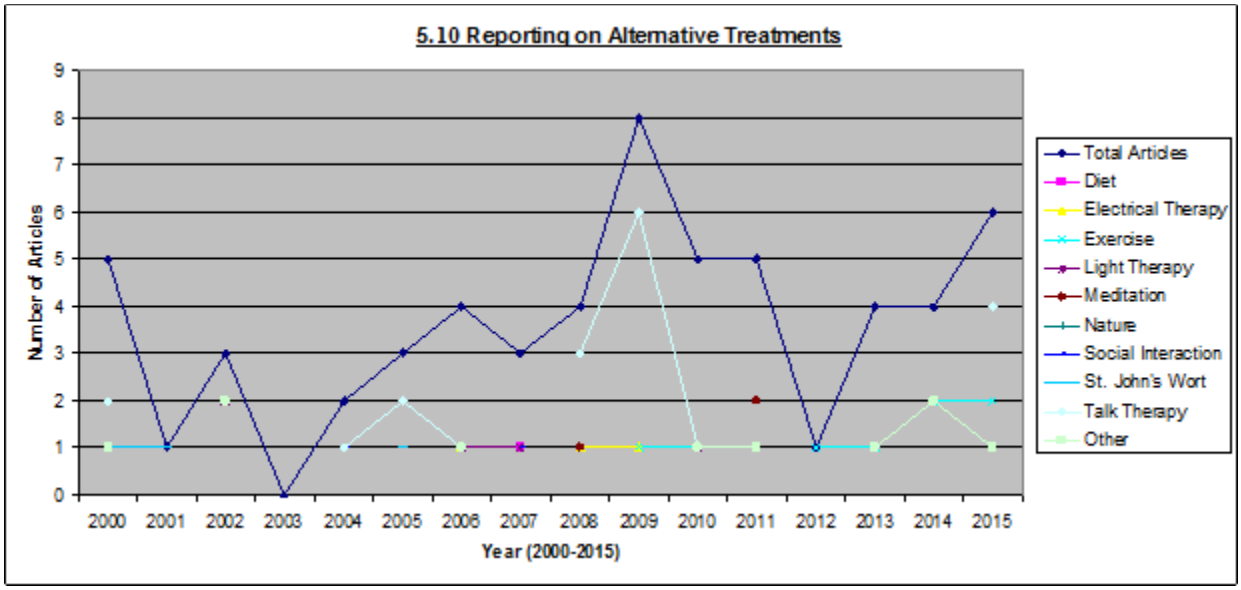
July 30th, 2012 - A meta-analysis looking at a total of 177 studies would find that a combination of psychotherapy and antidepressants provided a "slight advantage" over either alone. However, either alone were not "significantly different" from alternative therapies or active intervention controls, that is, the steps taken by medical professionals to make a placebo control appear legitimate. It concluded that, " These data suggest that type of treatment offered is less important than getting depressed patients involved in an active therapeutic program (Appendix B:26; Khan et al., 2012)." No article would mention this study specifically although one article almost three years later would discuss the success of therapy and the necessity to get people and keep people in active therapeutic programs (Appendix A: 22/05/15).

August, 2012 - A review of the existing literature would demonstrate that physical exercise is as effective a treatment for depression as antidepressant medication or psychotherapy

(Appendix B:40: Blumenthal, Smith, and Hoffman, 2012). No article would link directly to the study although articles would begin coming in explaining the same concept over the next couple years (Appendix A: 13/12/13, 22/08/14, 26/10/14).

March, 2014 - A meta-analysis of forty-seven trials would find meditation possessing benefits "comparable with what would be expected from the use of an antidepressant in a primary care population, without the associated toxicities (Appendix B:41; Goyal et al., 2014)." No article would directly mention this study but there had been coverage on the comparable or superior benefits of meditation versus antidepressants beginning in 2008 (Appendix A: 15/08/08, 10/01/11, 21/02/11).

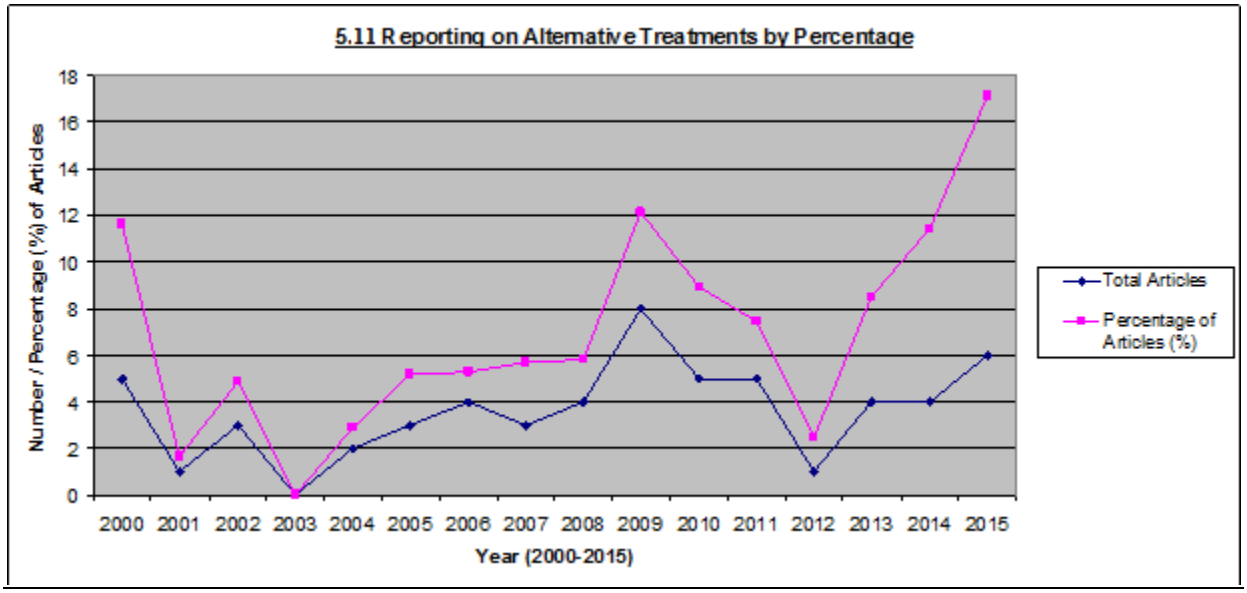
Analysis:



Although only seven out of eight of the studies in the timeline are directly reported on, there is significant reporting suggesting efficacy equivalency or superiority to antidepressants from a wide variety of alternative treatments and has been over the entire sixteen years being analyzed. This suggests a preference by *The Globe and Mail* for reporting novel findings, even

though they may be supported by minimal trial evidence at the time, and not reporting on the later and more definitive large-scale meta-analyses that can be more reliably said to define what is "true" since their size makes them less prone to routine randomness and bad individual trial design or execution. This is likely due to novel research that opens up new treatment possibilities being seen as more interesting to readers than research combining existing work to create accurate understandings of efficacy size.

Looking at Figure 5.10, talk therapy stands out as the most commonly covered with the largest number of articles being in 2009 when there was an on-going debate about the efficacy and side-effects of antidepressants in pregnant and post-pregnant women and alternatives were being discussed (Appendix A: 08/10/09, 24/10/09, 26/10/09). 2015 would also see an increase in articles discussing talk therapy as part of their series on alternative treatments, clearly demonstrating an embrace of an advocacy role in encouraging greater government support for psychotherapy.



Looking at Figure 5.11, there appears to be a clear embrace of alternative treatments from 2003 as an increasing percentage of articles make mention of the equivalency or superiority of

other treatments. 2009-2012 would see a decline in this reporting with 2012 being significantly below previous years but this would be temporary and the overall trend upwards in reporting is mostly consistent.

It is debatable how problematic it is that there is minimal reporting on the meta-analyses that actually combine all the high-quality trials together to create the most accurate facts on the ground. This is because it appears from this increasing coverage of alternative treatment superiority that the definitiveness they demonstrate is taken into account in the media coverage. It is difficult to know if presenting the source of this data would be useful for informing readers of where they can look for more information or if the dryness and general esotericism of scientific trials would make it less accessible to the masses. Either way, it appears clear that *The Globe and Mail* has become willing to take an advocacy role in pushing for alternative treatments for depression consistently and especially over the last several years.

5.7 Coverage Summary

Overall, there was significant reporting on the important issues albeit some relevant things were missed. Only 9/15 (60%) relevant regulator warnings and 14/24 (58%) studies or their findings would be mentioned in some way. However, although missing essential government warnings is decidedly unfortunate, the landmark studies chosen for Appendix B to be compared against the coverage were selected using specific criteria that favoured more definitive large-scale that could more accurately be said to constitute actual facts. These necessarily come later in time after smaller preliminary trials have already pointed out novel research that is interesting and attention-grabbing, aspects favoured by the media. This means the

media can cover some of these concepts without including all of the larger definitive studies included in Appendix B. However, both early evidence that tends to be weaker but interesting and later evidence that is more definitive and which corrects or reinforces earlier evidence should ultimately be reported on in order to give readers a comprehensive understanding. Favouring novelty at the expense of boring but ultimately more important and comprehensive findings can be said to be a weakness in reporting that may have contributed to people not understanding the actual limited efficacy of antidepressants compared to alternative treatments.

Equally important to making sure the main studies are covered is whether the main studies influence the agenda the newspaper is trying to set. Advocating for a change in how antidepressants are treated relies both on quality – ensuring you report the important facts located in Appendix B clearly – as well as quantity, that is, how antidepressants are treated in the majority of cases they are mentioned. If 95 percent of articles about antidepressants treat them as miracles of medicine that we need to use more of than it does not really matter if the other five percent mention the existence of massive, flawless studies stating they are no better than sugar pills. The move away from benzodiazepines as feel-good cures for all mental problems was resisted by many medical professionals and required both good scientific research, as exists now for antidepressants, as well as intense media scrutiny.

Arguably there appears to be significant coverage by *The Globe and Mail* on many of the issues surrounding antidepressants although there has been less reporting on antidepressants in general in the four most recent years being analyzed. This is possibly due to a natural reduction in novel facts coming to light that justify articles on them at all. After all, you can only discuss something for so long before everything has been said. However, if advocating against the current antidepressant-reliant status quo can be defined in this sense as having a larger

percentage of your coverage being negative and providing a negative context then it appears *The Globe and Mail* has made an attempt in some areas and not in others.

Although there were major spikes around the times of significant events, there has also been a routine increase in the number of articles referring to antidepressants as overprescribed, without being specifically tied to any new findings, for the last seven years with the exception of a minor and temporary set-back in 2014. There has been a general – albeit broken – upwards trend in the reporting on the superiority of certain alternative treatments since 2003 and the last four years would each see an increase in the percentage of articles discussing the superiority of various alternative treatments compared to the one before. The coverage implying lack of antidepressant efficacy and discussing side-effects in general spiked during years with major negative events but has also seen a gradual if not totally consistent increase as a percentage of total articles since 2006 and 2005 respectfully.

There would appear to be less advocacy on the issues of suicide/violence in addition to a genuine failure to emphasize the violence-related research at all until very recently. Reporting on the continuing-after-discontinuation nature of some side-effects would also vary apparently randomly and never seemed to be specifically advocated for despite the serious risk these pose for both individuals and the nation as a whole. Reporting intended to inform the audience about the compromised nature of the drug system would spike during major event years but also appeared to be a generally increasing trend from 2006 onwards. However, it would essentially completely stop in 2014 and 2015 in relation to antidepressants.

Overall, it is difficult to judge the quality of *The Globe and Mail*'s reporting and its efforts in attempting to advocate in pushing for a wiser depression-treatment policy. Their major

2015 three-part series (Appendix A: 23/05/2015, 24/05/2015, 26/05/2015) and reporting trends on overprescribing, side-effects, and alternative treatments clearly demonstrate that they have absorbed the relevant data on antidepressants and are emphasizing Canadians need to change our policies regarding how we treat depression.

However, as discussed in Chapter 2, it took the media treating the users of benzodiazepines as victims of the drug establishment to reduce overprescribing. The recent failure to discuss the systemic conflict of interest issues and advocate against the drug system that caused us to embrace for so long a treatment that is dangerously wrong for so many people suggests that they are not doing what is required of them to educate people in such a way as to prevent this from happening again with different drugs. This is not a theoretical problem either as it already seems underway with antipsychotics even as it continues with antidepressants.

Chapter Six

Conclusion

This thesis explored the current state of knowledge about the efficacy and safety of antidepressants and their continued centrality in the treatment of depression in Canada. It demonstrated that other developed countries are making efforts to alter their own treatment protocols and systems in an effort to better fit the existing science while Canada fails to do so. It looked at three theories for answers as to why this current state of affairs exists – placebo theory, psychiatry-driven theory, and political economy theory – and although each of them were likely partial contributors to the issue, argued the political economy version of events as being the fundamental perspective through which the situation must be viewed.

It drew on the insights of Robert Dahl that were represented by the evolution of his theory of pluralism into neopluralism in order to provide theoretical backing to the concept that industry's ability to influence the state is fundamentally different in society from any other participants and is prioritized. As the complexity of the subject and information asymmetry meant that normal market forces were ineffective in organizing supply and demand and in deciding value, democracies have demanded and relied on various formal and informal checks and balances on the system like government regulators and doctors. The neopluralist viewpoint already argued the state was more susceptible to industry influence but this was extrapolated for this thesis' purposes to suggest that many of the advantages held by industry that allows it to influence the state also allows it to influence essential non- or quasi-state actors like doctors, researchers, and patient groups. This influencing is rarely sinister or illicit in nature but the evidence shows it does not have to be in order to compromise the ability of these other groups to functionally fulfill their essential roles as safeguards in the system.

This thesis also included a historical analysis of the evolution of psychiatry, the understanding of depression, and how both of these were influenced by well-meaning but misguided policies as well as by ideologically-based neoliberal political and economic developments that created the modern pharmaceutical industry and its relationship to other relevant healthcare stakeholders. Essentially, efforts to make medicine more scientifically-based were combined with efforts to deregulate and offload responsibility from the state. This resulted in an industry is mostly responsible for creating the data that has become the main qualifier of the safety, efficacy, and necessity of its own products and that the state lacks the resources to police. This was possible because, due to the power of the placebo effect in humans and the subjective nature of depression, the science is extremely open to interpretation. This created space for the drug industry to use their wealth and associated influence to push their own interpretation and report the facts if and how they chose in order to create their own narrative surrounding depression and antidepressants that benefited them.

6.1 Review of Media Coverage

In an effort to explain why Canada was not changing course on antidepressant reliance, this thesis looked at the history of benzodiazepines and concluded sufficient media coverage was fundamental to delegitimizing an overprescribed drug after it has been widely accepted. *The Globe and Mail* would be used as a proxy for overall media coverage in order to find out if a failure to change policies was really a failure by the Canadian media to sufficiently inform and impassion Canadian citizens on the issue. Overall, the analysis of *The Globe and Mail* articles would suggest haphazard but relatively consistent and well-intentioned reporting on many of the troubling aspects of the antidepressant story even if an emphasis on novelty over thoroughness

meant some major findings were overlooked. Their recent reporting suggests the adoption of an advocacy role where they are hoping to encourage readers into forcing policy change in how depression is treated.

However, despite a substantial amount of promising reporting, there seems to be a lack of effort in the last two years to criticize the pharmaceutical system in a way that can be seen as advocating for a change in how drugs are researched, developed, regulated, and sold in order to alter the current problematic incentive structure. Exactly what changed, if anything, to cause this reduction in reporting on the compromised nature of the system as a whole in favour of reporting on individual cases where the system failed is unclear.

6.2 Discussion

Meta-analyses are now available showing the equal or superior benefits of cognitive therapy (DeRubeis, Siegle, and Hollon, 2008), meditation (Goyal et al., 2014), exercise (Blumenthal, Smith, and Hoffman, 2012), St. Johns Wort (Linde, Berner, Kriston, 2008) and light therapy (Golden et al., 2005) when compared to antidepressants. This is not to suggest that antidepressant medication is never useful since every treatment works in different way and will benefit different people to greater and lesser extents depending on the source of their depression. For example, antidepressants target the amygdala while cognitive therapy encourages a healthy prefrontal cortex, both of which areas of the brain are often malfunctioning in the depressed patient (DeRubeis, Siegle, and Hollon, 2008). This means antidepressants need to remain part of the tool-kit available to doctors and patients, especially for those with the most severe and debilitating depression who may be incapable of engaging in any alternative treatment that requires active participation. However, the long delay before they begin working, the side-

effects, and the often short-term benefits they provide suggest they should rarely be the first choice in treatment and should rarely be a choice in treatment at all for those whose depression is less than severe.

Cost alone cannot be considered a limiting factor in the use of alternative treatment since there is strong evidence demonstrating St. John's Wort as comparable in cost and efficacy to generic antidepressants and just as easy to take but easier to stay on as it possesses less side-effects (Soloman, Adams, and Grave, 2013). There is also evidence that Behavioral Activation is as effective as Cognitive-Behavioural Therapy, the gold-standard of cognitive therapy, but can be performed by junior mental health workers who have far less training, meaning it is far cheaper and more scalable than quality cognitive therapy was previously thought to be (Richards et al., 2016). There is also a sizable body of evidence demonstrating the relationship between diet and depression. Nutrient and vitamin-rich foods as well as anti-inflammatory foods like omega-3 fatty acids and olive oil are linked to reduced depression while inflammatory foods like trans-fats, sugars, and alcohol are linked to higher rates (Rao et al., 2008). Although unlikely to be a treatment on its own, a public-awareness campaign regarding nutrition and depression could likely pay dividends considering: "When we take a close look at the diet of depressed people, an interesting observation is that their nutrition is far from adequate. They make poor food choices and select foods that might actually contribute to depression (Rao et al., 2008)." These available but unembraced options imply that a lack of willingness to try antidepressant alternatives when treating depression is a result of political and cultural forces, not economic or scientific one.

In the same way that former-President Dwight Eisenhower warned about the US "military-industrial complex" warping the policies of the country in ways that were negative overall but profitable for the industry, it appears we need to consider capitalist incentive

structures as dangerous in the world of medicine. Entrenched interests naturally attempt to expand their scope and control events and narratives in ways that benefit and enlarge themselves as could be seen when pushing what they knew to be the scientifically unsound serotonin theory of depression that favoured drug products. An industry that needs people to be sick so that they will purchase their drugs has every incentive to influence people into considering themselves to be sick and believing that their drugs are the correct answer regardless of the direction that good-quality, unbiased science would move if left to its own devices. Although efforts to change this economic system in a way that would remove those incentives is likely impossible in the current political climate, real attempts need to be made to create and rely solely on unbiased data if this course is to be corrected. This will likely mean significant state expenditures on independently-designed and run drug trials but it is perhaps the only way to maintain the legitimacy of modern medicine and to provide mental healthcare that is based on objective instead of agenda-driven science.

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