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## Combating Depression: A History and Analysis of FDA Regulation of Selective Serotonin Reuptake Inhibitors

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<b>Citation</b>	Combating Depression: A History and Analysis of FDA Regulation of Selective Serotonin Reuptake Inhibitors (2004 Third Year Paper)
<b>Accessed</b>	February 19, 2015 9:42:54 AM EST
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**Combating Depression:**

**A History and Analysis of FDA Regulation of  
Selective Serotonin Reuptake Inhibitors**

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Class of 2004

April 2004

This paper is submitted in satisfaction of both the course requirement and the third-year written work requirement.

## Abstract

This paper explores historical and current regulation by the Food and Drug Administration (FDA) of the most widely-used class of antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs). To begin, I discuss the evolution of societal understanding of depression, and I highlight the pharmaceutical industry's role in shaping the public perception of the condition. Next, I describe the major classes of antidepressants, focusing on SSRIs and their promise of relief for depressed individuals, as well as their economic benefits to their manufacturers. Then I explore and analyze several interesting challenges posed by SSRIs and other psychotropic medications for the new drug application (NDA) process. Subsequent sections chronicle and critique two noteworthy FDA advisory committee hearings on the potential connection between SSRIs and suicidal and other violent tendencies in patients who take the drugs. Throughout the paper, I attempt to show that the agency strives admirably to fulfill its regulatory mandates that only safe and effective drugs reach the American consumer, and that prescribers and patients are aware of known risks. FDA considers varied and passionate viewpoints on the subject of SSRIs, and although it cannot ever entirely satisfy all interested parties, the agency seems to have recently struck an appropriate balance between widespread access to these drugs and warnings about their potential harms.

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## I. Introduction

The debate over governmental regulation of antidepressants in the United States is dominated by several players, including the Food and Drug Administration (FDA), pharmaceutical companies, the mental health industry, and the public. This paper focuses on the most widely-prescribed class of antidepressants, called selective serotonin reuptake inhibitors (SSRIs), which include well-known brand-name drugs like Prozac, Paxil, and Zoloft. It explores the condition we know as depression; chronicles the development of antidepressants and the enormous impact of SSRIs; discusses regulation regarding SSRIs; describes the influence competing voices have had on their regulation; and critiques governmental action in this arena.

During the second half of the twentieth century, people increasingly began to view depression as a physiologically-based illness, and the stigmatization of depression started to subside. The discovery of drugs to combat the illness led depressed individuals, their friends and families, and consumer representatives to clamor for FDA approval of, and widespread access to, these promising new medications. The discovery of SSRIs appeared particularly auspicious because these drugs were reported to cause fewer and less serious side effects than their predecessor antidepressants and were easier to use.

Ever looking to their bottom lines, the pharmaceutical industry in the last decade or so fueled these fires via direct-to-consumer advertising and public education campaigns that further raised the public's awareness of depression as well as its demand for SSRIs. Some critics of the drug industry assert that the pharmaceutical companies fostered the growth of a market for their antidepressant products by manufacturing (or at least manipulating public perception of) the "disease" of depression.

FDA's role in the regulation of antidepressants, as with all drugs, is to ensure that those that reach the American consumer are safe and effective for their intended uses. During the New Drug Application (NDA) approval process, FDA conducts a form of cost-benefit analysis based on data from trials provided by the drug's sponsor. The agency may approve a drug with higher risks so long as it shows promising clinical results, and conversely it may require less proof of efficacy for a drug that appears very safe.

Showing the efficacy of antidepressants is particularly challenging in that measuring their salutary effects is relatively subjective. Seeing improvements in depressed patients is less objective than seeing improvements in cardiac patients, for example. Given the relative difficulty of disproving data that relies in part on subjective observations, FDA may have given clinical data for SSRIs the benefit of the doubt during the NDA process because these promising new drugs appeared to have few major side effects.

Some members of the public and the mental health community have raised flags regarding the safety and efficacy of certain antidepressants. They assert that the long-term effects of antidepressant use are alarming, and they blame FDA for not acting more quickly to warn the public of such effects. There have also arisen concerns that antidepressant use may cause suicidal and other violent tendencies in some users. Thrown into the mix of what FDA considers when making regulatory decisions about antidepressants is powerful anecdotal evidence from both sides of the debate. There are people who say they could not live without antidepressants and others who claim that antidepressants have caused their loved ones

## II. The Condition to be Treated: Depression

### A. Brief History of Depression

Although the clinical description and understanding of depression have been significantly refined in modern times, people have long recognized that some individuals suffer from severe sadness and immobilization. Hippocrates and Aretaeus, ancient Greek physicians, wrote about patients with a depressive illness they termed *melancholia*, a condition named after the bodily humor they believed influenced mood.<sup>1</sup> From ancient times through the middle of the nineteenth century, the common perception was that people were either entirely sane and in control of themselves, or utterly mad and possessing no control over their faculties; little middle ground existed in the public understanding.<sup>2</sup>



While the concept of depression has ancient roots, its classification as a clinical disorder did not occur until the birth of psychiatry in the nineteenth century.<sup>3</sup> During the 1800s in Western Europe, the creation of the first modern asylums—meant for treating people with mental problems rather than merely sequestering them—resulted in hundreds of so-called “lunatics” being in the same place at the same time.<sup>4</sup> This phenomenon, in conjunction with the rise of the statistical movement, led observers to conclude that in fact there were many varieties and degrees of intensity of “insanity,” or mental illness.<sup>5</sup> This view slowly replaced the all-or-nothing view of mental illness that had previously prevailed in the public mind.

Based on his observations at asylums, the Frenchman Jean-Etienne-Dominique Esquirol published an influential classification of mental illnesses, in which he distinguished full from partial insanity. He termed partial insanities “monomanias,” and stated that patients who suffered from these seemed generally reasonable but had some limited affliction of judgment, mood, or will.<sup>6</sup> Esquirol’s great contribution to modern psychiatry was the notion that a mental disorder was not a disorder of the whole person, but rather a specific disease that perhaps could be specifically treated.<sup>7</sup> The German psychiatrist Emil Kraepelin was also a pioneer in the burgeoning field in the second half of the nineteenth century; his *Textbook of Psychiatry* distinguished among different types of mental illness and coined terms like “manic depressive disorder” that are still in use today.<sup>8</sup>

## B. Modern Clinical Definition of Depression

Attempts to describe and classify different types of mental illnesses in general, and depression in particular, have persisted since Esquirol and Kraepelin wrote their seminal works.<sup>9</sup> Although there remains uncertainty among experts regarding subtypes of depression (*e.g.*, endogenous depression, reactive depression, etc.), the medical profession generally agrees on the typical symptoms of depression. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders IV* (*DSM-IV*) defines unipolar depression (as opposed to bipolar depression, which refers to disorders that involve mania) as "a disturbance in mood characterized by varying degrees of sadness, disappointment, loneliness, hopelessness, self-doubt, and guilt."<sup>10</sup> Depressed people may have a harder time conducting their usual daily activities but they may still be able to cope.<sup>11</sup> According to the *DSM-IV*, a person suffering from major unipolar depression must have a depressed mood and/or markedly diminished pleasure in most activities consistently over the course of a two-week period.<sup>12</sup> In addition, the disorder is characterized by the presence of a majority of the other symptoms, listed below:

- significant weight loss or gain (*i.e.*, a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day;
- inability to sleep or excessive sleep;
- psychomotor agitation or retardation;
- fatigue or loss of energy;
- feelings of worthlessness or excessive or inappropriate guilt;

- 

diminished ability to think or concentrate, or indecisiveness; and

- recurrent thoughts of death (not just fear of dying), recurrent thoughts of suicide, or attempt to commit suicide.<sup>13</sup>

Curiously, although experts agree on the symptoms, no one really knows the exact causes or neurological effects of depression. There appears to be some connection between genetics and depression; people whose relatives have suffered from depression are more likely to suffer from it.<sup>14</sup> Sometimes physically or mentally stressful events cause depression. For example, medical problems like strokes, heart attacks, cancer, and hormonal disorders can cause depressive illnesses, as can serious emotional setbacks like financial or relationship problems or the loss of a loved one.<sup>15</sup> Other causes of depression include misuse of drugs or alcohol; physical, emotional, or sexual abuse; and major life changes, such as moving or retirement.<sup>16</sup> Sometimes, particularly once a person has had previous depressive episodes, depression occurs for no apparent reason at all.<sup>17</sup>

There is general agreement in the medical community that depression is associated with changes in brain chemistry and function.<sup>18</sup> Research has proven that the brains of people with depression are abnormal; specifically, the hippocampus is 9 to 13% smaller in women with a history of depression as compared to women who have never been depressed.<sup>19</sup> The hippocampus is a part of the brain that is vital to the storage of memories, and a smaller hippocampus contains fewer receptors for the neurotransmitter serotonin, which modulates mood, emotion, sleep, and appetite.<sup>20</sup> Depression is thus correlated with an imbalance in the way the brain regulates serotonin,<sup>21</sup> and, as will be discussed later, SSRIs work by correcting this imbalance. What remains unknown is whether the altered brain chemistry of depressed individuals is a *cause* or a *result* of depression.<sup>22</sup>

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<sup>13</sup>*Id.*

### C. Societal De-Stigmatization of Depression

While experts honed the clinical definition of depression, the public perception of the condition has dramatically transformed since 1950. In the 1950s, estimates were that 50 people per million suffered from depression, whereas today the estimate is 100,000 per million.<sup>23</sup> Approximately 10 to 20% of adults today experience depression during their lifetimes.<sup>24</sup> Although it may well be the case that many more people are depressed now than 50 years ago, such a dramatic increase must be at least in part the result of a societal re-conceptualization of what it means to be depressed.

Many believe that this evolution of public understanding of depression is a very positive occurrence in that it has resulted in less “blaming the victim” of a debilitating condition. Throughout history until recent decades, “melancholia” and depression were thought to be moral, personal failings. People blamed themselves for feeling hopeless, sad, and empty, and they thought that if they could only improve their attitudes or change something about their situation, they would overcome their negative feelings. Depressed people were much less likely to admit their condition or to seek help, and there was little help available to those who did seek treatment. However, in recent decades, people have come to view depression as a physiologically-based condition for which the person suffering from it is not responsible. The stigma of mental illnesses in general, and depression in particular, has greatly subsided. Granted, some stigma persists today; a 1996 survey of 1,166 American adults revealed that 54% still believe depression is a “sign of weakness.”<sup>25</sup> However, that same survey showed however that 69% would take an antidepressant if prescribed by a doctor,<sup>26</sup> indicating that even some who view depression as a character flaw realize that it has bases in biology and can be treated by medicine.

Society today commonly understands depression to be a disorder of the brain. Information published by the National Institute of Mental Health (NIMH) states that evidence from neuroscience, genetics, and clinical investigation demonstrate this fact.<sup>27</sup> The NIMH website informs the public: “A depressive disorder is an illness that involves the body, mood, and thoughts. It affects the way a person eats and sleeps, the way one feels about oneself, and the way one thinks about things. A depressive disorder is not the same as a passing blue mood. It is not a sign of personal weakness or a condition that can be willed or wished away. People with a depressive illness cannot merely ‘pull themselves together’ and get better. Without treatment, symptoms can last for weeks, months, or years. Appropriate treatment, however, can help most people who suffer from depression.”<sup>28</sup>

The American Medical Association (AMA) echoes the sentiment that physiology, not personal weakness, is to blame for depression: “It is important for a person who is depressed—and his or her family, friends and co-workers—to understand that depression is a disease. A depressed person has not caused these feelings and cannot simply decide to snap out of it and stop being depressed.”<sup>29</sup> Mental health advocates generally think that the public realization that depression is an illness is beneficial because it encourages depressed people to seek and obtain treatment, whether in the form of psychotherapy or medication or both. People are indeed seeking out help for depression in record numbers; a recent survey shows that depression is the 11<sup>th</sup> most common reason for patients to visit their family physicians in the U.S.<sup>30</sup>

#### D. Role of the Pharmaceutical Industry in Changing Perceptions of Depression

Drug companies help to de-stigmatize depression further by corroborating the widely-accepted notion that it is a treatable illness in their promotional materials for SSRIs. The website for Paxil emphasizes that depression is a mental condition from which approximately 16% of Americans suffer in any given year.<sup>31</sup> The Prozac website states: “Depression is a real illness, not a weakness. . . [and] it doesn’t reveal a personal weakness or inability to cope.”<sup>32</sup> Not surprisingly, all of the websites for SSRIs stress that depression is a treatable condition, and they imply that the drugs they are advertising can be part of a successful treatment program.

Some observers assert that the pharmaceutical industry is largely responsible for the evolution in societal perceptions of depression. Dr. David Healy, a British psychiatrist and leading historian of psychopharmacology, states: “[D]rug companies obviously make drugs, but less obviously they make views of illnesses.”<sup>33</sup> He argues that they accomplish this by selectively supporting certain scientific studies and views rather than others in order to create demand for medicines that they have discovered to be effective in treating certain conditions.<sup>34</sup> He points to an example from the early history of psychopharmacology: in order to promote an antidepressant called amitriptyline, Merck marketed the idea of depression as an illness by purchasing and disseminating 50,000 copies of a book on recognizing and treating depression.<sup>35</sup> Dr. Healy says this practice continues today, as drug companies invest in campaigns by mental health associations aimed at raising awareness and combating insufficient diagnosis and treatment of depression.<sup>36</sup> Put another way, Dr. Healy says: “Although there are clearly psychobiological inputs to many psychiatric disorders, we are at present in a state where companies can not only seek to find the key to the lock but can dictate a great deal of the shape of the lock to which a key must fit.”<sup>37</sup>

Dr. Healy thinks it somewhat inevitable that drug companies have “created” diseases. He points to the 1962 Kefauver-Harris amendments to the Food Drug and Cosmetic Act as channeling drug development toward clear diseases.<sup>38</sup> By requiring drugs to be proven effective as well as safe in order to garner FDA approval, the amendments favored drugs that could be shown to treat an identifiable, symptomatic, and measurable condition.<sup>39</sup> Thus, in order to market a drug in the U.S., pharmaceutical companies must be able to claim that the drug is effective in treating a certain disease-like condition, as opposed to improving health and well-being generally. As a result, the industry tends to view conditions as diseases and to shape public opinion in that direction.<sup>40</sup>

Whereas Dr. Healy sees the pharmaceutical company’s role in shaping the public perception of depression as preordained by the existing regulatory structure, Dr. Joseph Glenmullen, a clinical instructor in psychiatry at Harvard Medical School and practicing psychiatrist, offers a more cynical view in his 2000 book *Prozac Backlash*.<sup>41</sup> Glenmullen accuses the drug companies of buying the credibility of academic institutions and mounting “public interest” campaigns that are really aimed only at creating a market for their antidepressant drugs.<sup>42</sup> Increasingly, drug companies are entering into partnerships with academic institutions whereby the companies provide funding for research and in return retain rights over the results, including in some cases the right to suppress information discovered in the course of research.<sup>43</sup> An example of drug companies’ power to control research occurred in the 1980s, when Upjohn generously financed a study on one of its anti-anxiety drugs until it found out that the results were going to be unfavorable to its product.<sup>44</sup> At that point, the company not only discontinued funding for the study but also encouraged other professionals to criticize the study.<sup>45</sup>

Dr. Glenmullen also looks critically at public education campaigns like National Depression Day and automated telephonic screening services that are funded by drug companies; he views such efforts as manipulative attempts by the industry to artificially increase demand for antidepressants while posing as good corporate citizens.<sup>46</sup> He asserts that this type of marketing of a psychiatric diagnosis has redefined depression to include those suffering relatively mild symptoms, and that such efforts do more harm than good by convincing relatively healthy people who experience normal, albeit unpleasant, emotions that they suffer from major depression.<sup>47</sup> These people tell their doctors they think they are depressed, and many doctors obligingly yet inappropriately prescribe antidepressants.

Undoubtedly the drug companies have acted in a self-interested, profit-driven way in promoting awareness of depression. Approval or disapproval of the industry's conduct turns to some degree on what exactly one thinks depression is. If depression is indeed a common medical condition with some physiological bases that can be treated with drugs and/or psychotherapy, the fact that drug companies have made more people aware of depression is good. More depressed people will seek and obtain help, and families, friends, and co-workers of depressed people will be more understanding and supportive of those that suffer from the illness. On the other hand, if one thinks that the current popular understanding of depression is far too inclusive and that only the most severe cases are in fact depression, then the drug companies conduct is indeed deplorable, as Glenmullen argues. Seen in this light, the industry's marketing efforts have deluded many into thinking they can get a "quick fix" for their problems by popping a pill instead of pursuing more productive solutions.

### **III. Overview of Antidepressants**



The previous section gave a brief history of depression, discussed the modern clinical understanding of the disorder, and described the evolution of its public perception, emphasizing the influence the drug companies have exerted in this area. This section will set the stage for a discussion of FDA approval and regulation of antidepressants by offering succinct histories of the drugs and explanations of how they work. Three main classes of drugs are used in the treatment of major depression: monoamine oxidase inhibitors (MAOIs), tricyclics, and SSRIs. SSRIs are by far the most popular of these drugs today, and they are also the most controversial, as this paper highlights.

## A. Older Antidepressants

Discovered serendipitously in the 1950s, an MAOI called iproniazid was the first modern antidepressant.<sup>48</sup> It was initially developed to fight tuberculosis, but when it was observed to elevate mood and stimulate activity in many patients, researchers believed it could be used to treat depression.<sup>49</sup> In the late 1950s, over 400,000 depressed people took the drug before toxic side effects led to its discontinuation.<sup>50</sup> Subsequent research has shown that MAOIs work by slowing the breakdown in the brain of certain neurotransmitters, including serotonin and others, thus enabling them to assist communication among brain cells for longer periods.<sup>51</sup> They accomplish this by blocking the activity of monoamine oxidase, the enzyme that destroys these transmitters and gives this class of antidepressants their name.<sup>52</sup> MAOIs have a number of side effects, the most dire of which is that they can result in death if taken in combination with pickles, red wine, beer, or dairy products.<sup>53</sup>

The first tricyclic antidepressant, called imipramine, was also initially developed for use in the treatment of an indication other than depression.<sup>54</sup> After clinical trials failed to show its effectiveness in treating schizophrenia, other studies in 1957 and 1958 found that imipramine significantly alleviated symptoms of depression.<sup>55</sup> Interestingly, the studies found that although the drug seemed to activate depressed patients, improving their mood and energizing them, it actually had a sedative effect on non-depressed individuals.<sup>56</sup> These results led to the idea that tricyclics somehow work by reversing the depression, rather than simply causing a general activation in patients.<sup>57</sup> Later biochemical studies showed that tricyclic antidepressants do this by increasing the activity of neurotransmitters, once again including serotonin and others, by limiting their reuptake into neurons.<sup>58</sup> Despite their beneficial significant benefits, tricyclics cause a number of side effects of varying severity, including weight gain, dizziness, blurred vision, sweating, constipation, sedation, and even cardiovascular problems.<sup>59</sup> In addition, they can be dangerous or even deadly in the case of overdose, a particularly serious concern for depressed patients who have a much greater tendency than the average person to attempt suicide.<sup>60</sup>

## B. SSRIs

### 1. Promising Medications

The December 1987 introduction of Prozac by Eli Lilly, the first SSRI, marked a milestone for the treatment of depression. SSRIs work in generally the same way as the tricyclics, in that both classes of antidepressants improve mood by correcting a deficit in neurotransmitter activity that accompanies depression.<sup>61</sup> However, where tricyclics increase the activity of several neurotransmitters, SSRIs selectively inhibit the reuptake of serotonin alone (hence their name, *selective* serotonin reuptake inhibitors).<sup>62</sup> By interfering less with brain function, SSRIs alleviate depression without causing many of the side effects caused by tricyclics.<sup>63</sup> For example, clinical studies on Prozac showed a lower incidence of the following adverse reactions associated with tricyclics: cardiac effects, drowsiness, dizziness, and weight gain.<sup>64</sup>

Another advantage of Prozac over the older antidepressants is that their administration is much easier and more convenient. Whereas doctors have to use blood tests to determine the appropriate dose of tricyclics for each individual patient, the more focused nature of Prozac eliminates the need for blood testing.<sup>65</sup> Rather, most patients can take a daily dose of one or two 20-milligram capsules of the drug.<sup>66</sup>

In less than two years after hitting the market in 1988, Prozac became the best-selling antidepressant in history.<sup>67</sup> Prozac success stories abounded in the press and in communities; people who had suffered from depression throughout their lives and had unsuccessfully tried other treatments effectively managed their condition by using Prozac. A March 1990 *Newsweek* cover story entitled “The Promise of Prozac” touted the drug as a medical breakthrough.<sup>68</sup> The article recounted the experiences of several depressed patients, such as that of a 39-year-old woman from Seattle named Susan A.<sup>69</sup> Susan had suffered from depression, bulimia, and drug and alcohol abuse, and she had tried to kill herself twice. She had tried a tricyclic antidepressant but discontinued treatment because she did not like how it made her feel.<sup>70</sup> After her doctor prescribed Prozac, however, Susan turned her life around; she kicked her drug and alcohol habit, returned to school, and landed a full-time job.<sup>71</sup> According to the *Newsweek* article, as well as many reports since then, Prozac has successfully improved the lives of millions of people as it did Susan’s.

Sales of Prozac reached \$350 million in 1989, more than total sales of *all* antidepressants just two years earlier.<sup>72</sup> Even healthy people were requesting Prozac.<sup>73</sup> The popularity of Prozac and the SSRIs that followed can be attributed to the fact that they are far easier to tolerate than previous antidepressants while being similarly effective in treating depression. Research has shown that any of the antidepressants on the market—including tricyclics and SSRIs—will produce a favorable clinical response in approximately 70% of patients.<sup>74</sup> Referring to the targeted action of SSRIs, Dr. James Halikas, a professor of psychiatry at the University of Minnesota, noted, “Instead of using a shotgun [to stimulate serotonin activity], you’re using a bullet.”<sup>75</sup>

## 2. Concerns about Side Effects

That said, from the beginning of the SSRI era, there were voices cautioning against seeing the new drugs as a “magic bullet.”<sup>76</sup> Eli Lilly itself conceded that Prozac should be handled with care.<sup>77</sup> SSRIs cause their own set of side effects, albeit most are less common and severe than those caused by earlier generations of antidepressants. A significant number of people on Prozac, for instance, have reported headaches, nausea, insomnia, and nervousness.<sup>78</sup> In addition, SSRIs may cause other short- and long-term side effects, the severity or frequency of which were not discovered or publicized during clinical testing. The controversial claim that SSRI use may lead to violence and/or suicide in a small fraction of people who use them will be discussed at length later.

Drug industry critics point to numerous other adverse reactions to SSRIs—including weight gain, sexual dysfunction, and tremors—that they say occur much more often in practice than is indicated by the drug labeling. For example, Dr. Glenmullen reports that sexual side effects occur in 60% of patients who take Prozac,<sup>79</sup> whereas Eli Lilly’s official product information lists the incidence of sexual side effects as 2 to 5%.<sup>80</sup>

Serious withdrawal problems from SSRIS are another side effect on which Dr. Glenmullen focuses and about which healthcare providers need to be aware. Clinical tests, as well as anecdotal evidence, reveal that some patients experience dizziness, hallucinations, blurred vision, irritability, tingling or electric shock sensations, vivid dreams, nervousness, melancholy, and/or flu-like symptoms upon ceasing SSRI treatment.<sup>81</sup> Such symptoms usually last for days or weeks, but can last much longer.<sup>82</sup> Prozac very rarely causes such withdrawal effects; due to its long half-life, it slowly washes out of the body after the patient stops taking it.<sup>83</sup> Paxil, on the other hand, has a much shorter half-life and its discontinuation can cause acute withdrawal.<sup>84</sup>

Dr. Glenmullen asserts, “As with other serious, long-term side effects of these drugs, the frequency of withdrawal phenomena cited by pharmaceutical companies is much lower than what one sees in clinical practice and has now been demonstrated in the studies that are available.”<sup>85</sup> He cites a study showing that withdrawal symptoms occur in Paxil in as many as 50% of patients,<sup>86</sup> many times the 2.0 to 7.1% cited on the Paxil label.<sup>87</sup>

Another concern regarding SSRIs is that therapists and other doctors are prescribing SSRIs to people without taking the time to make sure that they are in fact depressed.<sup>88</sup> Doctors rarely prescribe the older antidepressants to a patient without conducting a full physical and psychological exam due to the high risk profiles of those drugs.<sup>89</sup> However, due to the convenience and apparent safety of SSRIs, some physicians prescribe them without undertaking such exams, which might for example show that a patient’s unhappiness is caused by something that drugs are unlikely to fix, such as job loss or other misfortune.<sup>90</sup>

Psychiatrist Peter Kramer’s 1993 book *Listening to Prozac* chronicled and contributed to the fame of Prozac, which at the time of publication had been on the market for five years. In the book, Kramer reports from his professional experience that Prozac treats depression quickly and dramatically in a wide range of patients. He states: “Prozac seemed to give social confidence to the habitually timid, to make the sensitive brash, to lend the introvert the social skills of the salesman.”<sup>91</sup> In this statement, Kramer professes admiration for the effectiveness of the drug but simultaneously hints at an attribute of Prozac that disturbs him.

Specifically, Kramer finds that the changes in brain chemistry caused by the drug, in addition to making people feel better, also contribute to noticeable alterations in patients' personalities. Some people who previously were cautious became assertive on Prozac; some who had been contrary became flexible and agreeable. Such a change caused Kramer and his patients to question which self was the patient's "real" self, the pre- or post-Prozac one. Kramer dubbed this transformative effect of SSRIs "cosmetic pharmacology,"<sup>92</sup> a concept which continues to be profoundly disturbing to many today.

Despite some negative attention, on the whole the medical profession, the public, and the media embraced Prozac, thrilled to have a medicine that quickly and safely treats people suffering from depression. Attracted by the huge success of Prozac, other pharmaceutical companies developed and marketed their own SSRIs. Pfizer introduced Zoloft in 1991; GlaxoSmithKline followed with Paxil in 1992; and Forest Labs with Celexa in 1998 and Lexapro in 2002.<sup>93</sup> By 1997, three SSRIs were among the 20 most-prescribed drugs in the U.S.<sup>94</sup> Prozac came in fifth; Zoloft 11<sup>th</sup>; and Paxil 17<sup>th</sup>.<sup>95</sup>

### 3. Cash Cows for Drug Manufacturers

These drugs as a class continue to meet with enormous commercial success. In 2003, Paxil had U.S. sales of roughly \$2 billion, and Zoloft had roughly \$2.8 billion.<sup>96</sup> Global sales of antidepressants ranked third among therapy classes in 2003, bringing in \$19.5 billion.<sup>97</sup> That said, SSRI sales are likely to stall during the next decade due to the loss of patent protection and generic competition.<sup>98</sup> Patent protection for Prozac expired in 2001 and for Paxil in 2003.<sup>99</sup> As shown in the chart below, Eli Lilly annual reports for the past four years reveal both how extremely lucrative Prozac was for Lilly, as well how dramatically generic competition can affect sales of brand-name drugs.



### Sales of Prozac and Related Fluoxetine Products

Year	U.S. Sales	Sales Outside U.S.	Total Sales
2000 <sup>100</sup>	\$2.23 billion	\$341 million	\$2.57 billion
2001 <sup>101</sup>	\$1.66 billion	\$330.1 million	\$1.99 billion
2002 <sup>102</sup>	\$451.7 million*	\$282 million	\$733.7 million
2003 <sup>103</sup>	\$398.6 million	\$246.5 million	\$645.1 million

\*Due to generic competition commencing in early August 2001, sales of Prozac declined 73% from 2001 to 2002.

#### **IV. FDA Approval of SSRIs for the Treatment of Depression**

##### A. Overview of the New Drug Approval Process

As with all new drugs, FDA must find that an antidepressant is both safe and effective for its intended uses before approving it for the U.S. market.<sup>104</sup> Of course, if this statutory requirement were interpreted to require *absolute* safety, meaning the drug must pose zero risk, very few if any new drugs would ever be approved. Thus, FDA has traditionally interpreted its mandate to mean that it should approve only those drugs for which the benefits outweigh the risks.<sup>105</sup>

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<sup>100</sup>ELI LILLY AND COMPANY, 2000 ANNUAL REPORT (2001).

<sup>101</sup>ELI LILLY AND COMPANY, 2001 ANNUAL REPORT (2002).

<sup>102</sup>ELI LILLY AND COMPANY, 2002 ANNUAL REPORT (2003).

<sup>103</sup>ELI LILLY AND COMPANY, 2003 ANNUAL REPORT (2004).

In seeking approval, the drug’s sponsor, usually the manufacturer, submits to FDA an NDA, which includes results from trials conducted on animals and humans during the Investigational New Drug (IND) phase of development as well as information about how the drug is manufactured and how it works in the body.<sup>106</sup> FDA’s role is to evaluate the studies contained in the NDA quickly yet thoroughly to determine whether the drug meets the safety and efficacy standards.<sup>107</sup> To accomplish this task, FDA employs medical doctors, chemists, statisticians, microbiologists, pharmacologists and other experts.<sup>108</sup> Uncertainty is inherent in the process of extrapolating from the results of limited clinical trials to the population at large, but FDA attempts to minimize this uncertainty by working with sponsors during the IND phase to design controlled clinical studies.<sup>109</sup> The chart below shows when FDA approved NDAs for five SSRIs for the treatment of major depressive disorder (MDD).

Date of FDA Approval of Major Brand-Name SSRIs for MDD<sup>110</sup>

Brand Name	Active Ingredient	Manufacturer	Date of Initial FDA Approval for Treatment of Depression
Prozac	Fluoxetine Hydrochloride	Eli Lilly	12/29/1987
Zoloft	Sertraline Hydrochloride	Pfizer	12/30/1991
Paxil	Paroxetine Hydrochloride	GlaxoSmithKline	12/29/1992
Celexa	Citalopram Hydrobromide	Forest Labs	7/17/1998
Lexapro	Escitalopram Oxalate	Forest Labs	8/14/2002

## B. Critique of IND and NDA Processes for SSRIs

The IND and NDA processes for SSRIs are noteworthy and potentially disturbing in several respects. Specifically, sponsors of NDAs for antidepressants face obstacles that many other drug sponsors do not face during pre-clinical trials due to the difficulties of modeling human psychiatric conditions in animals. Moreover, clinical trials on humans present their own set of problems for antidepressants, in light of the ill-defined indication to be treated. Critics of the SSRI NDA process claim that the instruments used to measure efficacy in clinical trials are inadequate and that the trials are too short to establish safety.

### 1. Pre-Clinical Animal Testing

New drugs are first tested on animals to establish a modicum of safety and efficacy. Pre-clinical animal testing of antidepressants is less reliable than such testing of other, non-psychiatric drugs. In part, this is because scientists still do not totally understand exactly how depression works biologically in humans, so they cannot duplicate it in animals. A 1998 study in *Psychological Medicine* concludes: “[S]tudies in animals, although necessary, must be regarded with caution” due in part to the fact that there is no “single theory about the pathogenesis and therapy of depression.”<sup>111</sup> FDA recognizes this obstacle and states in its *Guidelines for the Clinical Evaluation of Antidepressant Drugs* that “adequate models of human psychiatric illnesses are nonexistent.”<sup>112</sup>

Additionally, whereas a researcher can easily assess the efficacy of an antibiotic by seeing if an infection is killed in a rat, assessing the efficacy of antidepressants in animals is much more challenging since researchers cannot interview rats to see how depressed they are or how much better they feel after taking an antidepressant.<sup>113</sup> Interestingly, one of the ways that researchers currently use animal models to find potential human antidepressants is by injecting rats with different compounds and then looking for enhanced aggressive behavior, such as moving up in the colony's dominance hierarchy or exhibiting violence towards newcomers in the group.<sup>114</sup> The theory behind this practice, which is troubling to some experts, is that drugs that cause such aggression in rats may act to counteract depression in humans.<sup>115</sup>

## 2. Measuring Efficacy in Clinical Trials

Establishing the efficacy of antidepressants during clinical trials on humans is also more challenging than it is for non-psychiatric drugs. Clinical tests for antibiotics, for example, produce objective data that reveal whether or not treatment is working.<sup>116</sup> Such data includes temperature, blood tests, X-Rays, and bacterial cultures.<sup>117</sup> However, clinical tests on antidepressants cannot show efficacy by relying entirely on objective physical tests because there is currently no quantitative, universally-accepted diagnostic criteria for determining whether a patient is depressed or not.<sup>118</sup> Thus, SSRI sponsors rely on rating tests, the most widely used and accepted of which is the Hamilton Depression Rating Scale (the Hamilton scale), to attempt to quantify how depressed a patient is and to measure whether antidepressant treatment is effective. The FDA guidelines specifically encourage use of the Hamilton scale and other established rating systems in clinical tests.<sup>119</sup> Accordingly, the studies that established the efficacy of Prozac, Paxil, Zoloft, and Celexa for the treatment of depression all relied on the Hamilton scale (and in some cases, other rating scales as well) to show the drugs' superiority to placebo.<sup>120</sup>

The Hamilton scale and other rating scales are designed to assign a numerical value to a person's level of depression.<sup>121</sup> Based on a patient's answers to standard questions and interviewers' observations of the patient's behavior, the patient is ranked, usually from zero to four, with four representing the most frequent or severe symptoms, in 17 different areas.<sup>122</sup> For example, patients rate their feelings of guilt and suicidality, and interviewers rate observable patient behavior like agitation.<sup>123</sup> The scores from each area are then simply added together to produce a final tally, with a higher score representing more severe depression.<sup>124</sup>

The Hamilton scale has generated a fair deal of criticism since its first publication in 1960. Many clinicians are skeptical of the idea that adding up a series of numbers based on different items could produce a value with real meaning; for example, they question whether suicidality and problems sleeping should be given equal weight in the equation.<sup>125</sup> Dr. Glenmullen argues that instead of being scientific, the Hamilton and similar scales are entirely subjective.<sup>126</sup> He observes that “ethnic, cultural, and gender differences in how emotions are experienced and expressed” can greatly affect scores, making comparisons between patients impossible.<sup>127</sup> He further alleges that the Hamilton scale was designed in a way that highlights those physical symptoms of depression that most respond to antidepressants, thereby effectively “rigging” clinical tests to show the effectiveness of drug treatment.<sup>128</sup> The Hamilton scale fails to measure large areas of interpersonal functioning, like whether a patient makes eye contact, a behavior that turns out to be a good indication of response to treatment.<sup>129</sup>

FDA acknowledges the shortcomings of the Hamilton scale and other depression rating instruments currently used: “Although existing assessment measures and study designs are often capable of detecting clear evidence of clinical drug efficacy, the state-of-the-art in clinical psychopharmacology still requires the development of new and better techniques. The development of new, potentially useful approaches to drug evaluation are to be encouraged by the investigators, the industry, and the FDA.”<sup>130</sup> In other words, for the time being, the Hamilton scale is the best available measure of antidepressant efficacy, but improvements on existing scales are needed.

### 3. Duration of Clinical Trials

Another area of concern regarding clinical trials of antidepressants is their relatively short duration. The FDA guidelines state that the therapeutic activity of antidepressants can usually be established in about four weeks, but also suggest that at least one of the two required studies should run for six weeks in order to allow for a further assessment of safety.<sup>131</sup> However, once an antidepressant has been approved, physicians are instructed to prescribe it for four to six months,<sup>132</sup> and many patients stay on the drugs much longer. Thus, there is concern that FDA's recommended duration is too short to show that an antidepressant is indeed safe when taken for a much longer period of time, as is usually the case in practice. The chart at the top of the following page presents the lengths of the clinical trials relied upon in their NDAs by sponsors for five SSRIs:

Duration of Clinical Trials for SSRIs for the Treatment of MDD<sup>133</sup>

Brand Name	Number of Clinical Trials*	Duration of Trails
Prozac	2	5 weeks and 6 weeks
Zoloft	3	6 weeks, 8 weeks, and 44 weeks**
Paxil	3	12 weeks and 1 year**
Celexa	2	4 weeks and 6 weeks
Lexapro	4	8 weeks and 36 weeks**

\*This number refers to the clinical studies that provided a basis for a finding of efficacy in the NDA; sponsors may have run other tests of varying duration, but they are not required to report all studies conducted to FDA.

\*\*These three longer trials were all studies of outpatients who had responded to antidepressant treatment in shorter tests to determine the rate of relapse of MDD. The patients were randomized to continuation on the drug, or were put on placebo. Patients on the drug in each trial had significantly lower rates of relapse than patients on placebo.



As can be seen from the chart, most of the clinical studies that drug sponsors have conducted on antidepressants meet or exceed FDA's recommended duration, and, perhaps in response to critics, several sponsors have conducted significantly longer tests. Longer clinical trials might be desirable for every drug from a safety perspective, but on the other hand, the sooner relatively safe and effective drugs make it to the market, the better. Per usual, FDA has conducted a cost-benefit analysis to determine the minimum necessary duration of clinical trials for antidepressants.

A related issue is that clinical studies for these drugs are intended primarily to evaluate efficacy and thus do not systematically monitor subjects after they stop the drug; this set-up is especially problematic considering withdrawal symptoms that by definition occur at the end of drug treatment.<sup>134</sup> Paxil's label does inform readers of possible withdrawal problems. It states that an evaluation of spontaneous reporting of adverse effects reveals that a significant percentage of patients suffer the following symptoms after ceasing drug treatment: dizziness (11.9%), nausea (5.4%), nervousness (2.4%), and a number of other symptoms including electric shock sensations.<sup>135</sup> Thus, a meticulous prescriber or patient might be aware of this particular risk, but FDA should mandate additional, systematic monitoring of clinical subjects to provide a more accurate picture of the incidence of withdrawal symptoms, rather than relying on spontaneous reporting.

## **V. On-Going FDA Regulation of SSRIs**

### **A. Overview of FDA's Post-Market Regulatory Responsibilities**

FDA's regulatory mandate does not end after it approves drugs for market. The agency's Center for Drug Evaluation and Research (CDER) maintains a Post-Marketing Surveillance system to monitor the on-going safety of marketed drugs.<sup>136</sup> FDA regulations require periodic reports of all information relating to a drug's safety and effectiveness.<sup>137</sup> Accordingly, antidepressant manufacturers provide FDA with regular updates on their products, including any reported adverse effects. In 1993, FDA initiated a new program called "MEDWatch" to promote voluntary reporting of serious side effects by health care professionals and consumers.<sup>138</sup> Among the purposes of MEDWatch are to keep FDA, the healthcare industry, and consumers more informed about potential risks of drugs.<sup>139</sup> When FDA reassesses drugs based on data learned after the drug is marketed, it often recommends ways to appropriately manage newly-discovered risks.<sup>140</sup> FDA also continues to monitor drug labels, marketing, and advertising to ensure that they are truthful and balanced.<sup>141</sup>

In attempting to carry out these regulatory responsibilities as they relate to SSRIs, FDA has held two significant public hearings over the course of the past 13 years to determine whether there is sufficient evidence regarding a possible causal connection between the drugs and suicide and/or other violence. This section of the paper will briefly discuss the role of FDA's advisory committees in the regulatory process, and then it will chronicle and analyze the 1991 and 2004 hearings and resulting FDA action.

#### B. Role of FDA Advisory Committees

FDA relies on technical and scientific advisory committees to provide independent advice that will contribute to the quality of agency decision-making and lend credibility to the product review process.<sup>142</sup> These committees play a prominent role at the product approval stage, but they also offer advice earlier in the product development cycle or after a drug is marketed.<sup>143</sup> They typically are asked to comment on whether adequate data supports approval, clearance, or licensing of medical product for marketing.<sup>144</sup> Their discussions and final votes are non-binding on FDA, but the agency usually follows them.<sup>145</sup>

The Federal Advisory Committee Act in 1972 prescribed formal use of advisory committees throughout the federal government.<sup>146</sup> The law requires that the committees be “fairly balanced,” meaning as open and inclusive as possible, both in terms of types of interests represented as well as demographically.<sup>147</sup> Most members of FDA’s drug advisory committees are physician-scientists; other members include statisticians, epidemiologists, nutritionists, and toxicologists.<sup>148</sup> In addition, almost all committees include industry and consumer representatives.<sup>149</sup> Committees must allocate an hour of each meeting to open public comment.<sup>150</sup>

Not all products undergo advisory committee review, and the ones that do usually represent a new technology or are controversial.<sup>151</sup> The decision of whether to involve an advisory committee is usually made by the division director of one of the FDA’s five product centers.<sup>152</sup> In the hearings described in the following pages, CDER decided to utilize advisory committees to help it decide how to proceed in the face of significant controversy over potentially very serious side effects of SSRIs. The Psychopharmacological Drugs Advisory Committee (PDAC) advised CDER in both 1991 and 2004, and PDAC was joined by the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC) in 2004 due to the focus of the later hearing on children. In both instances, FDA followed the committee’s advice, although as will be seen this advice was very different in 2004 than in 1991.

## C. FDA Response to Concerns About SSRI Use and Suicide and Other Violence in Adults

### 1. Reports of Possible Link Between Prozac and Adult Suicide and Violence

In the early years after Prozac was approved, some alarming evidence came to light indicating that the drug might cause suicidal tendencies in a small percentage of adult patients who took it. One of the earliest and most publicized studies on this topic was conducted by Dr. Martin H. Teicher and other researchers in the Harvard Medical School Department of Psychiatry and reported in the *American Journal of Psychiatry* in 1990.<sup>153</sup> In this study, six depressed patients who were previously free of serious suicidal ideation developed intense and violent preoccupations with suicide after taking Prozac for two to seven weeks.<sup>154</sup> The preoccupations persisted for three days to three months after discontinuation of the drug.<sup>155</sup> As similar reports appeared in other medical publications, Prozac sales slackened somewhat.<sup>156</sup>

A number of theories exist for why SSRIs may possibly cause suicidal tendencies in patients. One such theory, and perhaps the most prominent, is that SSRI use may at first energize a patient before improving her mood and cognition, thus mobilizing her to carry out any suicidal thoughts she may have.<sup>157</sup> Another theory is that in some instances, SSRIs are ineffective altogether, and that the combination of disease progression and frustration with the failure of treatment may make patients more desperate.<sup>158</sup>

Public interest groups expressed their concern about the alleged link between SSRIs and suicide. The Public Citizen Health Research Group, a group affiliated with consumer rights' activist Ralph Nader, petitioned FDA to warn doctors and patients that some people taking Prozac have experienced intense, violent, suicidal thoughts, agitation and impulsivity after starting treatment with the drug.<sup>159</sup> Prozac's label at the time contained a precaution regarding "suicidal ideation," although it did not state that Prozac use in fact *causes* such thoughts.<sup>160</sup> A Lilly spokesperson defended against the petition, saying, "The approved labeling for Prozac is consistent with current medical and scientific information, and no additional warnings are needed."<sup>161</sup>

The Citizens Commission on Human Rights, a group sponsored by the Church of Scientology, well-known for its anti-psychiatric stance, mounted a full-frontal attack on the drug.<sup>162</sup> In the wake of Prozac-associated violence, the Church contacted families of some of the victims and persuaded them to sign a petition for a congressional investigation of the drug.<sup>163</sup> The Church took out full-page ads in *USA Today* criticizing Eli Lilly, and Scientologists went on television talk shows to air their views on Lilly and Prozac.<sup>164</sup> Experts generally agree, however, that the Church's attack was based on half-truths about Prozac. For example, even Dr. Teicher, the lead researcher on the main study relied upon by the Church and other critics of Prozac, admits that the patients in his study were "complicated, atypical, depressed patients," and he continues to prescribe Prozac to some patients, evidencing his continued faith in the drug.<sup>165</sup> Dr. Teicher noted, "[W]hat the Scientologists are doing is presenting the case in a one-sided, inflammatory way."<sup>166</sup>

Concern about Prozac's link to violence was not confined to the Church of Scientology, however. By the fall of 1991, FDA had received upwards of 14,000 reports of adverse side effects from Prozac, at least 500 of which involved suicide attempts.<sup>167</sup> Dr. Paul Leber, director of FDA's Division of Neuropharmacological Drug Products, acknowledged that this was a large number of adverse reaction reports compared to other drugs, but he noted that the reporting system does not distinguish between reactions to drugs and underlying conditions.<sup>168</sup>

## 2. 1991 FDA Hearing on SSRIs and Adult Suicide and Violence

In response to the widespread public and professional concern over the possible link between Prozac and suicidal and other violent tendencies in adults, FDA asked ten psychiatrists and psychologists on the PDAC to review the issue.<sup>169</sup> On Friday, September 20, 1991, the panel convened to hear testimony from many interested parties and to vote on whether there existed evidence that would justify any kind of warning on the Prozac label.<sup>170</sup>

More than twenty witnesses shared tragic tales that they blamed on Prozac.<sup>171</sup> They testified about sons and daughters who had killed themselves after taking the drug, and about people who had fatally shot themselves in front of their children.<sup>172</sup> Robin Schott of Denton, Maryland, showed the panel scars on her wrists from where she tried to kill herself shortly after stopping Prozac treatment.<sup>173</sup> She acknowledged that the evidence being presented to the panel was anecdotal but said that it was nonetheless very real.<sup>174</sup>

On the other side of the issue, opposing a warning label on Prozac, were some of the country's top specialists in treating depression and representatives of patient and family mental health groups.<sup>175</sup> Dr. Carolyn Rabinowitz, deputy medical director of the American Psychiatric Association, asserted that there was no scientific evidence indicating that Prozac rather than the underlying depression sparked the violent behavior.<sup>176</sup> Mental health experts stated that violent and suicidal tendencies are characteristic of depression—for example, John A. Smith, deputy director of the National Mental Health Association, said that 15% of untreated depressed patients commit suicide, as compared to a much smaller percentage of the average population.<sup>177</sup> Thus, Prozac proponents argued that the drug should not be blamed for such tragedies, absent greater proof than that provided by a series of anecdotes.<sup>178</sup>

In its presentation to the advisory committee, FDA staff gave an update on the substantial number of spontaneous reports of suicidality associated with the use of Prozac, but they discounted this evidence by showing that an increase in reporting coincided with publication of the Teicher report and other publicity of the issue.<sup>179</sup> FDA's presentation indicated a possible area of weakness in the agency's regulation of SSRIs and other drugs once they are on the market.<sup>180</sup> At the time, there was no systematic regulatory program in place to monitor or publicize side effects of already-approved drugs.<sup>181</sup> Under the system in place, doctors or patients could take the initiative to report side effects, but such voluntary reporting captured only a fraction of the true incidence, according to the agency.<sup>182</sup> Many of these reports were filtered through the drug's manufacture.<sup>183</sup> The resulting system was "weak" and "flaw[ed]."<sup>184</sup>

That said, the doctors and consultants on the panel did not think that SSRIs posed an imminent danger to the public. At the end of the day, having heard from the many and varied witnesses, the panel voted six to three to recommend against any label changes warning of suicide or other violent behavior for Prozac or any other antidepressant drugs.<sup>185</sup> They also voted unanimously that there was no sound evidence linking antidepressants to suicidal or violent behavior.<sup>186</sup> FDA followed the advice of the expert panel and did not require antidepressant manufacturers to place warnings on their labels at that time.<sup>187</sup>

### 3. Critique of 1991 FDA Review Process



Dr. Glenmullen is highly critical of the FDA hearing described above. First, he states that a number of the panelists had ties to the pharmaceutical industry and should have recused themselves from the proceedings due to conflicts of interest.<sup>188</sup> Further, he asserts that FDA knew that Lilly's clinical studies of Prozac did not really test whether the drug caused suicidal tendencies.<sup>189</sup> Dr. David Graham, section chief of FDA's Epidemiology Branch, wrote an internal memo stating that Lilly had acknowledged that their studies "were not designed for the prospective evaluation of suicidality."<sup>190</sup> Dr. Graham concluded that Lilly's data and analysis do not foreclose the possibility that Prozac and violent behavior are related.<sup>191</sup>

Moreover, Dr. Glenmullen reports that although four doctors from Eli Lilly were allowed to make formal presentations before the FDA panel, Dr. Martin Teicher, the Harvard psychiatrist whose reports had galvanized public outcry for a hearing, was not given this opportunity.<sup>192</sup> Even when Dr. Teicher did speak informally to the panel, the chairman did not permit him to show slides that he had prepared to support his testimony.<sup>193</sup> Glenmullen sees FDA's denials of Teicher as evidence of the agency's bias in favor of the drug companies and against scientists that dare to "rock the boat."

Finally, Dr. Glenmullen believes that Dr. Paul Leber, the director of FDA's Division of Neuropharmacological Drug Products, had an inappropriately intimate relationship with Eli Lilly, as evidenced by memos written by Lilly's chief scientific officer, Dr. Leigh Thompson.<sup>194</sup> Dr. Thompson at one point advised colleagues to deliver a report refuting the need to change Prozac's label to Dr. Leber as quickly as possible because "he is our defender" within the agency.<sup>195</sup>

Based on this evidence indicating that there were conflicts of interests within FDA and the appointed panel and that the panel appeared predisposed to protect Prozac and Eli Lilly, Dr. Glenmullen makes a compelling argument that the 1991 proceeding may not have adequately protected the public interest. As will be seen later, perhaps critics like Dr. Glenmullen lost this particular battle but may be destined to win the war over the connection between SSRIs and violence and suicide.

#### D. Suicide Precaution on Current SSRI Labels

SSRI labels do alert physicians and patients who read them closely to the risk of suicide. Consistent with the findings of the 1991 FDA panel, the labels seem to blame the risk on the underlying condition of depression as opposed to on the drug treatment. The alert appears under the section entitled “Precautions” rather than the more serious “Warnings” section. Thus, the following language appears on the Paxil label: “The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for PAXIL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.”<sup>196</sup> This precaution is duplicated almost verbatim on the labels for Prozac, Zoloft, Celexa, and Lexapro.<sup>197</sup>

Dr. Thomas P. Laughren, team leader of FDA’s Division of Neuropharmacological Drug Products within the CDER, asserts that this language lends itself to the interpretation that antidepressants may have a causal role in suicidality early in treatment.<sup>198</sup> He points out that “it has been part of medical lore for many decades that antidepressants may have an early activating effect that perhaps gives depressed patients the energy to follow through on suicidal impulses before the mood improvement associated with antidepressant treatment takes effect.”<sup>199</sup> Thus, the label precautions combined with what physicians learn in medical school and in practice may serve to put concerns about suicide on their radar screen when treating patients for depression. Despite Laughren’s assertion, however, critics have consistently called for a more prominent and clear warning for over a decade. Since the 1991 hearing, FDA has continued to monitor and study the potential SSRI-suicide link amid conflicting scientific reports, but before 2003 the agency took no further action on this issue.<sup>200</sup>

#### E. SSRI Use In Minors

## 1. Reports of Possible Link Between SSRIs and Pediatric Suicide

None of the SSRIs was initially approved for use in children and adolescents, but they have nonetheless been prescribed to the pediatric population in large numbers. Once FDA approves a drug for adults, physicians can prescribe it “off-label” for anybody, even though many drugs work differently in people of different ages. Studies indicate that depression occurs in as many as 10% of youth.<sup>201</sup> In 1994, doctors wrote approximately 200,000 prescriptions for Prozac and 300,000 for Zoloft for children aged five to 10 years old, and another 150,000 prescriptions of each for teen-agers.<sup>202</sup> More than 10 million antidepressant prescriptions were written for children in 2002.<sup>203</sup> One study published in the *Archives of General Psychiatry* concluded that about one percent of children in the U.S. are treated for depression annually, with 57% of those taking antidepressants, the vast majority of which are SSRIs.<sup>204</sup>

Treatment guidelines recommend prescribing antidepressants only for children with severe depressions and those for whom therapy fails.<sup>205</sup> In light of these narrow guidelines, Dr. Marc Olfson, professor of clinical psychiatry at Columbia University and lead author of the study from *Archives of General Psychiatry* cited above, expressed surprise and dismay at the high percentage of children on antidepressants.<sup>206</sup> He attributes the phenomenon to the dearth of trained child psychiatrists and psychologists, which may lead to reliance by non-experts on prescriptions, and to the financial incentives provided by managed care companies, which make drugs cheaper than therapy for families and insurance plans.<sup>207</sup>

Perhaps even more than is the case with adult depression and treatment, public controversy rages over the benefits and risks of the use of antidepressant drugs in children and adolescents. The lack of clinical data coupled with anecdotal evidence about suicidality in youth on SSRIs led to a demand for investigation into the effects of these drugs on minors. Recognizing the risks of inadequate drug studies on young people coupled with widespread off-label use of drugs in that population, Congress attempted to encourage additional research on pediatric patients with the FDA Modernization Act of 1997.<sup>208</sup> This act authorized FDA to grant so-called “pediatric exclusivity” for pharmaceutical manufacturers who conducted studies of their drugs in children in compliance with FDA regulations.<sup>209</sup> FDA thus incentivizes research on youth drug treatment by offering pharmaceutical companies six months of extra patent protection from generics on all uses of the tested drug, including adult uses.<sup>210</sup> Sponsors of all of the major SSRIs responded by conducting clinical trials of these drugs on children.<sup>211</sup> Prozac alone was proven effective in this population and thus garnered FDA approval for use for pediatric major depressive disorder.<sup>212</sup> In contrast, FDA’s review of trials for Zoloft, Paxil, Luvox, and Celexa did not result in their approval for the pediatric population.<sup>213</sup>

## 2. FDA Response

FDA has focused on the issue of a causal connection between SSRIs and suicide in children in the past year. Recent litigation involving claims against SSRI manufacturers has uncovered information previously unpublished by drug companies, which are not required by law or regulations to publish all relevant data on their products.<sup>214</sup> This newly-public data exacerbated worries that the drugs are not as safe and effective as they were previously believed to be. On June 19, 2003, FDA issued a talk paper recommending that doctors not prescribe Paxil for people under 18 for the treatment of MDD, due to a possible increased risk of suicidal thinking and suicide attempts in such patients.<sup>215</sup> This recommendation was based on analysis of data provided to FDA by GlaxoSmithKline pursuant to the pediatric exclusivity provision.<sup>216</sup> FDA said that it was reviewing the evidence to determine whether Paxil contributes to suicidality in minors.<sup>217</sup> Due to the aforementioned potential withdrawal effects, however, FDA cautioned against sudden discontinuation of the drug.<sup>218</sup>

Several months later, on October 27, 2003, FDA issued a public health advisory calling attention to reports of suicidal ideation and suicide attempts in clinical trials for various SSRIs in children with major depressive disorder.<sup>219</sup> It reminded prescribers of the precaution printed on all antidepressant labels advising that prescriptions be written for the smallest amount of the drug necessary for proper patient care.<sup>220</sup> The advisory acknowledged that suicidality is associated with depression, but stated that preliminary data suggests that its incidence was higher in patients on antidepressants than those taking placebo.<sup>221</sup> An article in *The New York Times* suggested that this October advisory backed off the June advisory discouraging Paxil use and made “clear the agency has grown increasingly skeptical that there is any link between antidepressant use and the risk of suicide in teenagers and children.”<sup>222</sup>

FDA conducted a preliminary review of reports for eight antidepressants studied pursuant to the pediatric exclusivity provision discussed above, and the agency determined that more data, analysis, and public discussion were necessary.<sup>223</sup> Thus, FDA announced intentions to hold an advisory committee on February 2, 2004, before the PDAC and Peds AC.<sup>224</sup>

Heightening public anxiety on the matter, in December 2003 the British Medicines and Healthcare Products Regulatory Agency, Britain's version of FDA, issued a strong warning against SSRI use in children, citing evidence of a two- to three-fold increase in suicidal thinking with some of the drugs.<sup>225</sup> The British health authorities determined that the risks of the drugs outweigh their benefits for young people.<sup>226</sup> Commentators say that the warning effectively bans the prescription of SSRIs for children in Britain.<sup>227</sup> However, the British agency exempted Prozac from this warning, saying that it alone among SSRIs is more beneficial than risky.<sup>228</sup>

### 3. 2004 FDA Hearing on SSRIs and Suicidality in Minors

The public notice of the February 2, 2004, advisory committee meeting summarized its purpose in the following way: "The committee will consider optimal approaches to the analysis of data from [clinical trials for various antidepressant drugs in pediatric patients with MDD], and the results of analyses conducted to date, with regard to the question of what regulatory action may be needed pertinent to the clinical use of these products in pediatric patients. The committee will also consider further research needs to address questions on this topic."<sup>229</sup> There was no expectation that definitive action would be taken on February 2<sup>nd</sup>. In his opening remarks at the hearing, Dr. Russell Katz, Director of the Division of Neuropharmacological Drug Products, asserted that FDA needed more time to review the "chaotic" data and probably would not act definitively until late summer 2004 after a second committee hearing on the issue.<sup>230</sup>

In preparation for the February hearing on the association between antidepressant drug treatment and youth suicide, Dr. Laughren, the team leader of the Division of Neuropharmacological Drug Products, circulated a memorandum providing background information to the PDAC and Peds AC committee members.<sup>231</sup> In it, he emphasized the importance of careful, thoughtful consideration of the matter at hand.<sup>232</sup> Laughren stressed that erring in either direction would be costly.<sup>233</sup> A failure to identify an increased risk of suicidality in children would give people a false sense of safety, but on the other hand, a premature decision that there is such an increased risk could result in reducing or eliminating availability of significant treatments for a debilitating condition.<sup>234</sup>

The memo stated that, as mentioned above, Prozac is the only SSRI proven to be effective in the pediatric population.<sup>235</sup> Although the focus on the committee was on the safety of SSRIs, proof of their efficacy or lack thereof in the given population is significant because ultimately the risks and benefits will be weighed to determine whether the drug is appropriate for pediatric use.<sup>236</sup> Thus, the lack of proven efficacy of most SSRIs in children was relevant to the advisory committee's deliberations.<sup>237</sup> That said, Laughren noted that absence of proof of efficacy is *not* equivalent to proof of ineffectiveness in FDA's eyes, thus leaving open the possibility that future studies could establish effectiveness for other drugs that have not yet shown benefits in children.<sup>238</sup>

In seeking to establish whether or not a link with suicidality exists, FDA is reviewing 20 studies of eight antidepressants, involving more than 4,100 patients under the age of 18.<sup>239</sup> No suicides occurred in the course of the studies, but early analyses, including the one conducted by the British health authorities, suggest a possible increase in suicide risk for patients taking these drugs.<sup>240</sup>



The task of figuring out whether SSRIs lead to suicidality in children is complicated by the lack of standardization of measurements and methods for assessing suicidality across different studies. The clinical studies under FDA review may not have been conducted in a way that adequately assesses patients for emergent suicidality or that allows aggregating the results of those studies.<sup>241</sup> Idiosyncratic classification of events of concern by clinicians may have resulted in some teen-agers and children being inaccurately labeled as suicidal.<sup>242</sup>

For example, different researchers appear to have varying standards for symptoms that constitute “injurious behavior;” at one end of the spectrum is a self-inflicted gun wound, which clearly indicates interest in suicide, whereas at the other end of the spectrum is a slap to one’s own face, which may indicate no suicidal intent at all.<sup>243</sup> Another example is that out of the 19 children classified as cutting themselves, most cut themselves only superficially, resulting in little bleeding.<sup>244</sup> Whether or not such conduct should be classified as suicidal is an open question.

In an attempt to make sense of this data and to obtain guidance on how the agency and physicians should proceed, FDA has retained the services of an outside group from Columbia University to review, reclassify, and reanalyze inconsistent summary data the agency has received from makers of the antidepressants under scrutiny.<sup>245</sup> Part of the task assigned the advisory committee was to offer advice on the development of guidance for more adequate assessment of suicidality in future studies.<sup>246</sup>

During the February 2<sup>nd</sup> panel, as at the similar panel in 1991, the physicians and other experts on the advisory committees heard impassioned pleas and supporting evidence from various parties. Approximately 450 people attended, and 54 spoke during the Open Public Hearing session.<sup>247</sup> On the one hand, dozens of relatives of youngsters who either committed or attempted suicide while on SSRIs testified before the panel that antidepressant drugs that were supposed to help these children were responsible for harming them instead. They blamed FDA for failing to warn physicians, parents, and children of the risk inherent in SSRIs. On the other hand, mental health experts asserted as they did in the 1991 hearings that leaving depression untreated is far more dangerous than prescribing SSRI treatment. These opponents of further regulation also presented scientific evidence tending to show that SSRIs are in fact not the cause of suicidality. They urged FDA to act cautiously, if at all, in limiting access to these potentially very helpful drugs.

a. Testimony in Favor of Additional FDA Action

Proponents of stronger warning labels on SSRIs regarding the risks to children claim that numerous studies and experience prove that SSRIs can lead previously non-suicidal youth to think about killing themselves. They attribute this change in thought and behavioral patterns to a “stimulation” or “activation” effect the drugs have on children’s brains.<sup>248</sup> Whereas before treatment a depressed child may simply not had the energy to even consider suicide, SSRIs may “jump-start” a disturbed youth and cause them to have, and to act on, self-injurious fantasies.

The sentiments of Tom Woodward, whose 17-year-old daughter Julie hanged herself after being on Zoloft for one week, are representative of many of the witnesses who urged FDA action by relating personal experiences.<sup>249</sup> Julie Woodward had no history of self-harm or suicide, nor did the family have a history of depression or suicide. She had been excited about attending college and had scored a 1,300 on her SATs weeks before her death. Mr. Woodward said that the prescribing physicians stressed the safety of Zoloft and failed to mention any possibility of suicide or other violence. He stated, “We are 100% convinced that Zoloft killed our daughter,” and he accused FDA of playing politics and catering to the financial interests of the pharmaceutical industry by failing to require warnings earlier. He lobbied for compelling the drug companies to produce all results of clinical studies, including negative ones, and for funding such studies with public funds.<sup>250</sup>

An attorney from a plaintiffs' firm that represents thousands of SSRI patients in cases against drug companies also presented compelling testimony. Karen Barth Menzies, of the law firm Baum, Hedlund, Aristei, Guilford & Schiavo, reminded the panel of the agency's regulatory mandate to require drug companies to amend their labeling to contain warnings "*as soon as there is reasonable evidence* of an association of a serious hazard with a drug; a causal relationship need not have been proved" (italics added).<sup>251</sup> She asserted that in addition to the link with suicidality that is currently being questioned, SSRIs's link with other serious adverse effects like akathisia (severe restlessness), psychosis, and mania is more established. She believes that there can be no doubt that there already exists reasonable evidence of a connection between SSRIs and several serious hazards, including suicide, and thus she called on FDA to warn the public immediately. Her testimony concluded with the plea, "Put me out of business for the right reasons; warn about these drugs."<sup>252</sup>

Dr. Glenmullen, oft-cited in this paper, flew to Washington, DC, for the hearings to air his criticism of FDA for its paternalism regarding patients.<sup>253</sup> Citing his clinical experience as proof, he asserted that informing patients of possible risks will not frighten them away from treatment, as advocates of the status quo claim. He deplored the lack of regulatory action by the agency in the decade-plus that had passed since the 1991 hearings, despite gathering evidence of a causal connection between SSRIs and akathisia, a condition which in his words "can make some patients so agitated that they feel death would be a welcome relief."<sup>254</sup>

#### b. Opposition to Additional FDA Action

People who did not want FDA to require a warning on SSRIs appeared to receive a boost for their arguments when days before the February 2<sup>nd</sup> hearing, the American College of Neuropsychopharmacology (ACNP) released a widely-publicized report stating that SSRIs do not increase the risk of suicidality in youth.<sup>255</sup> This special task force reviewed drug company-sponsored trials involving almost 2,000 children, including all published studies as well as some unpublished data provided to the British regulatory agency.<sup>256</sup> The group found that there was no significant difference in the number of children exhibiting suicidal thoughts or behavior when on Prozac, Paxil, Zoloft, or Celexa, versus children on placebo.<sup>257</sup> The ACNP task force concluded that in fact, the increased use of SSRIs appears to have lowered worldwide suicide rates; the rate of child suicide in 15 countries has declined by an average of 33% over the past decade and a half, during which time SSRI use has increased greatly.<sup>258</sup> That said, the committee emphasized that its findings were preliminary and were based on limited amounts of data.<sup>259</sup> The inconclusive nature of the ACNP report was emphasized during the advisory committee hearings, when FDA acknowledged for conflicts of interest purposes that one member of PDAC and one FDA presenter were on the ACNP task force that issued the report.<sup>260</sup>

At the hearing, a psychiatrist representing the National Alliance of the Mentally Ill cautioned against limiting access to SSRIs, citing the Surgeon General for the statistic that 80% of youth who need mental health treatment receive none at all.<sup>261</sup> She offered personal testimony as well to illustrate the significant good SSRIs do for children and the harm further restrictions on their use would cause. Her two sons had shown self-injurious tendencies before going on SSRIs, but with proper SSRI treatment, both were leading full and functional lives.<sup>262</sup> She said she “shudder[s] to think of their plight if these medications were not available.”<sup>263</sup> Many others urged regulatory caution as well, as in 1991, claiming that parents might be afraid to put their children on antidepressants due to exaggerated reports of their risks.

#### 4. Advisory Committee Recommendations and FDA Action

After reviewing relevant materials and hearing 10 hours of testimony, the FDA panel comprising PDAC and Peds AC issued its recommendation. It advised FDA to issue promptly stronger warnings to physicians about the possible risks to children posed by antidepressants, rather than wait until the agency's review is completed in late summer.<sup>264</sup>

The committee emphasized the need to warn pediatricians and family practitioners, among other health-care workers,<sup>265</sup> reflecting the concern expressed by many that non-psychiatric physicians sometimes misuse antidepressants as a line of first defense for children who appear depressed. The committee further recommended that FDA's warning explicitly state the need for close follow-up and monitoring of emergent side effects at the beginning of treatment of children.<sup>266</sup> Dr. Wayne K. Goodman, a member of the advisory committee and the chairman of psychiatry at the University of Florida College of Medicine, explained that the panel was particularly troubled by reports that some doctors were giving patients samples of antidepressants without scheduling follow-up appointment to ensure that patients were tolerating the drugs.<sup>267</sup>

Moreover, the committee stated that the proven efficacy of SSRIs for treating pediatric depression is less compelling than many of its members were previously aware, and that the risk-benefit calculus must be adjusted accordingly, echoing concerns expressed in Dr. Laughren's background memo.<sup>268</sup> Worried that similar lack of awareness pervades the rest of the health care community and leads to over-prescription of SSRIs, the committee recommended that FDA publicize the fact that the vast majority of randomized controlled trials fail to show superiority over placebo in treating MDD in children.<sup>269</sup> Dr. Matthew Rudorfer, Chairman of the PDAC and a scientist at the NIMH, stated that such a warning would serve to alert physicians to warning signs of suicidal or other violent thinking or behavior, but that it would not discourage them from prescribing the drugs.<sup>270</sup>

As in 1991, FDA followed its advisory committee's advice. On March 22<sup>nd</sup>, the agency issued a public health advisory requesting SSRI manufacturers to include in their labels a warning statement that recommends close monitoring of patients on these drugs for signs of suicidality.<sup>271</sup> FDA went even farther than the committee recommendations by asking for warnings regarding both pediatric and adult patients, despite the hearing's focus on children alone.<sup>272</sup> The public health advisory puts healthcare providers, patients, and families on notice to be particularly vigilant for signs of worsening depression or suicidal inclinations both when starting antidepressant therapy and when changing doses.<sup>273</sup> Dr. Katz of the CDER said that the proposed warning label will "include information about behavioral changes that may occur in patients who are prescribed antidepressant drugs" so that doctors and others will be attuned to warning signs.<sup>274</sup> FDA has still not concluded that antidepressants *cause* suicidality, but it is continuing to review available data on the issue and expects to update the advisory committees regarding its findings later this summer.<sup>275</sup>



## 5. Public Reaction and Critique of 2004 Hearing

Public reaction to FDA's request for a warning on SSRI labels was predictably mixed. Healthcare professionals familiar with the issue hoped that the warnings would encourage greater understanding of SSRI risks and closer monitoring of patients by doctors, but at the same time some worried that the warning would discourage patients desperately in need of psychiatric help from seeking treatment.<sup>276</sup> Dr. James H. Scully, Jr., medical director of the American Psychiatric Association, expressed his worry that primary care physicians (PCPs) might also lose confidence in the drugs and stop prescribing them altogether, despite the need for PCPs to continue to help combat depression with all available tools.<sup>277</sup>

Critics of FDA inaction on the issue up to this point must have been pleased by the sheer amount of press the agency's advisory received. Even the non-scientific, popular magazine *People* published a feature article in the wake of the FDA warning.<sup>278</sup> The article focused on the suicide of the aforementioned Julie Woodward, the rising high school senior who killed herself shortly after starting to take Zoloft, and her family's efforts to alert people to the risks of SSRIs.<sup>279</sup> Such media attention no doubt has helped to spread the message to many who were previously unaware that antidepressants are not necessarily as safe as previously assumed. However, many critics believe that FDA's request for warnings about the risk of suicide posed by SSRIs was both tardy and insufficient, and such concerns led to a Congressional investigation of the matter.

## 6. Congressional Oversight of FDA Regulation of SSRI Use in Minors

The House Energy and Commerce Committee's Subcommittee on Oversight and Investigations launched an investigation in early February 2004 to determine what FDA knew about pediatric suicidal tendencies potentially caused by SSRIs, and when it knew such information.<sup>280</sup> On March 24<sup>th</sup>, Representatives Joe Barton of Texas and James Greenwood of Pennsylvania sent a letter to FDA Commissioner Mark McClellan seeking answers. The letter stated that "the Committee is interested in learning the rationale for FDA's decision not to require stronger warnings on the labeling for pediatric use of an anti-depressant product when, for example, [GlaxoSmithKline's] own analysis of their data indicates an increased risk of suicide-related behavior in children."<sup>281</sup> FDA was also asked to justify its decision in light of the more rapid and protective action taken by the British regulatory authorities to limit the prescription of SSRIs to children in that country.<sup>282</sup> The letter requested from the agency a long list of documents related to the safety and efficacy of antidepressants in minors, including the following: intra-agency emails about suicide risk, communications between FDA and SSRI manufacturers on the same topic, and internal records pertaining to particular official FDA actions, including the June 2003 advisory on Paxil and the October 2003 advisory on possible effects of SSRIs on the pediatric population.<sup>283</sup>

Further, Barton and Greenwood inquired about allegations that FDA had suppressed findings of an internal study finding a causal connection between SSRI use and pediatric suicidality that would have been relevant to the February hearings.<sup>284</sup> It turns out that the agency did in fact bar the testimony of Dr. Andrew Mosholder, an FDA epidemiologist who had reviewed the pediatric clinical data and concluded that antidepressant treatment increases the risk of suicide in children.<sup>285</sup> In 2003, the agency assigned Dr. Mosholder the task of analyzing the more than 20 studies that the drug companies had submitted to determine whether a link with pediatric suicide exists, and in January 2004, he submitted a lengthy memo concluding that children taking antidepressants are almost twice as likely as those on placebo to become suicidal.<sup>286</sup> He urged his FDA colleagues to discourage doctors from prescribing all antidepressants (except for the proven-effective Prozac) to children.<sup>287</sup>

However, FDA higher-ups decided to keep Mosholder's conclusions private, and to preclude his testimony at the February 2<sup>nd</sup> advisory committee hearing, despite their previous intention to let him testify.<sup>288</sup> Dr. Robert Temple, FDA's associate director of medical policy, defends the agency's quelling of Mosholder's findings. He and others believe that Mosholder was insufficiently skeptical of reports of suicidal behavior contained in the drug companies' studies, and that therefore his determinations are not substantiated.<sup>289</sup> Temple sounded the now-familiar refrain: "It would have been entirely inappropriate to present as an FDA conclusion an analysis of data that were not ripe... If you get it wrong and over-discourage use of these medicines, people could die."<sup>290</sup> Critics of FDA like Dr. Glenmullen view FDA suppression of Mosholder's study and testimony as yet another example of agency misconduct; they say that given the agency's own evidence of a link between SSRIs and pediatric suicidality, FDA should have mandated a stronger warning on the drugs' labels.<sup>291</sup>

The Commerce Subcommittee on Oversight and Investigations also appealed directly to the drug manufacturers for more information that could help prove the existence or absence of suicidal side effects of SSRIs. On the day following the February FDA advisory committee hearing, the subcommittee sent letters to Pfizer, Wyeth, Eli Lilly, and GlaxoSmithKline soliciting all unpublished data concerning the use of antidepressants in youth. <sup>292</sup> Granted, the drug companies had already provided FDA a great deal of information pursuant to the pediatric exclusivity provision. However, Representative Greenwood requested more information "in light of protecting the public health of children and/or the need to expedite public and physician confidence in the use of antidepressants."<sup>293</sup>

The subcommittee's letter cites a January 29, 2004, article in *The Washington Post* that states that makers of popular antidepressants have refused to disclose details of most pediatric clinical trials.<sup>294</sup> The article notes that researchers familiar with the unpublished information say that most of the secret studies show that the drugs are no more effective than placebo in children.<sup>295</sup> Although there is no legal mandate to reveal negative data and despite a strong argument that even genuinely effective medicines sometimes do no better than placebo,<sup>296</sup> Greenwood's letter to the drug companies clearly reflects a judgment that in this particular instance the public interest demands that all relevant data be considered. A GlaxoSmithKline spokesperson said the company plans to comply with the request.<sup>297</sup> This example of congressional involvement in a regulatory matter reveals both the significant public interest at stake as well as the substantial role the media plays in influencing policy.

## **VI. Conclusion**

Depression is a debilitating condition that individuals have suffered since the beginning of recorded history. The de-stigmatization of mental illness and the discovery of SSRIs in the second half of the twentieth century bode well for mankind's fight against depression. Despite significant controversy over the best ways to treat it, experts agree that the biggest problem in the treatment of depression is under-diagnosis. The growing recognition that mental illness does not represent a moral failing encourages more people to seek treatment. Drug companies' efforts to push their products, via advertisements as well as "public interest" campaigns, also help to promote awareness of depression and available treatments for it. This paper has chronicled and analyzed several aspects of FDA regulation of one type of treatment for depression, namely the class of antidepressants known as SSRIs, and it has shown some of the challenges SSRIs pose for the regulatory regime both in the approval and post-market phases.

On the whole, FDA has made commendable efforts to ensure that SSRIs available to the American public are sufficiently safe and effective, and that their benefits outweigh their risks. The agency has allowed widespread access to these promising antidepressant drugs while alerting prescribers and patients to their known risks. The regulated industry and other interested parties have strong yet disparate views of the benefits and risk of antidepressants, thereby complicating FDA's job. Ultimately the agency is bound by its statutory and regulatory mandates and by scientific evidence,<sup>298</sup> as the continuing saga involving a potential link between SSRIs and suicide illustrates: FDA resisted requiring suicide warnings on SSRI labels for over a decade, despite intense public pressure, but then reversed this position when the weight of the science before it necessitated a warning. Although science is determinative, FDA must also be sure to maintain the high level of trust the public has in the agency by conducting its proceedings in a way that appear open and fair. Congressional oversight of FDA regulation and the involvement of advisory committees help to guide agency discretion and lend legitimacy to its processes.

This paper has shown several examples of how the regulatory process evolves and improves when its shortcomings are recognized. For example, in response to calls for more systematic reporting of adverse effects of drugs, FDA started its MEDWatch program. Similarly, when concerns arose about treating children with drugs that had never been tested on children, Congress acted to stimulate clinical testing on that population by enacting the pediatric exclusivity provision, which has resulted in a flurry of pediatric studies by the drug manufacturers. At times, public opinion can influence the regulated industry directly, for instance, when the pharmaceutical industry responded to criticism of the short duration of its clinical trials of SSRIs by voluntarily undertaking longer trials than are suggested by FDA guidelines.

That said, there are many areas for improvement in the regulatory process. The increasing influence the drug industry wields over academic research is disturbing and should be addressed through legislation or regulation. In addition, FDA, the industry, and academic researchers should work together to hone the way they evaluate the efficacy of antidepressants in animals and humans, and in particular, to create a more objective yardstick than the existing Hamilton scale. Further, at least in cases where there is some legitimate concern about a drug's serious adverse effects like suicide or other types of death, drug companies should be required to make all clinical studies available to FDA so that the agency can review all relevant information in deciding how best to protect the public.

Additionally, although MEDWatch is clearly superior to the absence of any reporting system, greater post-marketing monitoring of drugs is needed. For example, FDA should require longitudinal studies on antidepressants after drugs are on the market. Ideally, FDA would beef up post-market monitoring of drugs, but of course this type of regulatory would require significant extra resources. In addition, FDA should take great pains to allow and encourage people with views opposed to those of the drug industry to present their stance to the agency on controversial topics to avoid any appearance of impropriety. Following both the 1991 and 2004 hearings on the potential connection between antidepressants and suicide, the press reported that FDA effectively silenced certain individuals whose views were antithetical to the industry. In 1991, the influential Dr. Teicher was allowed to give only an abbreviated informal presentation, and in 2004 FDA's own scientist Dr. Mosholder was not permitted to testify at all. Of course there is a finite amount of time for testimony at these hearings and FDA cannot be expected to allow every person a formal presentation, but the agency should be aware of its responsibilities not only to actually *be* fair in the evidence it considers, but also to *appear* to the public to be fair.

Some people have pointed to the fact that PCPs often wrongly prescribe SSRIs as evidence of failure of FDA regulation. It is true that PCPs with minimal training in psychiatry write the vast majority of prescriptions for SSRIs; a 1997 source reports that PCPs are responsible for as many as 70% of antidepressant prescriptions.<sup>299</sup> Many generalist physicians and even mental health specialists do not know the risks of SSRIs and thus prescribe them to patients who may not need them on the assumption that the drugs are entirely safe. Supporting this assertion, a British study found that only 30% of PCPs and 72% of psychiatrists surveyed in England know that patients can experience severe withdrawal symptoms when they stop taking SSRIs.<sup>300</sup>



That said, FDA should not shoulder the brunt of the blame for doctors' prescribing habits. The FDA-approved labels for SSRIs contain numerous precautions that should alert doctors to the risks of the medications. For example, regarding withdrawal effects, the Paxil label states: "A gradual reduction in the dose rather than abrupt cessation is recommended wherever possible,"<sup>301</sup> so that anybody who reads the label carefully should realize that there are risks to going off the drugs too quickly. Similarly, FDA's numerous public health announcements over the past couple of years, as well as its request for a warning about suicide on SSRI labels, should serve to make doctors and patients more aware that these drugs are not entirely safe.

Some type of regulatory restriction on the distribution of antidepressants would indeed help to curb the problem of mis-prescription of antidepressants and inadequate follow-up by physicians who have insufficient knowledge of psychotropic drugs. However, for FDA to take on the responsibility of restricting distribution, the Food Drug and Cosmetic Act would have to be amended to grant the agency this authority, and it is unlikely such an amendment would pass. Thus, self-regulation by the medical profession on this subject is preferable to additional governmental regulation. In other words, rather than pushing for additional regulation of SSRIs, critics of physicians' prescription practices should look instead to further educating medical students or current physicians about appropriate use of SSRIs.

In conclusion, despite unique challenges presented to FDA regulation by SSRIs, the agency has done a good job overall of balancing the need for access to these medicines with the need to warn of their risks. FDA has afforded opportunity for most interested parties to be heard in the course of its deliberations over whether to require a suicide warning, and it has responded appropriately based on available scientific evidence and the advice of its advisory committees. That said, SSRI regulation could be improved by advances in the methods employed in clinical trials, greater post-market monitoring, and increased participation by drug industry critics in the regulatory process. Finally, the medical profession rather than FDA should be responsible for reducing the unnecessary prescriptions of these potentially risky drugs.