American Psychopharmacology and its Discontents: Tracing the Historical Underpinnings of the 2004 Regulatory Intervention in Antidepressant Use, 1950s-2004

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Introduction:

The landscape of mental health treatment has undergone significant transformation over the past century, propelled by advances in medical science, shifts in societal attitudes toward mental illness, and evolving regulation. Among the most notable developments in this trajectory is the emergence and proliferation of antidepressant medications, which have played a pivotal role in the management of depression and related mood disorders. Yet, the history of antidepressants is marked by a complex interplay of scientific discovery, clinical innovation, regulatory oversight, and socio-cultural dynamics, all of which have shaped the trajectory of psychiatric pharmacotherapy.

One pivotal juncture in the history of antidepressants occurred in 2004 when mounting concerns regarding the safety of these medications, particularly among adolescents and young adults, prompted congressional hearings and regulatory action by the Food and Drug Administration (FDA).[1] The catalyst for these events was the growing recognition of a potential link between antidepressant use and an increased risk of suicidal ideation and behaviors, particularly among pediatric populations. In response to these concerns, the FDA mandated adding a black box warning—a stern and prominently displayed cautionary statement—on all antidepressant packaging. This regulatory measure aimed to alert prescribers, patients, and caregivers to the heightened risk of suicidal thoughts and behaviors associated with antidepressant use, especially during the early stages of treatment. A black box warning represents the most severe safety warning issued by the FDA, reserved for medications with significant risks of serious or life-threatening adverse effects. It draws attention to specific safety concerns and informs healthcare professionals and patients about the potential risks associated

[1] "Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials." 2004. p. 18-49, 253-267. (Text from: ProQuest Congressional); Accessed: February 20, 2024.

with a particular medication. By appending a black box warning to antidepressant packaging, the FDA sought to strike a balance between ensuring patient safety and preserving access to effective treatments for depression and related conditions. However, the implementation of this regulatory measure sparked contentious debates within the medical community and broader society, raising questions about the appropriate balance between risk and benefit in psychiatric pharmacotherapy.

Against this backdrop, I explore the history of antidepressants in the market, with a particular focus on the 2004 policy regulation and its aftermath. Through a historical lens, I aim to interrogate the factors that led to the FDA's decision to mandate a black box warning on antidepressant packaging. By examining the historical context, regulatory processes, and socio-cultural dynamics surrounding the 2004 policy regulation, this study sheds light on the complexities of psychiatric pharmacotherapy and the challenges inherent in balancing safety, efficacy, and access to mental health treatments. In pursuing these objectives, I engage with the existing historiography of antidepressants, drawing on the insights of scholars such as Anne Harrington and David Healy. Harrington's seminal work, *Mind Fixers: Psychiatry's Troubled Search for the Biology of Mental Illness*, offers valuable perspectives on the broader historical context of psychiatric treatments and the quest for biological explanations of mental illness, which she argues was troubled. Similarly, Healy's research, particularly in *The Creation of Psychopharmacology*, provides critical insights into the intertwined relationship between pharmaceutical companies, regulatory agencies, and clinical practice in antidepressant medications, explaining how each of these factors contributed to antidepressant dynamics. Each of these authors argue that there were several key factors influencing the evolution of antidepressants aside from scientific advancement, which was controversial in its magnitude,

complicating the story of their production. However, I am focused on the subject from a policy lens rather than a scientific standpoint, with a focus on the factors influencing legal and regulatory change.

Methodologically, I employ an interdisciplinary approach, combining textual analysis of primary sources, including advertisements, congressional records, and news articles, and critical examination of secondary literature to reconstruct the historical narrative surrounding the 2004 policy regulation and its implications. I argue that the policy regulation implemented in 2004, mandating the inclusion of a black box warning on antidepressant packaging, was influenced by several interconnected factors. With mass awareness of antidepressants, there was widespread positivity in medical circles and popular culture regarding the introduction of antidepressants, buoyed by optimistic media portrayals, which set the stage for my discussion. These enthusiasms were further fueled by the FDA's relaxation of pharmaceutical advertising regulations in 1997, leading to a surge in direct-to-consumer antidepressant advertisements.[2] However, these ads inadvertently raised concerns over exaggerated efficacy claims and a lack of comprehensive education about adjunct treatment options and potential risks.

Furthermore, a lack of transparency in clinical trial data from pharmaceutical companies bred skepticism among regulators and healthcare professionals. The subsequent release of this data revealed controversies surrounding antidepressant efficacy, particularly in pediatric populations, and raised safety concerns. The 2004 congressional hearings on antidepressants emerged as a crucial moment, highlighting regulators' worries regarding consumer transparency and the necessity for more stringent oversight of antidepressant prescribing practices. Ultimately, the thesis posits that the interplay of advertisement portrayals, regulatory shifts, and clinical trial

[2] Block, "Costs and Benefits of Direct-to-Consumer Advertising: The Case of Depression," *Pharmacoeconomics* 25, no. 6 (2007): 511-521, doi: 10.2165/00019053-200725060-00006.

transparency issues regarding safety and efficacy collectively shaped the path leading to the 2004 antidepressant policy regulation.

The Freudian Context

Understanding the Freudian framework within American psychiatry is crucial for evaluating the diverse perspectives on the origins and therapeutic approaches to mental illness. Even in contemporary psychiatry, which predominantly integrates biological and environmental factors, Freudian-inspired psychotherapy remains a common adjunct to medication.

The pursuit of biological explanations for mental illness predates the so-called biological revolution of the 1970s. Emil Kraepelin considered the architect of modern scientific psychiatry, championed the belief that mental disorders primarily stemmed from biological and genetic malfunctions.[3] His meticulous observational approach and systematic classification of mental disorders represented a significant departure from earlier, more speculative methods. Kraepelin's work laid the foundation for a more scientific understanding of psychiatric conditions, emphasizing the importance of detailed clinical descriptions and longitudinal studies in diagnosis and prognosis. Throughout the early 20th century, Kraepelin's perspectives held sway over the field.[4] However, despite Kraepelin's efforts and the subsequent intensification of research into the biological basis of mental illness, progress in this area was largely fruitless during his lifetime. The tools and techniques necessary to investigate the brain and its functions were rudimentary compared to those available today, limiting researchers' ability to uncover the biological mechanisms underlying psychiatric disorders. Additionally, the complexity of the brain and the heterogeneity of mental illnesses posed significant challenges to early researchers, further

[3] Emil Kraepelin, *Psychiatrie: Ein Lehrbuch für Studierende und Ärzte* (Leipzig: Barth, 1883).
[4] Anne Harrington, *Mind Fixers: Psychiatry's Troubled Search for the Biology of Mental Illness* (New York: W. W. Norton & Company, 2019), xii. Kindle.

impeding their progress. Despite landmark discoveries such as the biological cause of general paralysis of the insane (GPI) being linked to syphilis, neurologists experienced limited scientific breakthroughs during this era.[5]

In 1909, Sigmund Freud, accompanied by his student Carl Jung, delivered a notable address at Clark University in the United States, marking a significant moment in the history of psychoanalysis.[6] Following World War II, Freud's influence experienced a resurgence, a phenomenon historian Anne Harrington partially attributes to the remarkable success of Christian "mind cure" movements.[7] These groups centered on fostering genuine and profound belief in recovery through practices such as affirmation exercises, prayer, chanting, and visualization.[8]

The aftermath of this resurgence, coupled with failures in biological research, witnessed a surge in Freudian thinkers in America who rejected biological explanations for mental illness.[9] Instead, they delved into the realms of the "unconscious mind," "repressed traumatic memories," and sexual "impressions" to elucidate and address neuroses. This intellectual shift reflected a broader movement from biological determinism toward a more psychoanalytic understanding of the human psyche. One of the fundamental principles of Freudian thought is the emphasis on the unconscious mind, which informs his theories on topics such as psychosexual development and defense mechanisms.[10] According to Freud, a significant portion of mental life operates at an unconscious level, where thoughts, desires, and memories exert a profound influence on conscious thoughts and behaviors.[11] This concept of the unconscious mind became a cornerstone

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[5] Harrington, *Mind Fixers*, 6.
[6] Harrington, *Mind Fixers*, 35.
[7] Harrington, Anne, *The Cure Within: A History of Mind-Body Medicine* (New York: Norton, 2008).
[8] Ibid.
[9] Sigmund Freud, *The Unconscious*, (London: Hogarth Press, 1915), 25.
[10] Shorter, "History of Psychiatry."
[11] Shorter, "History of Psychiatry."

of Freudian psychiatry, influencing how mental processes were conceptualized and explored. Freud also proposed a theory of psychosexual development, suggesting that individuals pass through distinct stages, such as the oral, anal, and genital stages, with each characterized by specific conflicts and developmental tasks.[12] The introduction of defense mechanisms is another crucial aspect of Freudian psychiatry. Freud argued that individuals employ psychological strategies, known as defense mechanisms, to cope with anxiety and protect themselves from distressing thoughts and emotions.[13] Mechanisms such as repression, projection, and denial were seen as crucial components of Freud's conceptualization of the mind.[14]

Psychoanalysis, a form of talk therapy in which patients engage in open-ended discussions to explore their unconscious thoughts, is a hallmark of Freudian psychiatry. This therapeutic approach aims to uncover hidden conflicts and promote psychological healing through introspection and self-reflection. Despite these incredibly influential insights, Freud's post-war hold on psychiatry had shaky foundations. Kraeplin's ideas would be revived by the end of the twentieth century.

[12] Shorter, "History of Psychiatry."
[13] Shorter, "History of Psychiatry."
[14] Shorter, "History of Psychiatry."

The Birth of Psychiatry and Antidepressants

The accidental discovery in 1950s France of the drug chlorpromazine as an antipsychotic catalyzed modern psychiatry and psychopharmacology, eventually paving the way for antidepressants and fundamentally altering societal perceptions of human behavior. Although Lithium as a treatment for mania predates Chlorpromazine, it was a naturally occurring substance and thus not patentable. Chlorpromazine (later launched as Thorazine) was the first profitable psychotropic drug and showed promising effects in addressing psychosis.[15] Once introduced in the United States, it was quickly viewed as more effective than psychotherapy or alternative medicines in treating symptoms of psychosis. The companies lucky enough to have previously acquired chlorpromazine patents saw huge profits. In New York, "State mental hospital doctors were so eager to use the drug that when chlorpromazine was finally launched as Thorazine in 1955, even though the license application had been for antiemetic, the take-up in psychiatry was astonishing — SK&F reportedly took in $75 million the first year the drug was sold."[16] In response, other American pharmaceutical companies wanted a share of the wealth after seeing how much money antipsychotic chlorpromazine had made for its patent owners, but their research continuously hit dead ends.[17]

In 1956, while searching for a low-cost antipsychotic alternative to chlorpromazine, Swiss psychiatrist Ronald Kuhn experimented with a drug called imipramine.[18] While it was unsuccessful in treating his schizophrenic patients, Kuhn noticed a significant improvement in the mood of three patients whose psychoses coincided with severe depression symptoms. In

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[15] Healy, *The Creation of Psychopharmacology.*
[16] Healy, David, *The Creation of Psychopharmacology* (Chicago: University of Chicago Press, 2002), 97.
[17] Harrington, *Mind Fixers*, 194.
[18] Harrington, *Mind Fixers*, 194-196.

1957, this drug surprised everyone when Kuhn reported the results of his first trials on a group of forty severely depressed patients, slowly winning over his skeptical European colleagues. Kuhn described imipramine as different from existing treatments because it may have addressed the root of the problem, possibly correcting something that had gone wrong in the *physiology* of depressed patients. In 1958, Geigy, a Swiss pharmaceutical company that owned chlorpromazine, began marketing imipramine by the brand name Tofranil.[19] One company researcher told the *Wall Street Journal* that 1959 "probably will go down as the 'Year of the Antidepressant.'"[20] Other companies entered the market, launching various drugs that were chemically similar to imipramine but with minor tweaks. These drugs became known as tricyclic antidepressants, the first generation of such medications.[21]

The evolution of second-generation antidepressants represents a significant milestone in the treatment of depression and related mood disorders. Emerging in the late 20th century, these medications, such as selective serotonin reuptake inhibitors (SSRIs), were developed as successors to the first-generation tricyclic antidepressants. Their introduction shifted towards safer and more tolerable pharmacological options with fewer side effects. As these second-generation antidepressants entered the market, they revolutionized the landscape of psychiatric pharmacotherapy, offering clinicians and patients a more comprehensive range of treatment options with improved tolerability and efficacy profiles.

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[19] Ibid.
[20] Ayd, Frank, interview by Thomas A. Ban, July 19, 2001, Archives of the American College of Neuropsychopharmacology.
[21] Shorter, "History of Psychiatry."

Initial Media Exuberance (late ‘90s - early 2000s)

Within just five years after European researchers introduced the United States to the antipsychotic drug chlorpromazine, Swiss pharmaceutical company Geigy would launch Tofranil, the first antidepressant, solidifying this paradigm shift towards a “biological revolution.”[22] A boom of overwhelmingly positive media reactions followed shortly after; unprecedentedly, they provided the critical context of prevailing attitudes about psychiatry.

My analysis of these media responses shows that, in clinical circles, this academic development represented the field's movement away from what critics would come to refer to as the "pseudoscience" of the Freudian model and towards psychiatry as an empirical science grounded in biology and aligned with the rest of Western medicine. For the pharmaceutical industry, these new drugs provided opportunities for significant profits and ultimately motivated them to expand their user base through broadened definitions of depression. Media representations and advertisements explored the nature of personalities with increasing fluidity, which would be the messaging focus of later advertising campaigns. Most significantly, to the many Americans who have mental illness, it provided a beacon of hope for an improved social standing and quality of life.

[22] Healy, *The Creation of Psychopharmacology.*

Media Analysis

Although psychopharmacological research stems back to 1950 with the synthesis of the antipsychotic chlorpromazine, it took time for this research to gain legitimacy and permeate the scientific culture. However, given the previous decade's continued research and scientific developments, in 1981, *The Washington Post* announced that everything their readers knew about mental illness would soon fundamentally change.[23] In this article, using case histories of inspiring patient stories, prominent psychiatrists Klein and Wender emphasized that discoveries of the underlying biological causes of mental illness would illustrate that many principles of the time's psychodynamic theory would be proven "irrelevant or even misleading."[24]

In 1984, psychiatrist Nancy Andreasen released *The Broken Brain: The Biological Revolution in Psychiatry*, which helped publicly announce psychiatry's biological transition.[25] In this book, she argues that recent advancements in biological treatments for mental health remove the guilt and shame associated with illness, allowing society to view the afflicted "as human beings who deserve as much sensitivity and love as people who have cancer, muscular dystrophy, or heart disease."[26] Thus, she communicates how advancements in science destigmatize those suffering from such conditions, inspiring greater compassion from society and more effective treatments. Andreasen also comments on how such shifts in mental health research and treatment options legitimize psychiatry by "realigning [the practice] with the mainstream biological traditions of medicine."[27] Through this message, she reflects on psychiatry's dissonance with the

[23] Klein, Donald F. and Wender, Paul H., "The Promise of Biological Psychiatry," *Psychology Today* 15 (1981): 25.
[24] Klein and Wender, "The Promise of Biological Psychiatry."
[25] Nancy Andreasen, *The Broken Brain: The Biological Revolution in Psychiatry* (New York, NY: HarperCollins, 1984).
[26] Andreasen, *The Broken Brain*.
[27] Andreasen, *The Broken Brain*.

rest of Western medicine, speculating that a transition towards medicalized care will allow the mentally ill a superior framework of care.

In 1988, the medical community widely recognized mental health treatment as a biological discipline.[28] That year, psychiatrist Samuel Guze gave a lecture at London's Maudsley Hospital titled: "Biological Psychiatry: Is There Any Other Kind?" He concluded his lecture by arguing that "continuing debate about the biological basis of psychiatry is derived much more from philosophical, ideological and political concerns than from scientific ones."[29] This speech represented the paradigm shift within clinical communities on the causes of mental neuroses, with the dominant theory now depending on biology rather than psychodynamic theories.

Prozac was manufactured by pharmaceutical company Eli Lily, who bet on the drug. In 1993, shortly after Eli Lily's legal troubles (see p. 28), American psychiatrist Peter Kramer published *Listening to Prozac: A Psychiatrist Explores Antidepressant Drugs and the Remaking of the Self.*[30] Kramer is overall incredibly enthusiastic about Prozac's results in treating patients. Further, *Listening to Prozac* provocatively argues that Prozac was not only correcting chemical imbalances but also enhancing people's personalities. Kramer illustrates his argument through case studies, highlighting that Prozac transformed his depressed patients into new people. *Listening to Prozac* was so culturally influential that it was on the best-seller list for twelve weeks in 1993, and Prozac sales increased that year by 15 percent. The simultaneous surge was so glaring that an independent commission in France investigated the possibility of Eli Lily having hired Kramer to write *Listening to Prozac* to boost profits. They concluded that this was not true.[31]

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[28] Harrington, *Mind Fixers*, xii.
[29] Guze, Samuel B., "Biological Psychiatry: Is There Any Other Kind?" *Psychological Medicine* 19, no. 2 (May 1989): 322.
[30] Peter D. Kramer, *Listening to Prozac* (New York: Penguin, 1994).
[31] Harrington, *Mind Fixers*, 213.

Listening to Prozac includes the story of a woman called Tess, who, upon taking Prozac, underwent a profound transformation in her personality from a wallflower to a social butterfly. Tess was not suffering from depression at this stage of her treatment. Though happy, she "talked of a mild, persistent sense of wonder and dislocation." Kramer feared that by prescribing her Prozac, he would be entering into a realm of "cosmetic pharmacology," but explained his decision with a line that was quoted in many articles. He asked: "Who was I to withhold from her the bounties of science?"[32] The metamorphic results inspired conflicts within Kramer about whether the medications were too far-reaching in their effects or whether his concerns were arbitrary and aesthetic rather than medical.[33] He feared that specific characteristics viewed as awkward or endearing may now signify ailments that must be pitied or corrected. He asks:

> Might we not, in a culture where overseriousness is a medically correctable flaw, lose our taste for the melancholic or brooding artists — Schubert, or even Mozart in many of his methods?[34]

However, he simultaneously reflects on how Prozac could do in days that psychiatrists often fail for years at achieving: "to restore to a person robbed of it in childhood the capacity to play."[35]

Kramer's writing was incredibly influential, garnering significant media attention and sparking further discussions about when physicians should prescribe antidepressants. Henry Blissenbach, president of Diversified Pharmaceutical Services, a managed-care unit of the significant health maintenance organization company United Healthcare Corporation, discussed Kramer's book and this increase in Prozac sales.[36] During this interview, he told the New York

[32] Kramer, *Listening to Prozac*, 13.
[33] Kramer, *Listening to Prozac*, 20-21.
[34] Ibid.
[35] Ibid.
[36] Freudenheim, Milt, "The Drug Makers are Listening to Prozac," *New York Times*, January 9, 1994, Late Edition (East Coast), https://www.proquest.com/newspapers/drug-makers-are-listening-prozac/docview/429432936/se-2.

Times that "People take Prozac for things other than clinical depression. They say, 'Doctor, I just don't feel very good.' And the doctor says, 'A lot of people I've given it to feel better.'"[37]

Ultimately, Kramer's book grapples with what Prozac means for society's understanding of the "self," which would become a significant theme in antidepressant advertising. Kramer reports that Tess and other patients in her situation described locating a rehabilitated self that was "true, normal, and whole."[38] In other words, taking Prozac made them feel they could finally access their true personality despite it being new and unfamiliar.

Kramer comments:

> Charisma, courage, character, social competency—Prozac seemed to say that these and other concepts would need to be reexamined, that our sense of what is constant in the self and what is mutable would need revision.[39]

Pharmaceutical companies adopted this language for their ad campaigns in the late '90s and early '00s, which indicates the effectiveness of *Listening to Prozac's* ideas in inspiring Americans to seek antidepressant prescriptions.

In 1994, Harvard University student Elizabeth Wurtzel published a memoir titled *Prozac Nation: Young and Depressed in America*, contributing to Prozac's establishment as a household name.[40] *Prozac Nation* became a regular on bestseller lists and ignited national conversations about depression.[41] Its impact was novel because Wurtzel wrote as a patient rather than a medical practitioner and wrote for a general audience, allowing *Prozac Nation* to permeate broader

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[37] Freudenheim, "The Drug Makers are Listening to Prozac."
[38] Kramer, *Listening to Prozac*, 20-21.
[39] Kramer, *Listening to Prozac*, 20-21.
[40] McKelvey, Tara "How Prozac Entered the Lexicon," BBC News, April 10, 2013, https://www.bbc.com/news/magazine-22040733.
[41] Dwyer, Colin "Elizabeth Wurtzel, Who Stirred Conversation with 'Prozac Nation,' Dies at 52," NPR, January 7, 2020, https://www.npr.org/2020/01/07/794233422/elizabeth-wurtzel-who-stirred-conversation-with-prozac-nation-dies-at-52.

swathes of popular culture. *Prozac Nation* was a novel because of how candidly and unglamorously Wurtzel spoke of her severe depression. Her confessional writing is often criticized for being "self-aggrandizing and solipsistic," or even desperately self-absorbed.[42] In the beginning she writes:

> You won't even notice it coming on, thinking that it is somehow normal, something about getting older, about turning eight or turning 12 or turning 15, and then one day you realize that your entire life is just awful, not worth living, a horror and a black blot on the white terrain of human existence. One morning you wake up afraid you are going to live.[43]

Wurtzel chronicles her life of drug use and frequent sexual encounters, detailing her serious mood and regulation issues in vivid detail. The content was sensationalistic, and people had strong negative or positive reactions, prompting extensive discussion about her work. Towards the end of the book, Wurtzel encounters Prozac, but not before she hits rock bottom and attempts suicide. However, as the medication takes effect, it begins to help her, and she notices slow improvements and begins to view it positively. She then writes about her hope that drugs like Prozac will encourage people to approach their mental health with more openness.[44] While these benefits do not last long-term, her work helped include Prozac into the public lexicon while promoting a more open dialogue about clinical depression.[45]

The exuberant media reception and widespread public enthusiasm for antidepressants in the late 20th century represented more than just medical progress. It signaled a profound cultural shift in how society viewed and understood mental health. Medical experts were enthusiastic

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[42] McKelvey, "How Prozac Entered the Lexicon"; and Erica Wagner, "With 'Prozac Nation,' Elizabeth Wurtzel Blew Open the Memoir as We Know It," *The Guardian*, January 8, 2020, accessed March 17, 2024.
[43] Wurtzel, Elizabeth, *Prozac Nation: Young and Depressed in America* (New York: Houghton Mifflin, 1994), 36.
[44] Wurtzel, *Prozac Nation*,
[45] McKelvey, "How Prozac Entered the Lexicon."

about the biological revolution's implications for the legitimization of their field among Western scientific models and improved treatment options for patients. The overwhelming majority of media commentary at this time reflected on how these adaptations not only destigmatized mental illness but also raised complex questions about identity and the boundaries of medical intervention. Pharmaceutical companies capitalized on this optimism, crafting advertising campaigns that promised relief from symptoms and a path to a newfound self. This media narrative shaped public perception and fueled a growing openness to antidepressants.

Pharmaceutical Marketing Campaigns and Advertising Analysis

In the late 1990s and into the early 2000s, not only was Prozac widespread, but it was trendy.[46] In some ways, American culture saw a reduction in the taboo surrounding mental illness, evidenced by the surge in depression diagnoses and treatments, as well as a rise in public conversations about mental health. Between 1996 and 2005, the percentage of Americans above the age of six using antidepressants during one year increased from 5.8% to 10.1%, or from approximately 13.3 to 27.0 million people.[47]

Pharmaceutical marketing played a significant role in the mass-prescriptions of antidepressants during this period. Before 1997, it was generally considered taboo for pharmaceutical companies to market their products directly to consumers, and they advertised to physicians instead. However, conventions changed in 1997 after the FDA relaxed regulations concerning direct-to-consumer advertising (DTCA) of prescription drugs.[48] Notably, DTCA is legal in America and New Zealand but illegal everywhere else in the world.[49] Where pharmaceutical companies previously advertised to doctors, they could now advertise directly to the American public. Sales across medications exploded from less than $800 million in 1996 to $2.5 billion in 2000, reaching their peak at $4.8 billion in 2007.[50] Psychiatric drugs were among the most heavily advertised prescription medications.[51] Between 1987 and 2001, revenue generated from psychiatric drugs increased sixfold, twice the rate generated by sales of

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[46] Ibid.
[47] Paulose-Ram, et. al."Trends in psychotropic medication use among US adults." *Pharmacoepidemiol Drug Safety* 2007, 16(5): 560-570; and Mojtabai R. "Increase in antidepressant medication in the US adult population between 1990 and 2003." *Psychother Psychosom* 2008; 77(2): 83-92.
[48] Block, "Costs and Benefits of Direct-to-Consumer Advertising: The Case of Depression," *Pharmacoeconomics* 25, no. 6 (2007): 511-521, doi: 10.2165/00019053-200725060-00006.
[49] Ibid.
[50] Pauline Anderson, "Direct-to-Consumer Ads Boost Psychiatric Drug Use," *Medscape Medical News* (September 19, 2016), www.medscape.com/viewarticle/868880.
[51] Block, "Costs and Benefits of Direct-to-Consumer Advertising."

prescription drugs overall.[52] This steep increase in antidepressant prescriptions poses multiple questions: was America becoming more mentally ill, were physicians better equipped to notice depression, or did pharmaceutical advertising broaden the bounds of mental illness? Regarding these possibilities, it is difficult to determine whether Americans were becoming more mentally ill and to what extent physicians' prescription attitudes played a role in this change.

Further, in addressing these questions, one must consider the decrease in adverse side effects from first- to second-generation medications in this period, with the popular medication Prozac showing particular success in patient tolerance.[53] There is no doubt that this reduction in the sometimes intolerable side effects associated with the first-generation antidepressants of the past contributed to the medication class' widespread accessibility for those with milder symptoms of depression, broadening their potential uses. That said, when considering the American public's perceptions of their *efficacy*, it is evident that the advent of loosely regulated, direct-to-consumer pharmaceutical advertising of antidepressants substantially influenced cultural attitudes in favor of antidepressant medications, potentially inflating expectations of their scientific backing. Later, the mismatch between societal expectations and declassified clinical trial data would create the underpinnings for Congressional Energy and Commerce Committee members' antidepressant skepticism, general distrust in the pharmaceutical industry, and hearings culminating in the 2004 black box warnings on all antidepressant packaging.

Historians including Anne Harrington and David Herzberg have commented on the connection between pharmaceutical giants' marketing campaigns and the sharp rise in antidepressant sales between the late '90s and early 2000s, arguing a causal relationship between the two phenomena.[54] Both of these historians believe that this boom in advertisements

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[52] Ibid.
[53] Reuters,"Eli Lilly Passes a Test," *New York Times,* September 12, 1987.
[54] Harrington, Anne, *Mind Fixers*.; David Herzberg, *Happy Pills in America*.

broadened American physicians' and patients' perceptions of behaviors constituting mental illness, characterizing more common problems as pathological symptoms requiring medical treatment.[5] I will take a slightly different approach, contextualizing my analyses of the marketing campaigns' major themes and similarities across brands in hindsight within later events and research. In doing so, I will reflect on these advertisements' broader societal significance to argue that the increased commodification of mental health treatment through DTCA for antidepressants inadvertently set the stage for regulation.. This is because regulators felt they inflated efficacy claims and overlooked the risks. I argue that these ads often lacked the nuance of mental health treatment, typically involving a case-by-case plan based on the individual patient. Further, they skipped over psychotherapy and behavioral treatment to portray medications as one-size-fits-all solutions to ever-growing populations. These inflated expectations later combined with revelations of pharmaceutical trial data secrecy and meager efficacy results, as well as increased suicidality in children and adolescents, to create a hotbed for skepticism in American congressmen and regulators.

Ad Analysis: Case Studies on Prozac, Zoloft, and Paxil

By their nature, direct-to-consumer advertisements oversimplify the conversation of medication prescriptions and fail to educate customers on their risks and benefits. They also inherently encourage financial incentives to mislead the public about the safety and efficacy of medications. In analyzing media campaigns for the influential drugs Prozac, Zoloft, and Paxil, I found similarities in their widely relatable headlines and simplified before-and-after medication dichotomies.

Many antidepressant headlines begin with broadly applicable quotes about regaining your true personality. Pharmaceutical company Eli Lilly was the first to advertise antidepressants using DTC messaging for its drug, Prozac. The ad campaign was titled "Welcome Back."[55] Zoloft's headlines were variations of the line: "Things Just Don't Feel Like They Used To."[56] Paxil titled their ad: "Your Life is Waiting."[57] Each of these catchy headlines implies that the viewers have potentially lost themselves and can tap into their true personalities through the aid of medications, harkening back to the ideas discussed earlier regarding Kramer's *Listening to Prozac*.[58] The titles can also relate to a broad audience, including those without depression.

Further, the campaigns for Prozac, Zoloft, and Paxil each create a false binary between patients before and after SSRI treatment, further simplifying perceptions of medications as quick, one-size-fits-all fixes.

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[55] Grow, Jean, "'Your Life is Waiting!': Symbolic Meanings in Direct-to-Consumer Antidepressant Advertising," *Journal of Communication Inquiry* 30, no. 2 (2006): 172.
[56] Grow, et. al., "Your Life is Waiting!," 175.
[57] Grow, et. al., "Your Life is Waiting!," 176.
[58] Peter Kramer, *Listening to Prozac.*

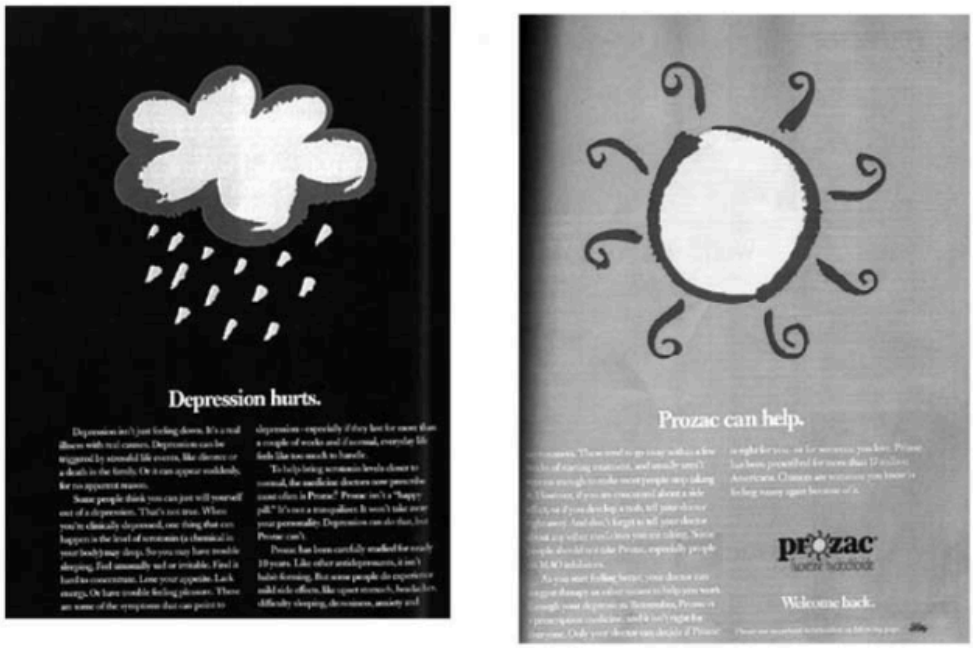


Figure 1. Leo Burnett, *Prozac "Welcome Back"* 1997, Eli Lilly.

Pictured above is a typical two-page Prozac advertisement, where depression is dark and rainy, while life on Prozac is bright and sunny. It reads, "Depression hurts/Prozac can help." Here is a stark dichotomy before and after using the medication, presenting medical treatment as a neat, linear progression forward. The text privileges medication benefits over risks and ignores alternative or adjunctive treatment methods such as therapy and lifestyle changes, including exercise. This campaign was extremely effective. Before the FDA's DTCA decision, Prozac sales slowed in mid-1996 because drugs such as Zoloft and Paxil were eating into Eli Lilly's market share.[59] However, following the launch of their "Welcome Back" campaign in twenty general-interest magazines, by 1997, earnings had risen 9% to reach $2.56 billion.[60]

[59] "Prozac Print Campaign," *Marketing Campaign Case Studies,* October 15, 2008, https://marketing-case-studies.blogspot.com/2008/10/prozac-print-campaign.html.
[60] "Prozac Print Campaign."

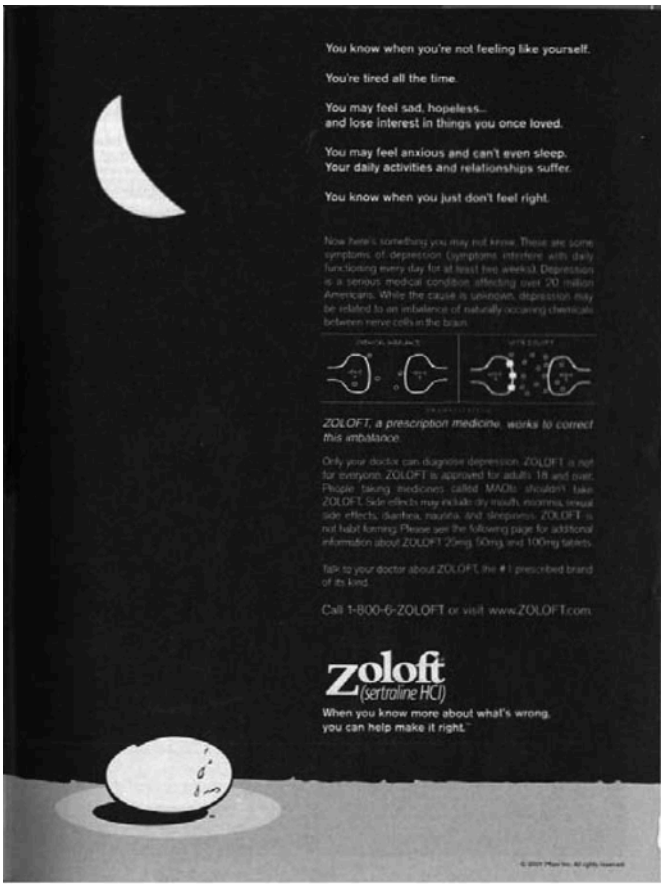
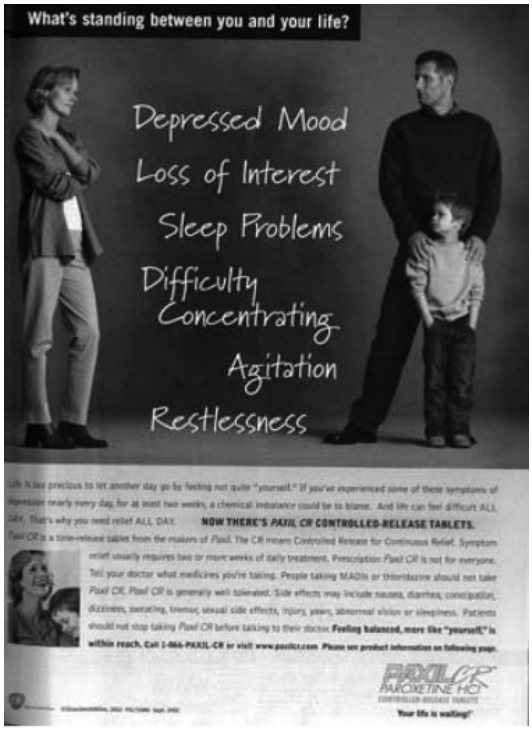


Figure 2. Zoloft Advertisement.[61]

Similarly, a traditional Zoloft advertisement pictures depression as a dark nighttime sky (Fig. 2). It describes emotional states like feeling "tired all the time," "sad," or "hopeless". It states that these, when severe enough to interfere with daily activities, are symptoms of depression. Below this list of symptoms is a diagram that explains how Seretonin Selective Reuptake Inhibitors (SSRIs), the second-generation class of antidepressants, work in the brain. The drawing explains that depression is a chemical imbalance, depicted through a before and after sketch. Before, the naturally occurring chemical serotonin is blocked. After taking Zoloft, the flow of serotonin is unclogged. There is a small disclaimer at the bottom of the advertisement

[61] Grow et. al. "Your Life is Waiting," 183.

that reads that Zoloft is not for everyone and that only a doctor can diagnose depression. Overall, this advertisement appears to be relatively informative in explaining the theory behind antidepressants and the symptoms associated with their prescription. However, it still fails to mention the risks associated with Zoloft and the full context of treatment options.



Figures 3 and 4. Paxil Advertisements.[62]

Lastly, pictured are two Paxil advertisements (Figs. 3 and 4). While gender is not a central theme of this paper due to the regulatory focus on children and adolescents, it is essential to consider that the advertisements above portray depression as a feminine illness, with both picturing depressed, middle-aged white women. They list symptoms such as "loss of interest," "restlessness," and "worry" as indications of depression. They also include after images of the same women on Paxil, where they are smiling. In the first ad, the depressed woman even transforms from looking scornfully at her husband and son to taking Paxil and being able to perform her motherly duties. Again, there is no mention of risks or holistic treatment plans. Notably, GlaxoSmithKline, the pharmaceutical company that owns Paxil, later received legal punishment for knowingly misleading consumers about the effectiveness of their product (see p. 34). They also submitted the pediatric clinical trial data, which most influentially raised alarm

[62] Grow, et. al., "Your Life is Waiting!," 185.

bells in the UK about increased suicidality in their young patients and prompted other agencies' further research.

Overall, cross-analyzing the advertisements for Prozac, Zoloft, and Paxil shows that each campaign included widely identifiable headlines and simplistic dichotomies between depressed patients before and after medications. Further, they failed to educate consumers on medication risks and other treatment options. In hindsight, we can contextualize these analyses within the history that follows. As discussed below, the released and unreleased clinical trial data do not support this portrayal of their medications' efficacies. Moreover, this consumer misdirection became a justification for legal action, and a central critique legislators made in the 2004 pediatric clinical trial hearings. Importantly, most pharmaceutical companies, with the exception of Eli Lilly, could not legally advertise their product to children because the Food and Drug Administration had not formally approved these medications for use in minors (although they were still commonly prescribed to children off-label). Even Eli Lilly, despite their technical permission, refrained from doing so. However, these marketing campaigns following 1997 effectively reframed societal expectations of mental health treatments, emphasizing medicalized approaches. Although advertisements such as that in Figure 2 specify that only physicians can diagnose depression and that Zoloft is not for everyone, many physicians noticed that DTCA, in general, encouraged patients to request specific medications based on their own analyses of their symptoms. Eventually, and in the wake of damaging revelations, most physicians tended to view DTC advertisements negatively for all pharmaceuticals. Based on a 2004 study of American physicians studying physician-patient relationships, 94.9% of them agreed that advertisements rarely educated consumers on alternative treatment options, and 54.8% felt they did not properly

explain the potential risks.[63] Moreover, 80.7% reported that DTCA encouraged patients to request specific medications rather than deferring to the physician's expertise.[64] Overall, only 29.0% of respondents felt that DTC advertising was a positive development in healthcare.[65] I would argue that DTCAs for psychiatric drugs are inherently harmful because of their short-form, broadly inclusive nature and their further commodification of antidepressants. These characteristics skew education on treatment towards the most lucrative options rather than those best for patients on a case-by-case basis. Further, as later exemplified with the 2004 GlaxoSmithKline misinformation lawsuits (see p. 34), DTCAs further enable pharmaceutical companies to inflate the American public's expectations of medication efficacy. This simplified portrayal of antidepressants through DTCAs, later combined with controversies in the public release of clinical trial data, contributed to skepticism among members of the U.S. House of Representatives Energy and Commerce Committee regarding a perceived lack of consumer transparency.

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[63] Robinson et. al, "Direct-to-Consumer Pharmaceutical Advertising: Physician and Public Opinion and Potential Effects on the Physician-Patient Relationship," *Archives of Internal Medicine* 164, no. 4 (February 23, 2004): 427-432, https://doi.org/10.1001/archinte.164.4.427.
[64] Ibid.
[65] Ibid.

Policy, Law, and the 2004 Congressional Antidepressant Hearings

Critical Legal and Policy Context (1990-2004)

While Prozac had gained a reputation as the antidepressant with the fewest adverse side effects and, by 1990, pharmaceutical company Eli Lilly was filling one million prescriptions a month, a negative shift in public perception emerged.[66] In 1990, the company was confronted with a barrage of lawsuits asserting that Prozac might not be as safe as commonly believed.[67] Drawing from research led by psychiatrist Martin Teicher, plaintiffs contended that Eli Lilly had withheld evidence indicating that Prozac could potentially trigger violent or suicidal behavior in a subset of patients who had not exhibited such tendencies before.[68] Many psychiatrists criticized Teicher's findings, arguing that they relied too heavily on individual patient cases rather than a formal scientific study with a placebo group and comparisons to other antidepressant medications.[69] Despite vehement denials from Eli Lilly, the company ultimately settled out of court and continued its operations.[70]

While the FDA also held a 1991 panel addressing potential suicidality in people taking Prozac, they concluded there lacked sufficient evidence to determine this connection. The FDA convened a panel of experts to consider a possible link between Prozac or other antidepressants and suicide or violent behaviors following reports of adverse drug reactions from patients. Notably, this inquiry addressed not just children and adolescents, which would later become the focus of investigations, but all populations. By the time of their 1991 discussion, the FDA had received 14,100 reports of adverse side effects, 500 of which involved suicide attempts since

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[66] Marcus, "Prozac: The Wonder Drug? The Maker of an Antidepressant Once Hailed as Safe is Fighting Claims that the Drug Turned Patients Violent," Washington Post, September 9, 1990.
[67] Marcus, "Prozac: The Wonder Drug?".
[68] Teicher, et. al., "Emergence of Intense Suicidal Preoccupation During Fluoxetine Treatment," *American Journal of Psychiatry* 147, no. 2 (1990): 207.
[69] Marcus, "Prozac: The Wonder Drug?"
[70] Ibid.

Prozac's introduction in the market in 1987.[71] During their panel's meeting, scientists were moved by harrowing witness accounts of suicide and violence committed by people taking Prozac. However, they also raised questions about whether these patients had received adequate care during these instances. Ultimately, the panel concluded in a 6 to 3 decision against label changes on antidepressant packaging warning of suicide or violent behavior.[72] Some members expressed that more information was required to make such a change.

Overall, the question of suicidality and antidepressants is complicated, and it is difficult to pinpoint which behavior causes the other. This chicken or egg situation exists because users had preexisting mental health issues that motivated their antidepressant prescription, making it difficult to determine the cause of adverse behavior during pharmaceutical treatment. Scientists at the meeting expressed this sentiment. Panel member Dr. Jeffrey Liebmern expressed: "It's hard to say there's much evidence" that antidepressants, rather than the depression the drugs are intended to treat, cause so many reported suicide attempts.[68] Ultimately, the majority of panel members felt unconvinced that accounts of suicidality and violence were side effects of Prozac or other antidepressants and concluded that warnings of such behavior on packaging were unnecessary. This reflects multiple overarching dilemmas experts face when addressing antidepressant safety, many of which continue through the 2004 congressional hearings on this matter. For one, behavioral manifestations of psychiatric conditions like depression are deeply personal to the individual, and it is difficult to ascertain which actions are expressions of a person's evolving health condition and which are because of their prescription drug use. Secondly, the FDA must balance maintaining transparency on drug side effects and avoiding the potential fear-mongering of life-saving medications based on limited data.

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[71] AP, "Warning Label on Antidepressant is Opposed," *New York Times*, Sep 21, 1991, Late Edition (East Coast), https://www.proquest.com/newspapers/warning-label-on-antidepressant-is-opposed/docview/428192855/se-2.
[72] Ibid.

Around this time, legislators sought to address a broader pharmacological issue regarding the lack of clinical trial data for pediatric populations, creating legislation that prompted research on antidepressant effects in young people. In general, even today, most pharmaceutical drugs are studied primarily in adult populations, meaning there is a deficit in research on young people. In 2002, Congress passed the Better Pharmaceuticals for Children Act (BFCA) to increase the production of trial data on children and adolescents to improve the safety and efficacy of pharmaceutical treatment for these groups. BFCA incentivized pharmaceutical companies to conduct pediatric studies of their patented drugs by granting them an additional six months of patent exclusivity in return. While antidepressants, except Prozac were not approved in pediatric populations, the majority of prescriptions to this population were off-label, meaning that they were for unapproved antidepressant drugs. BFCA law encouraged various pharmaceutical companies to conduct and submit to the FDA clinical trials on antidepressant effects on young populations, later providing a scientific basis for the Energy and Commerce Committee's 2004 Congressional investigations into this matter.[73]

In 1999, SmithKline Beecham sought a license from the FDA to sell the antidepressant Paxil not only for depression but also for the treatment of a relatively unknown disorder that the DSM called "social anxiety disorder." Before marketing Paxil for social anxiety disorder, SmithKlein Beecham realized they first needed to make social anxiety disorder a more well-known illness and launched an advertising campaign titled "Imagine Being Allergic to People." The PR campaign resulted in more than a billion media references to social anxiety disorder, up from roughly 50 in previous years, almost all of which mentioned that Paxil

[73] "Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials." 2004. p. 18-49, 253-267. (Text from: ProQuest Congressional); Accessed: February 20, 2024.

was the only approved treatment for the condition.[74]

In June 2003, British drug company GlaxoSmithKline submitted clinical trial data to the FDA's British counterpart, the Medicines and Healthcare Products Regulatory Agency (MHRA), for its antidepressant drug paroxetine (Paxil), which was one of the most widely-prescribed antidepressants.[75] They sought approval for Paxil's use in adolescents with obsessive-compulsive disorder (OCD) and social anxiety disorder. Upon evaluation, the MHRA requested all clinical trial data, including unpublished results from GlaxoSmithKline. After noticing a higher rate of suicide attempts in adolescents taking Paxil for major depression disorder (MDD) than in the placebo-controlled group, the agency ultimately launched a broader investigation, requesting data from all pharmaceutical companies concerning major medications, including Prozac, Zoloft, Luvox, Celexa, Wellbutrin, Effexor, Serzone, and Remeron. Their studies showed little to no efficacy on average for children. British health regulators took swift action in a short period of time in 2003. In June, officials spoke of dangers associated with Paxil for adolescents.[76] In September, officials warned against the use of Wyeth's antidepressant Effexor in adolescents because of risks of hostility or suicidal thoughts.[77] Overall, a meta-analysis of all relevant clinical trial data led the Committee on Safety of Medicine's Expert Working Group to publish a report

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[74] Bali Sunset, "Social Anxiety Disorder Campaign," *Marketing Campaign CaseStudies* (blog),March 28, 2009, http://marketing-case-studies.blogspot.com/2009/03./social-anxiety-disorder-campaign.html.

[75] AMA Journal of Ethics. "Antidepressants and FDA's Black-Box Warning: Determining Rational Public Policy in the Absence of Sufficient Evidence." June 2012. Accessed February 19, 2024. https://journalofethics.ama-assn.org/article/antidepressants-and-fdas-black-box-warning-determining-rational-public-policy-absence-sufficient/2012-06.

[76] Gardiner. "Britain Says use of Paxil by Children is Dangerous," *New York Times*, June 11, 2003, Late Edition (East Coast), https://www.proquest.com/newspapers/britain-says-use-paxil-children-is-dangerous/docview/432437949/se-2.

[77] Company News, "Britain Issues Warning On Wyeth Antidepressant," *New York Times*, New York Times Company, 2003, https://www.proquest.com/blogs-podcasts-websites/company-news-britain-issues-warning-on-wyeth/docview/2229789229/se-2.

recommending *against* prescribing SSRIs (except Fluoxetine) in children due to their lack of medicinal benefit and apparent suicide risk.[78]

This policy change in the UK prompted the FDA to conduct an independent investigation into a possible increase in suicidality among adolescents with MDD taking SSRIs.[79] The FDA took a different approach from the MHRA by contracting independent pediatric suicidologists from Columbia University to evaluate clinical trial data. One challenge the independent group faced was comparing suicidality across clinical trials because the existing studies were not primarily intended to compare suicidality and potentially reported its instances differently. To address this lack of systematization, Columbia's experts conducted a blind reclassification of suicidality in each trial under standardized metrics. Upon meta-analysis of the reclassified data, they concluded all of the antidepressants increased risks of suicidality among pediatric patients with MDD.[80] The FDA then tasked their top expert, Dr. Andrew Mosholder, with analyzing the data, and he concluded children are twice as likely to become suicidal when taking antidepressants (except Prozac).[81] However, the American medical community remained split. Distrust from American legislators mounted when it leaked to the media that the FDA barred Mosholder from sharing his findings at their public hearing because the FDA believed his interpretation was alarmist and premature.[82] "It would have been entirely inappropriate to present

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[78] Medicines and Healthcare products Regulatory Agency. Selective serotonin reuptake inhibitors (SSRIs): overview of regulatory status and CSM advice relating to major depression disorder (MDD) in children and adolescents including summary of available safety and efficacy data. http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON019494?useSecondary=&showpage=1. Accessed February 20, 2024.

[79] Medicines and Healthcare products Regulatory Agency Committee on the Safety of Medicine. Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants. http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con019472.pdf; 2004. Accessed Febuary 20, 2024.

[80] Hammad, et. al., "Suicidality in pediatric patients treated with antidepressant drugs," *Archives of General Psychiatry* 63, no. 3 (2006): 322-339.

[81] Gardiner, Harris. "Expert Kept from Speaking at Antidepressant Hearing." *New York Times,* Apr 16, 2004, Late Edition (East Coast). https://www.proquest.com/newspapers/expert-kept-speaking-at-antidepressant-hearing/docview/432744722/se-2.

[82] Ibid.

as an F.D.A. conclusion an analysis of data that were not ripe," Dr. Robert Temple, the Food and Drug Administration's associate director of medical policy, said in an interview with the *New York Times*. He elaborates, saying: "This is a very serious matter. If you get it wrong and over-discourage the use of these medicines, people could die."[83] House legislators in the Energy and Commerce Committee were unsatisfied with this response, especially considering what they viewed as the FDA's lack of transparency with data and failure to cooperate with their requests.[84]

By early 2004, the MHRA was conclusive on suicidality risk while the FDA was not, posing questions of how and why each country chose its respective approach despite relying on the same data. A number of cultural and economic differences can partially explain this divergence in interpretations. To begin, during this time, a much larger percentage of American children than British children were taking antidepressant medications.[85] When adjusted for population, American children were five times more likely to receive an antidepressant prescription. This could be because most British physicians viewed psychotherapy as the first line of defense in treating depression. In America, pills are cheaper than psychotherapy, potentially explaining their increased popularity. Further, as British University of Kent sociologist Frank Ferudi put it, British culture is hesitant to medicalize childhood behavioral problems. In contrast, Americans potentially place greater faith in medications and technological progress. The United States allows direct-to-consumer pharmaceutical marketing, while the UK prohibits it completely, reflecting consumer culture differences. Economically, access to drugs is regulated by NHS coverage. In the U.S., insurance coverage for the drugs is far less uniform and consistent, while those with the means to purchase them without insurance have access to the

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[83] Ibid.
[84] "Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials." 2004. p. 18-49, 253-267. (Text from: ProQuest Congressional); Accessed: February 20, 2024.
[85] Satel, Sally M. D. (2004, May 25). Antidepressants: Two countries, two views. *New York Times* Retrieved from https://www.proquest.com/newspapers/antidepressants-two-countries-views/docview/432760589/se-2.

comparatively deregulated market. These factors may converge to influence the degree of caution with which regulatory agencies approach antidepressant labeling.[86]

Pharmaceutical distrust among American governmental officials heightened when a 1998 GlaxoSmithKline memo leaked, showing the company intended to conceal adverse medication data from the public. In June 2004, New York Attorney General Eliot Spitzer filed a lawsuit against GlaxoSmithKline for committing consumer fraud by withholding information from misrepresenting data for Paxil's safety in children. The lawsuit referenced that GlaxoSmithKline repressed four studies that failed to demonstrate drug efficacy and raised concerns of increased suicidality. It also cited an internal Glaxo memo from 1998, which showed that the company intended to "manage the dissemination of data in order to minimize any potential negative commercial impact." The pharmaceutical company defended itself, explaining that it had submitted its data to the FDA and other international regulators. It is important to note that this unfavorable data was unavailable to the general public. New York's lawsuit reflects two controversies, both of which would come up in the 2004 Congressional hearings, concerning whether pharmaceutical companies have to publish all of their clinical trial data and whether antidepressants increase suicidal thoughts and actions in children. In AG Spitzer's view, "By concealing critically important scientific studies on Paxil, GlaxoSmithKline impaired doctors' ability to make the appropriate prescribing decision for their patients and may have jeopardized their health and safety."[87]

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[86] Ibid.

[87] *New York Sues GlaxoSmithKline*. New York: New York Times Company, 2004. https://www.proquest.com/blogs-podcasts-websites/new-york-sues-glaxosmithkline/docview/2228967483/se-2.

Pediatric and Adolescent Antidepressant Congressional Hearings (2004)

The House Energy and Commerce Committee held a hearing titled "Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials" in September of 2004. Committee members questioned a representative from the FDA, top executives from pharmaceutical companies, and members of significant medical organizations. Ultimately, the Food and Drug Administration decided to append a black box warning of suicide risk for children and adolescents on all antidepressant packaging. This is the strongest warning the FDA can give short of an outright ban on a medication.[88]

The House Energy and Commerce Committee members involved began with opening statements where they expressed ire towards the FDA's representative for the organization's failure to cooperate with requests and lack of transparency regarding clinical trial data. Republican Congressman Joe Barton from Texas opened the discussion and stated the Food and Drug Administration met Congress with stonewalling, slow rolling, and plain incompetency. He expressed concerns over publication and disclosure issues, questioning why the Food and Drug Administration only published three of the fifteen relevant clinical trials until recently. Barton noted that twelve of the fifteen studies showed no efficacy and questioned whether the public had sufficient information to make consumer decisions. This is especially notable when considering that while Prozac was the only antidepressant cleared to treat adolescent depression, the majority of youth prescriptions were off-label for antidepressants, which performed concerningly in

[88] "Publication and Disclosure Issues."

clinical trials. He emphasized that many people still want to know what was in the twelve other studies and why they were not published. Barton goes on to mention that the FDA refused to transfer some of the requested documents and bash the regulatory agency's "spotty record" of publicizing information despite section nine of the Best Pharmaceuticals Act (2002), which mandated they reveal pediatric clinical data within 180 days of submission. Several of Barton's colleagues echoed these themes while emphasizing that this hearing was a bipartisan effort. In the hearings, both Democrats and Republicans levied similar criticisms at the FDA and pharmaceutical giants.[89]

Representative Henry Waxman, a Democrat from California, urged for mandating a registry containing all clinical trial records to provide full transparency to medical professionals. Diana DeGette, a Democrat from Colorado, also commented that this information would need to be presented in language accessible to the public. Democratic senator Ed Markey from Massachusetts exclaimed that pharmaceutical companies cannot pick and choose which information to upload and that a full-disclosure approach should be enforced criminally to ensure compliance. Overall, legislators were unified in their concerns with pharmaceutical companies selectively publishing trial data to skew public opinion towards their product and potentially mislead physicians about their drug's safety and efficacy. Further, their critiques were not confined to the topic of antidepressants, and several legislators explained that this public registry would be necessary for all prescription drugs.[90]

In their questioning of FDA representative Janet Woodcock, the organization's acting deputy commissioner of operations, several legislators criticized their noncompliance, sluggishness for publicizing clinical trial data, and general lack of proactivity in addressing

[89] Ibid.
[90] Ibid.

health risks associated with adolescent antidepressant use. However, Woodcock asserted she supported transparency in clinical trial data and that the FDA was publicizing as much information as possible while within the constraints of laws such as the Freedom of Information Act and statutes governing commercial information, which sometimes impede these efforts. Woodcock assured lawmakers that they would soon consider how to address how to navigate the lack of efficacy shown in most pediatric trials. She also argued that it is very common for effective drugs in adult depression to show no effect, implying this could also be the case in pediatric studies as well.[91]

Pharmaceutical representatives from giants like Pfizer, Wyeth, and GlaxoSmithKline were questioned for their collective failure to publish critical information regarding their drugs and for misleading the public about the nature of their clinical trial research. At one point, a Republican representative from Oregon, Greg Walden, read aloud an internal memorandum from a GlaxoSmithKline marketing executive announcing antidepressant drug Paxil's performance as "remarkable" in treating depressed children and teenagers when the study in question had failed to prove the drug was effective.[92] Dr. David Wheadon, senior vice president at the company, replied that he would not have used those particular words to describe the study. In another instance, Republican representative Charles Bass from New Hampshire asked a Forest Laboratories executive why the company only published information representing one trial, which showed a positive response for their drug Celexa, while withholding the second trial, which showed no benefit. Dr. Lawrence Olanoff, a Forest executive vice president, responded that they published information based solely on the successful trial and did not intend to represent all of their research. All of the company representatives said they supported a proposal

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[91] Ibid.

[92] Gardiner, H. (2004, Sep 10). Lawmaker says F.D.A. held back drug data. *New York Times* Retrieved from https://www.proquest.com/newspapers/lawmaker-says-f-d-held-back-drug-data/docview/432862823/se-2.

from the Pharmaceutical Research Manufacturers of America, the industry's trade group, to publish all clinical trial data within a timely manner on a joint website. However, several lawmakers argued that this voluntary proposal did not go far enough and that the situation requires legislation mandating full disclosure.[93]

In this second round of witness hearings, congressional representatives questioned the FDA's role in regulating antidepressant medications, including drug labeling and clinical trial publication. By this point, the FDA had already held an AC meeting to consider the issue on September 13 and 14th, and the Advisory Committee Members voted 15 to 8 in favor of a boxed warning to the labeling of antidepressants.[94]

They began by questioning Dr. Mosholder, the FDA expert who concluded that children and adolescents were twice as likely to experience suicidality on antidepressants and was previously barred by the FDA from speaking. In his opening statement, he outlines his recommendation against off-label prescriptions for pediatric antidepressants. Mosholder explains that the controversy lies in the FDA's apprehension in abandoning the utility of antidepressant drugs prematurely and concerns of whether trials failing to prove efficacy indicate the drug's ineffectiveness or issues with the clinical trial setup.[95] However, Columbia University's reclassification process confirmed Dr. Mosholders's findings.[96] He also points out that most of the studies analyzed were short-term and that it is possible that the long-term medication benefits would outweigh the short-term risks. He concluded that the information is still unclear on that point.

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[93] "Publication and Disclosure Issues."
[94] "FDA's role in protecting public health: examining FDA's role in safety and efficacy concerns in antidepressant use by children." 2004. p. 23. (Text from: ProQuest Congressional); Accessed: February 20, 2024.
[95] "FDA's role," 28.
[96] "FDA's role," 29.

Overall, the journey through the policy, legal, and congressional landscape surrounding antidepressants from the 1990s to the early 2000s paints a nuanced picture of the challenges inherent in balancing pharmaceutical innovation, regulatory oversight, and public health concerns. The 2004 Congressional Antidepressant Hearings stand as a pivotal moment in this narrative, encapsulating the culmination of years of scrutiny, debate, and advocacy surrounding antidepressant safety, particularly in pediatric populations. Against a backdrop of mounting evidence linking antidepressant use to increased suicidality among young patients, legislators, regulators, and pharmaceutical stakeholders grappled with questions of transparency, accountability, and patient safety. The hearings were a forum for bipartisan critique of regulatory practices, pharmaceutical transparency, and the broader issue of off-label prescribing in vulnerable populations. Calls for mandatory registries, enhanced clinical trial disclosure, and regulatory intervention underscored a collective commitment to promoting informed decision-making and safeguarding public health. However, beyond the specific policy implications, the hearings reflected broader tensions within the healthcare landscape, including the delicate balance between innovation and safety, the influence of corporate interests on public health outcomes, and the challenges of navigating cultural, economic, and institutional differences in pharmaceutical regulation.

As the hearings concluded and policy reforms were set in motion, they left an indelible mark on the antidepressant debate, setting a precedent for greater transparency, accountability, and caution in psychotropic medication use. Moving forward, the lessons learned from this period underscore the importance of patient-centered care, and continuous vigilance in monitoring the safety and efficacy of psychiatric medications. Ultimately, the journey through the policy, legal, and congressional realms of antidepressant regulation serves as a poignant

reminder of the complexities inherent in addressing mental health challenges in a rapidly evolving healthcare landscape.

Conclusion:

Overall, I have presented an examination of the factors influencing the policy regulation implemented in 2004, mandating the inclusion of a black box warning on antidepressant packaging. Through an analysis of interconnected factors, including the evolution of antidepressants, exuberant media portrayals, advertisement campaigns, law, and policy regulation, I have elucidated the seeds leading up to regulation in 2004.

I argue that the confluence of direct-to-consumer advertising inflating public expectations of antidepressants, questions of safety and efficacy, policy shifts in the UK, and a lack of transparency in clinical trial data inspired regulatory shifts in 2004. The surge in direct-to-consumer advertisements for antidepressants which arguably failed to inform consumers, coupled with concerns over exaggerated efficacy claims, underscored the need for greater transparency and oversight in pharmaceutical marketing practices. Moreover, I highlight the role of clinical trial transparency issues in breeding skepticism among regulators and healthcare professionals. The subsequent release of data revealing controversies surrounding antidepressant efficacy, particularly in pediatric populations, fueled concerns and prompted the 2004 congressional hearings on antidepressants.

The hearings served as a pivotal moment, encapsulating years of scrutiny and advocacy surrounding antidepressant safety. Calls for enhanced clinical trial disclosure, regulatory intervention, and greater transparency underscored a collective commitment to promoting informed decision-making and safeguarding public health. As the hearings concluded and policy reforms were set in motion, they left an indelible mark on the antidepressant debate, setting a precedent for greater transparency and caution in psychotropic medication use. Moving forward,

the lessons learned underscore the importance of evidence-based practice, patient-centered care, and continuous vigilance in monitoring the safety and efficacy of psychiatric medications.

Ultimately, the journey through the realms of antidepressant regulation serves as a poignant reminder of the complexities inherent in addressing mental health challenges in a rapidly evolving healthcare landscape. By navigating these complexities with diligence and integrity, we can strive towards a future where the benefits of psychiatric medication are maximized, and the risks are mitigated to ensure the well-being of all patients.

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