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Pediatric Depression Treatment in the Aftermath of the Black Box Warning: Implications for Prescription Drug Policy

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Abstract

In 2004, the Food and Drug Administration (FDA) directed pharmaceutical manufacturers to add a black box warning to antidepressants describing an increased suicide risk in children. We describe the events and evidence that led the FDA to act, the specific actions taken by the agency, and the changes in treatment patterns that followed. We then consider the outcomes of this case in the context of recent regulatory changes aimed at increasing the availability of information on the efficacy and safety of prescription medications.

Introduction

In October 2004, the Food and Drug Administration (FDA) directed pharmaceutical manufacturers to add a black box warning to antidepressants describing an increased suicide risk in children. This ruling highlighted the difficult challenges confronting the FDA in fulfilling its mission to protect the public's health by assuring the safety and efficacy of prescription drugs. A central tension for Congress and the FDA is how to balance the need to inform providers and consumers about new safety risks that emerge after market approval without unduly curtailing the use of effective treatments. The case of pediatric antidepressant use and suicide risk brought this tension into sharp relief. Supporters of FDA regulation argued that available evidence of an elevated risk of suicidality linked to antidepressant use in children and adolescents was sufficiently serious to warrant informing providers and consumers through a labeling change. Critics countered that FDA regulation would reduce the use of an effective treatment for depression thereby producing poorer mental health outcomes including a possible increase in youth suicide.

Following the release of information by the FDA on safety risks associated with antidepressant use by children and adolescents, several studies found evidence of substantial declines in both pediatric and adult antidepressant use. Yet, there was little evidence at this time that adults were subject to these risks. Moreover, specific recommendations highlighted in FDA safety warnings related to the importance of monitoring and the use of fluoxetine (generic Prozac) were not reflected in post-warning practice patterns.

In this paper, we describe the events and evidence that led the FDA to act, the specific actions taken by the agency in 2003 and 2004, and the changes in treatment patterns that followed. We then consider the outcomes of this case in the context of recent regulatory changes aimed at increasing the availability of information on the efficacy and safety of prescription medications.

Background

Prior to the late 1980s, few evidence-based treatments for pediatric depression were available. The introduction of SSRI-class antidepressants led to a substantial increase in depression treatment in children and adolescents.[1] Because depression is an under-treated disease with the potential for long term negative consequences, this increase in prescribing was viewed by

many as an important reduction in unmet need. At the time, evidence appeared to support the efficacy of antidepressants in treating major depression in children. Six published studies were available, three of which provided strong evidence for the efficacy of fluoxetine in treating children with depression.[2] Three additional studies provided some evidence for the efficacy of sertraline, citalopram and paroxetine. In January 2003, fluoxetine became the first SSRI approved by the FDA for use in treating pediatric depression, although pediatric treatment with other SSRIs was common.

Concerns about the safety of pediatric antidepressant use surfaced in May 2003, when the manufacturer of Paxil notified the FDA of clinical trial data indicating an increased risk of suicidal thoughts and actions in children. That June, the FDA issued a statement recommending that Paxil not be used in treating children with major depression (Exhibit 1). The FDA also launched an investigation requesting clinical trial data from other antidepressant manufacturers.

In October 2003, the FDA issued a public health advisory to alert physicians and consumers to reports of suicidal thinking among pediatric patients with depression in clinical trials data for eight SSRI-class antidepressant drugs. Several months later, in February 2004, the news media dedicated extensive coverage to the disclosure of a decision by FDA officials not to allow an FDA employee, Andrew Moshholder, to present his preliminary findings showing an association between antidepressant use and suicide risk at a public hearing.[3] Subsequent, a somewhat broader public health advisory was released in March 2004.

In these public health advisories, the FDA specified two concrete recommendations for improving the risk-benefit ratio of pediatric antidepressant use. The FDA indicated that “[H]ealth care providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases.”[4] The FDA also explicitly noted that in the clinical trial data analyzed by the FDA, fluoxetine was the only drug molecule demonstrated to be efficacious in treating major depression in children,[5] and the only SSRI approved for the treatment of pediatric depression.[6] Around this time, it was revealed that results from several negative pediatric antidepressant trials were unpublished. When these findings came to light, policymakers were quick to criticize pharmaceutical firms for not publishing results from these trials, although this is not uncommon.[7]

In September 2004, an FDA joint advisory committee was presented with results from an FDA-sponsored meta-analysis conducted by Columbia University researchers. Analyzing data from approximately 24 randomized placebo-controlled efficacy trials involving approximately 4400 children and adolescents, those receiving antidepressants had approximately twice the number of suicidal ideations and behaviors as those receiving placebos (4 versus 2 percent). Although no child completed suicide in these trials, research suggests that suicidal ideation is itself an important outcome, and one precursor to suicide in many cases.[8] This evidence led to a decision by the joint advisory committee to recommend a black box warning (15-yes, 8-no). This recommendation was adopted by the FDA in October 2004 and finalized in January 2005. The boxed warning applies to 36 drugs including SSRI/SNRI-class drugs, atypical antidepressants, and MAOIs.

Changes in Treatment Patterns

In the aftermath of this risk disclosure, studies found evidence of substantial declines in pediatric antidepressant use.[9] It is important to note that these studies described practice patterns before and after risk disclosure; no study had a relevant comparator group, so causal effects are difficult to establish. In particular, it is difficult to determine whether changes are due to FDA action, media coverage of new risk information, regulatory action by other

countries or other causes. Due to differences in data, sample and methods, analyses produced estimates ranging from a 7 percent increase in antidepressant prescribing to a 58 percent drop in prescribing. Some studies assumed steep increasing trends in antidepressant use would have continued, and calculated the reduction in antidepressant use as the difference between projected and actual volume. Other analyses calculated reductions from the peak of pediatric antidepressant use, producing smaller estimates of prescribing declines. Some analyses focused on changes in treatment for a specific diagnosis, while others examined overall prescribing volume. While methodologies differed across these studies, taken together they provide robust evidence of a substantial decline in use of antidepressants in this age group. Other studies found declines in adult use of antidepressants, although at this time there was little scientific evidence of an association between antidepressant use and suicide risk in older populations.[10] Large increases in the number of children diagnosed by psychiatrists (versus primary care providers, including pediatricians) were also detected,[11] perhaps due to primary care providers having less experience prescribing these drugs and their resulting fear of malpractice suits.

The inclusion of information on the importance of monitoring in FDA warnings did not translate into significant changes in treatment patterns, however. Morrato and colleagues examined monitoring before and after the FDA warnings, and found no significant increases in provider monitoring.[12] Likewise, the FDA's emphasis on the efficacy of fluoxetine relative to other antidepressant medications in treating children did not prompt dramatic shifts in prescribing. Evidence from the nationally representative Medical Expenditure Panel Survey indicated that, comparing calendar years 2002 and 2005, among children under age 19, the share of all antidepressant prescriptions that were for fluoxetine significantly increased, but only from 9 to 19 percent[13] indicating that the overwhelming majority of children treated with antidepressants continued to receive drugs other than fluoxetine in the period after the FDA safety warnings.

Asymmetric Information

This case highlights the informational asymmetries between pharmaceutical manufacturers and regulators. Pharmaceutical firms have more information than regulators about the efficacy of their products. These firms often set the agenda by requesting drug approvals[14] and disclosing risk information to the agency, as was the case with pediatric use of Paxil. The reticence of firms to publish the results of negative drug trials is an often noted concern and was an issue in the case of pediatric antidepressants risks. This reduces public access to information on the comparative efficacy of medications. However, even manufacturers are limited in their access to full information on the safety of their medications. Clinical trials are not typically powered to provide evidence on rare safety risks and may exclude patients with comorbid conditions.

Providers have less information on the safety and efficacy of medications than regulators. They obtain information through published studies, detailing or other promotional activities by the pharmaceutical industry, their own or their colleagues' clinical experiences and news media reports. Providers are also limited in their ability to access information by time and resource constraints. Before treatment, patients typically have the least clinical information. Patients learn about drugs through interactions with providers, direct-to-consumer advertising and the news media. While patients have greater access to medical information than in the past, they are still limited in their ability to decipher often complex health information. One task of the FDA is to provide information to providers and patients about newly emerging safety risks in a timely manner. This case illustrates the limited ability of the FDA to target specific populations and practice patterns once a safety risk is disclosed, even though this may be important in protecting the public health.

Pediatric Depression Treatment in the Aftermath of FDA Safety Warnings

It is puzzling that FDA safety warnings resulted in substantial declines in pediatric and adult antidepressant use but little change in fluoxetine use or provider monitoring, even though the agency highlighted the benefits of both. The content of news media coverage, consumer decision making biases, drug promotion by pharmaceutical firms, and scientific uncertainty regarding the comparative benefits of antidepressants may all have contributed to the selective attention by providers and consumers to the specific language of the FDA safety warnings.

While no studies have systematically analyzed news media coverage of pediatric antidepressant use and suicide risk, it is likely that many providers and parents learned about this issue through the news media. Over half of the American public describes national, local, or cable news as their most important source of health information,[15] and providers also report learning about new health issues via the news media.[16] If news outlets overemphasized the possible harms of antidepressant but failed to note the benefits of fluoxetine and monitoring, this selective news reporting could translate into the treatment patterns observed. Research indicates that the news media functions as an imperfect conduit for communicating health information to the public. Moynihan and colleagues found, for example, that news media coverage of medications often included inadequate or incomplete information.[17]

Even with perfect information on the risks and benefits of treatment options, patients may be subject to certain biases in decision making that lead to treatment choices that are inconsistent with their own stated preferences. For example, individuals tend to be more concerned about dangers caused by their own actions than dangers that occur more indirectly. [18] In the case of pediatric antidepressant use, parents may overemphasize the comparatively small safety risks associated with their child taking antidepressants compared with the risks of untreated depression. How risk information is presented may also play a role. Individuals are known to respond differently when outcomes are framed in terms of gains versus losses. [19] Framing the possible consequences of pediatric antidepressant use in terms of suicidality risk (a loss frame), may have led more individuals to forego antidepressant treatment. Also important, patients may disproportionately weigh anecdotal versus statistical evidence.[20] If media coverage relied heavily on anecdotes of individual children harmed by antidepressants, this may have led to larger declines in pediatric antidepressant use than would have otherwise occurred.

Pharmaceutical promotion might also help explain why providers continued to prescribe antidepressants other than fluoxetine for children after the release of FDA safety warnings. Antidepressants were the most heavily promoted drug class in 2005, with over 1 billion dollars in promotional spending.[21] While antidepressants were not specifically promoted for use in children, the high level of spending on detailing and direct-to-consumer advertising and the availability of free samples may have influenced prescribing patterns for children. Fluoxetine was available in generic form, so there was little incentive for Eli Lilly to promote its use.

Finally, the lack of conclusive scientific evidence on the comparative effectiveness of antidepressant medications may have influenced treatment patterns. Although a number of antidepressants had negative results in pediatric trials, many providers with experience using these medications still viewed these drugs as effective. Simon suggests that the failure of some pediatric trials may reflect the difficulty of applying diagnostic criteria developed for adults to childhood depression and the challenges inherent in assessing the severity of depression in children.[22]

Policy Changes to Increase the Regulatory Power of the FDA

FDA action on pediatric antidepressant use occurred amid existing concerns that the FDA had insufficient authority and resources to fulfill its mission to protect the public's health. This

prompts the question of whether a more robust regulatory environment could have provided the FDA with earlier and more complete information on benefits and risks of antidepressants in treating children.

Historically, one important tool available to the FDA has been a pediatric exclusivity provision, which extends patent protection for drugs to encourage clinical trials on medication effects in child populations. Enacted by Congress in 1997, this provision grants manufacturers an extra six months of patent protection for performing FDA-requested pediatric clinical trials. Relevant to this case, the FDA's meta-analysis assessing the risks of suicidality included several clinical trials conducted under the pediatric exclusivity provision. This provision has substantially increased the available evidence on medication use in children,[23] and has been reauthorized twice by Congress in 2002 and 2007. Benjamin and colleagues found, however, that pediatric study results were often not widely disseminated to clinicians through peer-review; only 36 percent of studies where results were unfavorable were published in peer-reviewed journals.[24] This provision had been important because the FDA has been limited in its ability to compel firms to comply with requests to complete post-market studies. Between 1991 and 2003, only 24 percent of post marketing studies agreed to during the drug approval phase were completed.[25]

In 2007, Congress took steps to strengthen the FDA's regulatory authority with passage of the Food and Drug Administration Amendments Act (FDAAA). The FDAAA included many of the recommendations of the Institute of Medicine's 2007 report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*.[26] The agency now can require additional studies be performed either at the time of drug approval, or if new safety concerns come to light, post approval. Importantly, the agency was given significant tools to enforce this provision. Also, changes were enacted to improve the usefulness of the FDA's Adverse Event Reporting System (AERS), the voluntary post market surveillance system for providers to report of adverse drug reactions. Another important provision of the FDAAA requires the FDA establish a post-market risk identification and analysis surveillance system in collaboration with public, academic, and private entities to identify risks associated with products already on the market. The Sentinel Initiative, scheduled to be operational in 2010, will use large datasets to identify risks associated with products already on the market. In May 2008, the FDA announced efforts to include data from the Medicare prescription drug benefit in this initiative. Several other recent initiatives, including newly funded centers in the Center for Education and Research on Therapeutics (CERTs) program, have been aimed at increasing the amount of post marketing observational data available regarding prescription drugs. The post-market phase is crucial to identify safety concerns because, as noted above, clinical trials are powered to identify clinical efficacy but may be under powered to detect risks.

Evidence suggests that post-market surveillance systems in other countries have been informative in signaling and assessing potential safety concerns. A study from Finland illustrates the advantages of such systems to study rare events. Linking several national data sources, Tiihonen and colleagues found that current use of an antidepressant (in both adults and children) is associated with both an increased risk of *attempted* suicide, and a decreased risk of *completed* suicide and mortality.[27] If a post marketing surveillance system had been in place in the U.S., such information may have been available to the FDA.

The FDAAA also enacted policy changes aimed at improving the availability of information to providers and patients on prescription drug safety and efficacy. One provision requires that the results from clinical trials be made available publicly in the National Library of Medicine clinical trials database. In the case of pediatric antidepressant use, if data from negative or inconclusive trials had been disclosed, clinicians may have had earlier access to information on the comparative efficacy of antidepressants in treating children. Also important, Congress

gave the FDA new regulatory authority under the FDAAA to require a pharmaceutical manufacturer develop a plan to manage known risks associated with a medications use. Risk Evaluation and Mitigation Strategies (REMS) may require the inclusion of risk information in a package insert, a communications plan to inform providers about safety concerns associated with a drug, provisions that can restrict prescribing to certain types of providers or health care settings, as well as other strategies. A REMS plan can be required by the FDA before drug approval or post approval if new safety information is discovered. Since this provision is newly enacted, it is not yet known the extent to which REMS will be effective in improving the overall risk-benefit profile for drugs with safety issues.

Conclusion

By enacting many of the recommendations of the Institute of Medicine's 2007 report on drug safety, Congress attempted to enhance the FDA's ability to identify and address safety problems in a timely manner. These policy changes could improve provider and consumer access to information on the comparative effectiveness and safety of treatments for depressed children. The effects of these policy changes will be clearer over time. In recent years, the FDA has relied more heavily on labeling changes to communicate health information to the public and providers. In 2007, 68 black box warning labels were issued compared with only 21 in 2003.[28] The antidepressant case highlights information asymmetry problems and suggests that the FDA's practice of issuing public health advisories may not be sufficient to insuring that important health information is communicated to providers and the public. As noted above, more evidence is needed on how these risks are communicated by the news media to the public. Also, investigation of how the FDA might take consumer decision making biases into account in communicating risk information is warranted. As consumers assume a larger role in health care decision making, the FDA has the ongoing responsibility to identify ways to communicate in a clear and interpretable manner increasingly complex health risk information.

Exhibit 1: Events Related to Pediatric Antidepressant Use and Suicide Risk

May 2003: Manufacturer of Paxil notifies FDA of clinical trial data indicating an increased risk of suicidal thoughts and actions in children and adolescents

June 2003: FDA issues a public statement on possible safety risks related to use of Paxil

October 2003: FDA issues a public health advisory on possible safety risks related to use of antidepressants

February 2004: FDA holds a public hearing on pediatric antidepressant use

March 2004: FDA issues a public health advisory on possible safety risks related to use of antidepressants

September 2004: FDA advisory committees vote in favor of recommending the FDA issue a black box warning on the antidepressant product labels

October 2004: FDA publicly announces the decision to issue a black box warning on the antidepressant product labels

January 2005: Manufacturers are required to begin including a black box warning on antidepressant product labels.

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