The Food and Drug Administration's Deliberations on Antidepressant Use in Pediatric Patients

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The Food and Drug Administration's Deliberations on Antidepressant Use in Pediatric Patients

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Abstract

On February 2, 2004, the Food and Drug Administration organized a joint meeting of the Neuro-Psychopharmacologic Advisory Committee and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee to examine the occurrence of suicidality in clinical trials that investigate the use of the newer anti-depressant drugs in pediatric patients. Committee members reconvened on September 13–14, 2004, and concluded that there was a causal link between the newer antidepressants and pediatric suicidality. This article provides a summary of the Food and Drug Administration deliberations for the pediatric clinician. We also provide research, regulation, education, and practice implications for care for children and adolescents who may be eligible for treatment with these medications.

Keywords

depression; pediatrics; children; adolescents; antidepressants; suicide; regulation; mental health; FDA

ABBREVIATIONS

FDA, Food and Drug Administration; MDD, major depressive disorder; DD, dysthymic disorder; BPD, bipolar disorder; CBT, cognitive behavioral therapy; SSRI, selective serotonin reuptake inhibitor; FDAMA, Food and Drug Administration Modernization Act; BPCA, Best Pharmaceuticals for Children Act; MHRA, Medicines and Healthcare Products Regulatory Agency; TADS, Treatment for Adolescents With Depression Study

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The authors of this article all were voting members of or expert consultants to 1 or both joint meetings of the Neuro-Psychopharmacologic Advisory Committee, the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee, and the Pediatric Advisory Committee to the FDA on the use of antidepressants in children and adolescents. The comments reflect the perspectives of the authors and should not be interpreted as reflecting the position of the FDA, the FDA Advisory Committees, or the American Academy of Pediatrics.

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On February 2, 2004, the Food and Drug Administration (FDA) organized a joint meeting of the Neuro-Psychopharmacologic Advisory Committee and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee and expertise consultants to evaluate the safety of selected antidepressants in children and adolescents. Specifically, these 2 committees were charged with examining the occurrence of suicidality (suicidal thinking, behavior, or attempts) in clinical trials that investigate the use of the newer antidepressant drugs in pediatric patients with major depressive disorder (MDD) and other psychiatric disorders. At the February meeting, committee members concurred with the FDA's decision to reanalyze data available from current pediatric trials, which had been conducted by or in conjunction with pharmaceutical companies. On September 13–14, 2004, the Neuro-Psychopharmacologic Advisory Committee and the newly formed Pediatric Advisory Committee and consultants met again to review these data and advise the FDA on the use of these medications in pediatric patients. The committee's conclusion: there was a causal link between the newer antidepressants and pediatric suicidality. On October 15, 2004, the FDA ordered pharmaceutical companies to add to antidepressant advertisements, package inserts, and information sheets developed for patients and clinicians a "black-box" warning (a statement in prominent, bold-faced type and framed by a black border) regarding pediatric use. By issuing this warning, the federal drug regulators imposed one of their toughest requirements, short of banning a medication.

The intense controversy surrounding these antidepressants and the concurrent public media coverage have spawned widespread discussion regarding the use of antidepressants in pediatric patients. The question of whether there is a causal link between the newer antidepressants and suicidality has major consequences. Suicidality is associated with several of the mental health disorders for which these medications are used, and treatments to protect against this outcome are desperately needed. However, it is equally important not to indiscriminately give youths medications that may increase risk for suicidality.

This article provides a summary of the FDA deliberations for the pediatric clinician. We begin by reviewing the scope of problems that children and adolescents with depression and other psychiatric disorders face. We then review the role of the FDA in evaluating these medications in the past decade and summarize the information presented to members of the committees. We delineate the decisions reached by the FDA committees during their deliberations. Last, we provide research, regulation, education and practice implications for quality care for children and adolescents who may be eligible for treatment with these medications.

SCOPE OF THE PROBLEM

Mental Health Needs of Children and Adolescents

Recent estimates of the rates of mental health disorders in pediatric populations are staggering, suggesting that at least 1 in 10 children and adolescents has mental illness severe enough to cause some level of impairment.[1–5] Taken in the aggregate, mental health disorders are the most common pediatric disorders that negatively affect quality of life across the domains of home, school, and peer functioning. Many youths with these disorders go on to display an inability to function fully as adults, costing society in terms of both human and fiscal resources.[6]

Of particular concern are the mood disorders, including MDD, dysthymic disorder (DD) and bipolar disorder (BPD). These disorders can be identified in youths of all ages but become increasingly prevalent in adolescence, with cumulative rates of 16% to 22% by late adolescence.[3,5] Although MDD, DD, and BPD can result in serious morbidity, including interpersonal difficulties, poor social and school performance, family problems, and substance

abuse, these disorders also carry with them the very real possibility of suicidal ideation, attempts, and completion. Suicidality is common in youths; data from the Centers for Disease Control and Prevention's National Youth Risk Behavior Survey for the year 2003 indicated that 16.9% of students in grades 9 to 12 had seriously considered suicide and 2.9% had made an injurious suicide attempt during the 12 months preceding the survey.[7] Data from the year 2001 indicate that although rates of suicide completion decreased in the 1990s, suicide was documented as the third leading cause of death among young people aged 10 to 24 years and accounted for 6.8% of total deaths in youths aged 10 to 14 years and 11.9% of youths aged 15 to 24.[8]

The high prevalence rates of the mood disorders and the serious consequences of suicidality have prompted research regarding possible treatments, including both psychotherapeutic and psychopharmacologic regimens. In the past decade, studies have provided a growing evidence base for psychotherapeutic treatments for these disorders, especially cognitive behavioral therapy (CBT).[9] Psychopharmacologic treatments have also been commonly used in the treatment of mood disorders in youths for a variety of reasons, including child, family, or provider choice; lack of responsiveness to psychotherapeutic techniques; possible synergism of combined psychotherapeutic medication treatment strategies; and limited access to psychotherapeutic services (as a result of provider, insurance, or geographic constraints).

The use of antidepressants in pediatric patients, particularly the selective serotonin reuptake inhibitors (SSRIs), has rapidly increased in the past decade. Because of their limited anticholinergic side effects and cardiovascular toxicity, SSRIs offered several therapeutic advantages over earlier antidepressants.[10] In the 1990s, the SSRIs were used increasingly as first-line treatment for affective disorders in pediatric patients.[11–15] Published research estimated that the rate of antidepressant use in youths aged 18 years and younger was 1.0 per 100 people by 1996.[16] More recent analyses, conducted by the FDA Division of Surveillance, Research & Communication Support on data collected through the IMS Health, National Prescription Audit Plus and National Disease and Therapeutic Index programs, found that an estimated 10.8 million prescriptions were dispensed in 2002 for youths aged 1 to 17 years. The primary pediatric diagnoses associated with the use of the SSRIs and newer antidepressants were anxiety disorders in children aged 1 to 11 years and mood disorders in adolescents aged 12 to 17 years. More than 60% of the prescriptions for children aged 1 to 11 years and adolescents aged 12 to 17 years were prescribed by psychiatrists, with 17% of prescriptions written by pediatricians.[17]

Status of Drug Testing for Safety and Efficacy in Pediatric Patients

Much of the use of these newer antidepressants occurred "off-label," without adequate testing regarding their safety and efficacy in pediatric populations. Off-label usage of many medications in pediatric populations had always been common and necessary, as most drugs had not been studied adequately in children. In the 1990s, the extent of off-label usage for medications such as the SSRIs in pediatric patients became increasingly important. Research in many clinical areas suggested very real differences in the absorption, distribution, metabolism, excretion, efficacy, and safety of some medications in children and adolescents compared with adults.[18] Most salient to this paper were a series of published findings from multiple studies that provided no evidence of efficacy of the typical tricyclic antidepressants in the pediatric population, despite evidence to the contrary in adults.[19–26] The absence of specific pediatric labeling information potentially exposes pediatric patients to both safety- and efficacy-related risks. First, if pediatric pharmacokinetic studies are not available and dosing regimens are extrapolated from adult data, then pediatric patients might experience potential adverse reactions that would not be expected, either as a result of physiologic differences between children and adults or as a result of improper dosing. Second, pediatric

patients might receive ineffective treatment through under-dosing or through treatment with a less effective medication in the face of insufficient pediatric information about a more effective drug.[27]

These concerns led to the passage of several seminal policy initiatives in the 1990s regarding medications in pediatric populations. On December 13, 1994, the FDA published its Pediatric Labeling and Extrapolation Regulation (59 FR 64240), with the aim to foster the study of drug pharmacokinetics, efficacy, and safety in youths.[28] The FDA proposed an additional guideline on August 15, 1997, which required new drugs to have labeling regarding how the medication could be used safely in pediatric patients. Two months later, on November 21, 1997, Congress enacted Section 505a of the Food and Drug Administration Modernization Act (FDAMA), [29] further addressing the needs for improved information about drug use in youths. This legislation included a provision that authorized market exclusivity incentives to manufacturers who voluntarily conducted and submitted to the FDA safety and efficacy studies in pediatric patients in concert with FDA guidance documents. The drugs that required such studies would be decided by the FDA in consultation with pediatric organizations; the SSRIs and other new antidepressants were included in the list of medications that needed additional studies.[30] After passage of FDAMA, the FDA received 8 pharmaceutical reports investigating the effects of antidepressants on pediatric patients.

Over the next several years, additional regulations regarding the FDA review process for pediatric medications were put into place. In 1998, the FDA published the “Pediatric Rule,” which required that all new applications with new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration include an assessment of efficacy in all relevant pediatric subpopulations, unless the sponsoring organization had obtained a waiver or deferral of pediatric studies.[27] In 2002, Congress passed the Best Pharmaceuticals for Children Act (BPCA),[31] which renewed the exclusivity clause, provided a process for off-patent drug development, required public posting of results, and mandated reporting of all adverse events for 1 year after exclusivity was granted.[28] This was quickly followed in 2003 by the Pediatric Research Equity Act,[32] requiring the study of drugs and biologics for pediatric populations and creating a new Pediatric Advisory Committee to advise the FDA.

Why a Focus on the Newer Antidepressants?

As part of the regulatory process, the FDA reviewed studies that were provided by pharmaceutical companies to identify any adverse effects identified during the medication trials. The FDA reviewer for the paroxetine study in 2003 noted that events suggestive of possible suicidality were categorized under the term “emotional lability” rather than under a phrase more directly suggestive of suicidality, possibly obscuring any results regarding potentially serious adverse events. This raised concern that additional adverse events might have been misclassified. After an internal review, the FDA requested that GlaxoSmithKline, the manufacturer of paroxetine, separate out all terms suggestive of suicidal ideation, attempts, or completion.

The possibility that these medications could trigger suicidality was not unheard of; similar concerns had been raised in adults during the early 1990s.[33–37] In 1991, the FDA had assembled an expert panel to probe reports that suggested a causal link between SSRIs and suicidality in adults. The advisory group concluded that there was insufficient evidence for causality.[38] Questions regarding both the efficacy and the safety of antidepressants in adults, however, have continued to be raised.[39–46] In addition, 2 studies in the literature reported increased psychiatric adverse effects in children and adolescents who used SSRIs.[47,48] One GlaxoSmithKline-sponsored study did report more psychiatric adverse events with paroxetine compared with placebo,[49] but the article failed to report that the increase was statistically

significant and claimed that because the clinical investigators did not consider these events to be related to paroxetine, causality could not be determined.

In response to the FDA request, GlaxoSmithKline conducted a reanalysis of their data. The revised analyses documented an increased risk for suicidality in pediatric patients who take paroxetine compared with placebo, which was greater than what would be expected by chance alone. This report was submitted in May 2003 to the Medicines and Health-care Products Regulatory Agency (MHRA; the British equivalent to the FDA) in the United Kingdom and to the FDA. On June 10, 2003, the MHRA ruled that the use of paroxetine by general practitioners was contraindicated for children under the age of 18. This contraindication, however, did not prohibit psychiatrists from using these medications if they believed that they were indicated. Nine days later, the FDA issued a public health advisory, suggesting that paroxetine should not be used in children and adolescents for the treatment of MDD until the results of additional analyses became available. The FDA also asked pharmaceutical manufacturers of 8 other newer antidepressants to review data from their research trials for the occurrence of suicidality in pediatric patients. These medications included 4 other SSRIs (fluoxetine, sertraline, fluvoxamine, and citalopram) as well as several of the atypical antidepressants (bupropion, venlafaxine, nefazodone, and mirtazapine; Table 1).

Several events followed this request. First, Wyeth, the producers of venlafaxine, addressed the FDA's mandate by voluntarily changing their labels to discourage use of venlafaxine in pediatric patients and publishing a Dear Health Care Professional letter in August 22, 2003. Both the label alteration and the letter reflected increased reports of hostility and suicidality in pediatric patients who participated in the venlafaxine arm during clinical trials, particularly those trials of medication in youths who had a diagnosis of MDD. Second, the data that were available for each of the 8 antidepressants (other than paroxetine) were reviewed by FDA staff; their studies suggested an increase in the risk for suicidality. Although the increase in suicidality in many individual trials was not statistically significant, most studies had trends in that direction and none had confidence intervals that excluded a significant increase in suicidality. This association prompted the FDA to release an updated public health advisory on October 27, 2003, stating that preliminary data showed an excess of reports of suicidality in the SSRIs and the related antidepressants but that there was a need for additional data analyses before anything definitive could be concluded. Last, as the FDA received and reviewed the pharmaceutical companies' reports on pediatric suicidality and the newer antidepressants, it became clear that there was a lack of methodologic uniformity across the drug manufacturers' responses. Different analyses were performed by each company with respect to ascertaining all events of potential suicidality in the drug treatment group as well as in control subjects. For example, 1 company acknowledged that they had excluded cases that were not considered "treatment emergent." Another company selected cases on the basis of knowledge of treatment assignment. Review of excluded cases by another drug sponsor demonstrated substantial differences in risks for suicidality between the FDA analysis and the analysis submitted by the sponsor.[50]

INFORMATION AVAILABLE TO THE ADVISORY COMMITTEE

Because of the nonstandardized use of definitions of suicidality across the studies, the FDA contracted with experts at Columbia University to develop a standard classification scheme for reclassifying all adverse events suggestive of suicidality across available studies. In addition, the Neuro-Psychopharmacologic Advisory Committee and the Pediatric Subcommittee of the Anti-Infectives Committee were jointly convened to review the data and provide recommendations to the FDA. Also invited were expert consultants in pediatric and psychiatric care processes, psychopharmacology, and epidemiology and biostatics. These 2 advisory committees and consultants first met in February 2004 to review preliminary

information regarding the antidepressants and to approve the FDA's analytic plan. In September 2004, the newly formed Pediatric Advisory Committee to the FDA and the Neuro-Psychopharmacologic Advisory Committee reconvened. Materials that were reviewed by the committees at this meeting addressed both safety and, to a lesser extent, efficacy of the newer antidepressants. These materials came primarily from 3 sources: (1) narrative testimonies from >100 families, health care providers, and representatives from consumer groups; (2) the FDA reanalyses of the data from the pharmaceutical trials recoded by Columbia University researchers; and (3) an additional National Institute of Mental Health–funded randomized clinical trial on the use of fluoxetine in pediatric patients.

Narrative Testimonies

During both the February and the September meetings, committee members heard from family members, community organizations, and health care professionals regarding the use of newer antidepressants in pediatric patients. The committee did not view these narratives as evidence about a causal link between the newer antidepressants and suicidality because case reports of this nature are subject to both sample and information biases. However, the members did see the narratives as important to their deliberations in 3 ways. First, the narratives reminded committee members of the importance of weighing potential harm to families regardless of the decisions made regarding a causal link between the newer antidepressants and suicidality. Second, some of the narratives also described hostile acts of violence to others by youths who took these medications and emphasized the importance of studies to examine these additional adverse effects of antidepressants.[33,48] Third, families described the use of these medications for indications such as nail biting, insomnia, and migraine headaches as well as lack of follow-up by prescribing physicians, suggesting that non–evidence-based, casual use of these medications might be occurring and that this perspective needed to be shared with professional medical organizations.

Data Classified by Columbia University and Reanalyzed by the FDA

Data from the Columbia Project was also presented to the Advisory Committees. The FDA had pooled data from 24 studies to provide to the Columbia investigators to examine the association between suicidality and the newer antidepressants. These studies included published and unpublished studies conducted by pharmaceutical sponsors for a variety of mental health indications as well as data from the Treatment for Adolescents with Depression Study (TADS), a randomized, clinical trial that compared fluoxetine, CBT, and combination therapy with placebo.[51] The FDA contracted with suicide experts at Columbia University to review all narratives of reports of adverse events from these trials and recode the narratives with respect to suicidality. Of the 24 studies, only 109 events were classified as pertinent to the FDA's question regarding suicidality. It is important to note that there were no cases of completed suicide in the 24 studies. The FDA then conducted a reliability study on the Columbia classification and used the recoded narratives in a pooled analysis of the data.

Because many of the studies that were reviewed by the FDA Advisory Committees were conducted under the FDAMA provisions described above, before implementation of the BPCA and Pediatric Research Equity Act legislation, it is important to review how this legislation may have affected the data that were available to both the Columbia and the FDA investigators. FDAMA required that, if requested by the FDA, manufacturers provide documentation of at least 1 clinical investigation in pediatric age groups in which the drug's use was anticipated, although some group other than the manufacturer could perform the study. In addition, studies needed to be conducted and filed with the FDA before expiration of an existing exclusivity period to gain an additional 6 months of exclusivity. However, the FDA did not require the manufacturer to provide definitive information on pediatric efficacy (ie, the results could be inconclusive). In addition, exclusivity not only would apply to the product being studied in the

pediatric population but also would be expanded to cover all formulations, dosage forms, and indications that contained the same active moiety.[52] Companies could have substantial financial benefit from the exclusivity extension if the drug had a large adult market.

The studies that were provided to the FDA regarding the use of antidepressants in pediatric patients thus had several limitations. First, because many of these drugs were already in use in adults, pharmaceutical companies were allowed to estimate study sample size and pediatric dosages on the basis of studies that were conducted in adults. Pediatric pharmacokinetic studies were not required. Second, the absence of requirement that the studies demonstrate efficacy may have provided less incentive to ensure careful management of the studies. These criteria also may have influenced study design; studies often were short in duration (none was longer than 16 weeks), with small sample sizes. Committee members were informed by the FDA that sponsors may have had more incentive to complete studies quickly for new drugs or off-label drugs rather than to maintain the quality of the study at the level required by the FDA. Fourth, because the studies were not specifically designed to assess suicidality, most were not powered adequately. The studies also lacked detailed, methodical instrumentation to capture these results. Most of the studies did not use specific instruments to identify adverse events such as suicidality; rather, adverse events were collected using open-ended probes. A recent study by Greenhill et al.[53] showed that the open-ended method is more likely to result in underreported adverse events. Finally, investigators for the different studies used a variety of exclusionary criteria, diagnostic mechanisms, data collection methods, and coding strategies, making it difficult to compare across the studies. For example, only 4 of the 24 studies did an extensive diagnostic screen at the beginning of the trial to delineate participants' diagnosis and the presence of any coexisting conditions. Studies varied as to whether they evaluated a youth for BPD before inclusion. Only 11 of the 24 studies excluded children when there was a family history of BPD. Studies varied in their inclusion of youths with a history of suicidality; 5 of the studies permitted youths who were identified as being at risk for suicide (at baseline), and 16 studies did not exclude youths despite a history of suicidal attempts. Fifteen of the studies examined the use of the newer antidepressants in MDD; the others studied their use in obsessive compulsive disorder (4), anxiety disorders (3), and attention-deficit/hyperactivity disorder (1).[54]

These limitations make the results of the pooled analyses even more compelling. When all 24 studies were pooled, the rate of possible or definitive suicidality among youths who were assigned to receive antidepressants was 2.19 times greater compared with youths who were assigned to the placebo groups (95% confidence interval: 1.50–3.19).[55] An excess of suicidality in 1 group at least this large would occur by chance only 1 time in 20 000 ($P = .00005$). Importantly, most of the limitations of the data (small sample size, inadequate power, wide variations in sample inclusion, and possible misclassification of outcomes) would make it more, not less, difficult to detect differences between groups in randomized, double-blind trials, causing falsely low estimates for the relative risk of suicidality and falsely high *P* values.[56]

Members of the 2 committees also realized the importance of weighing the benefit-to-harm ratio of these medications for use in pediatric patients. Limited information regarding efficacy was summarized for committee members on the efficacy trials, specifically, that FDA analyses indicated that only 3 of the 15 trials of the newer antidepressants in youths with depression found a statistically significant benefit of drug over placebo.[55] However, specific analyses were not shared with committee members, and committee members were not able to determine efficacy adequately from the brief amount of information provided. Two published meta-analyses that delineated the limitations and potential biases of the available studies were also presented. These meta-analyses suggested that the efficacy of the antidepressants in children and youths was likely to be overestimated, because published trials had more favorable results

than unpublished trials.[57,58] Alternatively, the committees were cautioned that the time limitations under FDAMA might have subjected the trials to a type II error, ie, missing a finding when one was present.

One other aspect regarding the FDA analyses bears consideration. There were no completed acts of suicide in the 24 studies; the causal link demonstrated in the FDA analyses therefore focused entirely on suicidal ideation and behavior. Analyses were conducted to examine these 2 outcomes as a single construct.

Data From the TADS Study

The committees last examined data from the recent TADS study alluded to above. The TADS study recruited a volunteer sample of 439 patients who were between the ages of 12 and 17 years and had a diagnosis of MDD. Patients were randomized to 4 treatment arms: (1) fluoxetine alone, (2) CBT alone, (3) CBT with fluoxetine, and (4) placebo. Youths in all 4 arms of the study, including placebo, improved significantly on the primary outcome, the Children's Depression Rating Scale–Revised, although fluoxetine with CBT was the only treatment arm that showed statistical significance compared with placebo. On some of the other outcome measures, planned pairwise contrasts indicated that the combination treatment and fluoxetine alone were superior to placebo, whereas CBT was not. Thus, although there was evidence for the efficacy of treatment with fluoxetine alone or in combination with CBT in the TADS study, the high placebo response rate indicates why families and clinicians believe that these medications are effective, even if 85% of the benefits observed also would have occurred with placebo.

Suicidal ideation was present in 29% of the TADS sample at baseline, despite the exclusion of youths who were at high risk for suicidality. Ultimately, suicidality improved significantly in all 4 treatment arms. Suicide attempts were rare (1.6%), and there were no completed suicides. The only statistically significant adverse finding was an odds ratio of 2.19 (1.03–4.62) for harm-related adverse events in youths who were taking fluoxetine compared with youths who were not taking fluoxetine. Data from the TADS study also suggested a possible protective effect of CBT against suicidality when used in combination with fluoxetine.

CONCLUSIONS OF THE FDA ADVISORY COMMITTEES AND CONSULTANTS

Members reached the following 4 conclusions. First, the reclassification of adverse events conducted under the direction of Columbia University as described to the committee members seemed to have been conducted appropriately with sufficient scientific rigor to decrease biases inherent in previous classification schemas and to draw conclusions, despite serious limitations of the available data. Second, analyses that were conducted using the reclassified data demonstrated that there was an increased risk for suicidality causally related to use of the SSRIs and related antidepressants. Third, although the data in aggregate supported the finding of increased suicidality, the studies were too underpowered to draw any conclusions regarding safety for specific antidepressant agents or for specific disorders. The committees also considered whether to include "older" antidepressants, although the committees had not specifically reviewed data on these drugs. Monoamine oxidase inhibitors and tricyclics had even less evidence for efficacy than the SSRIs and the newer atypical antidepressants and high risks (especially the possibility of suicide from overdoses). The committees decided to recommend to the FDA that all antidepressants, both current and future products, have language added to their label regarding the risk for suicidality.

Finally, the committee addressed the issue of whether the FDA should strengthen the existing warning on the label of antidepressants or pursue a more aggressive course by applying a black-box warning for antidepressants. Black-box warnings are used to signal an extremely serious

risk and have implications for the public marketing of drugs with this type of warning. Committee members were in agreement that warnings on antidepressants needed to have sufficiently strong wording to provide adequate protection to the public. Many committee members and public speakers expressed concerns that the black-box warning might decrease access to treatment for some youths, if the warning made non-psychiatrists reluctant to prescribe the drugs. Members cited the current limited number of child and adolescent psychiatrists and the small numbers projected for the next decade.[59] In addition, many members commented on the difficulties encountered in gaining access to psychotherapeutic mental health services for some pediatric subpopulations, including inner-city underserved, underinsured youths and youths who reside in rural communities.

The final vote was in favor of the black-box warning. Committee members also urged the FDA to develop an antidepressant MedGuide, patient educational material to be included with medications that are distributed by pharmacists when an antidepressant prescription is filled for an adult or a pediatric patient. Members recognized that this strategy would provide families and caregivers access to education about antidepressants but would not guarantee that the patient, family, and clinician would discuss the risk/benefit ratio of these medications before initiation of medication treatment. It should be noted that the committees did not address the specific wording of the black-box warning.

The committees did not recommend that antide-pressants be contraindicated for pediatric patients, as had been decided by the MHRA in the United Kingdom. Although a "contraindication" in the United Kingdom would confine use to patients who are cared for by subspecialists, a contraindication in the United States signifies that these medications could not be used in pediatric patients. Committee members were unwilling to ban medications that in the future may demonstrate efficacy in some patients, given adequately designed research studies, and did not want to preclude treatment for those patients.

RECOMMENDATIONS

During the deliberations of the committees, many issues regarding the diagnosis and treatment of children and adolescents with MDD and other mood disorders were raised. Although both committee members and public speakers individually urged that a number of strategies be taken to address these issues, no formal recommendations were made by the committees. However, as members of and consultants to the committees, we propose that a number of follow-up actions be considered by the appropriate federal agencies, professional organizations, and health plans. These steps fall into 2 categories: (1) research and regulations and (2) clinical education and practice.

Research and Regulations

The debate over the newer antidepressants highlights considerable flaws in the current system of medication testing and approval. The SSRI controversy was quickly followed in the fall of 2004 by other signs and symptoms of a system of regulation and research needing change, including (1) reports of selective dissemination of data regarding adverse drug reactions with other medications such as rofecoxib (Vioxx)[60] and cerivastatin (removed from the market in 2001),[61,62] (2) federal hearings by the Committee on Energy and Commerce regarding the FDA's role in protecting the public health and publication and disclosure issues, and (3) the ongoing lawsuit filed by the New York Attorney General against GlaxoSmithKline claiming suppression of adverse events information regarding Paxil. Journal editors have also called for changes in the current system; several journals now require that researchers publicly register all trials if they plan to pursue publication at a later date. The FDA has asked the Institute of Medicine to conduct a report on the current system of drug safety assurance and provide the

FDA with recommendations for change. In addition, the FDA recently announced a plan to restructure their current drug testing, approval, and monitoring system.[63]

We advocate a number of changes in the current system and available research:

- Guarantee the FDA sufficient independence, authority, and freedom from political and economic influence to demand high-quality drug trials. These studies should pass a peer-review process that ensures use of diagnostic assessments, standardized measures, and appropriate data collection and coding.
- Develop a mechanism for postmarketing surveillance, whether as part of the FDA or through a separate agency that does not rely on physicians and pharmaceutical companies to report voluntarily problems with new drugs after the mandated period required of the pharmaceutical companies. New drugs may introduce new risks that are relatively rare and may be not apparent until the medication has been in wide use after marketing.
- Push for disclosure to the public of all safety and efficacy results found in drug trials, including those that do not support the hypothesis being tested or that are contrary to the intended outcome. Provide disclosure of results, in a standardized and interpretable format, on publicly available clinical trial registries such as the new US government web site www.clinicaltrials.gov and in other informational sources that are available to the public and the medical professions.
- Additional study is needed regarding suicidality when these medications are used for other indications, such as anxiety. Data from existing pharmacologic studies presented to the FDA as well as available large data sets, such as the data from the Research Unit on Pediatric Psychopharmacology Anxiety Study Group's randomized, clinical trial regarding the efficacy of the SSRIs in childhood anxiety, could potentially be examined to answer this question more specifically.[64]
- Encourage long-term studies in larger samples that are more reflective of the target population to examine better both the efficacy and the safety of the newer antidepressants. These studies should be conducted across mental health conditions for which the newer antidepressants are used, including the mood, anxiety, and obsessive-compulsive disorders. They should examine both hostility and suicidality as outcomes and consider the role of pharmacogenetic variation. Because of the rarity of these types of adverse events, studies will probably not be undertaken by individual pharmaceutical companies and will require substantial fiscal and scientific support from the National Institutes of Health. There is legal precedent for this action; the 2002 BPCA ruling does authorize several institute funding mechanisms as vehicles for funding studies of drugs if the manufacturers of those drugs decline to conduct the requested safety and efficacy studies.

Clinical Education and Practice

One of the major concerns of the committees was the need for access to effective and safe care for children and adolescents with mental health disorders, provided by thoughtful, well-trained clinicians. Although the FDA regulates pharmaceutical products, its role should not include the regulation of the practice of medicine. Nonetheless, the black-box warning developed by the FDA includes specific language detailing that physicians who prescribe these medications should closely monitor patients with observation that "would generally include at least weekly face-to-face contact during the first 4 weeks of treatment" with specific visit intervals specified after those 4 weeks.[65]

Professional organizations, including the American Academy of Pediatrics (AAP) and the American Academy of Child and Adolescent Psychiatry, have rapidly mobilized internal working groups to respond to the FDA's proposed black-box warning. Both organizations are concerned about the potential access issues for patients and their families, reimbursement under many health plans, and the medicolegal implications of specified numbers and types of visits. In addition, both organizations are developing provider and family fact sheets regarding these medications and recommended practice guidelines. The American Academy of Child and Adolescent Psychiatry is already fast-tracking revision of their 1998 guidelines on the use of antidepressants in children and adolescence.[66] Similarly, evidence-based guidelines for the diagnosis and treatment of MDD, DD, obsessive compulsive disorder, and the anxiety disorders need to be updated.

We see the AAP, the American Academy of Family Physicians, and the National Association of Pediatric Nurse Practitioners as critical primary care partners in the development of these guidelines. The scope of pediatric mental health disorders is predicted to continue to grow; recent evidence compiled by the World Health Organization indicates that, by the year 2020, these disorders will increase proportionately by >50%, internationally, to become 1 of the 5 most common causes of morbidity, mortality, and disability in children.[6] Clearly, out of necessity, the management of these disorders will continue to fall to primary care clinicians. Professional organizations will have to balance the need to ensure the provision of high-quality care with the limited availability of psychiatric providers in certain communities and the potential medicolegal complications of overly rigid practice pattern standards. We recommend that these organizations partner with medical education groups and health plans to

- Design practical tools and educational programs to assist the primary care clinician in the diagnosis, referral, and treatment of these disorders and in the evaluation of risk factors for suicidal ideation and attempts and ensure that the content of these programs address practical aspects of care, including risk/benefit ratios of psychotropic medication treatment, indications for pharmacologic treatment, the use of psychotherapy both as solo and as adjuvant therapy, the content of informed consent and discussions regarding risks and benefits, mechanisms for monitoring pediatric patients for both benefits and side effects from treatment, and the importance of and mechanisms for reporting adverse events.
- Concurrently, conduct studies to determine the role of primary care clinicians in the identification and treatment of youths with mood disorders. There is currently a paucity of research regarding the ability of primary care clinicians to identify correctly youths with these types of disorders and then partner with other professionals in their treatment. Similarly, studies regarding feasible and effective follow-up and monitoring schedules need to be conducted in primary care settings.
- Last, 3 events in winter 2004–2005 that have implications for ongoing medical education included (1) announcements of previously unreported adverse effects with other psychotropic medications including atomoxetine (Strattera) and mixed amphetamine salts (Adderall), (2) the recent publication of several contrasting large-scale studies that examined the association between suicide attempts and the SSRIs in adults,[40,41,67] and (3) another recently published observational study that found no association between suicide attempts and the SSRIs in pediatric patients.[68] These events highlight that medical knowledge regarding medications is not static. We need to remind the medical community, health plan administrators, and the public that treatment recommendations and practice standards must continue to be reexamined and updated to incorporate new knowledge as it becomes available.

CONCLUSIONS

The FDA Commission hearings on the use of antidepressants in youths raised a number of important issues regarding the safety and the efficacy of the SSRIs and related antidepressant medications. Furthermore, the investigation brought attention to the needed areas of improvement in our current system for drug approval and postmarketing surveillance in pediatric as well as adult populations. It will require strong advocacy, greater oversight, and cross-organizational partnerships between clinicians, professional organizations, federal agencies, health plans, and consumers to ensure the provision of safe and efficacious treatments for children and adolescents with mental health needs.

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TABLE 1

The Newer Antidepressant Drugs Examined by the FDA

Drug/Manufacturer	Initial FDA Adult Use Approval Dates	FDA Pediatric Approval Dates	Current Approval Status
Prozac (fluoxetine)/Eli Lilly	1987	2003	Approved for adult MDD, OCD, bulimia, and PD Approved for pediatric MDD and OCD
Zoloft (sertraline)/Pfizer	1991	1997	Approved for use in adults with MDD, OCD, PD, PTSD, PMDD, and SAD Approved for pediatric OCD
Paxil (paroxetine)/GlaxoSmithKline	1992		Approved for use in adults with MDD, OCD, PD, SAD, GAD, and PTSD Not recommended for use in pediatric populations
Luvox (fluvoxamine)/Solvay	1994	1997	Solvay Pharmaceuticals, Inc, voluntarily requested discontinued use as antidepressant in the United States in 2002 for commercial reasons
Celexa (citalopram)/Forest	1998		Approved for use in adult MDD
Wellbutrin (bupropion)/ GlaxoSmithKline	1985		Approved for use in adult MDD
Effexor (venlafaxine)/Wyeth	1993		Approved for adult MDD, GAD, and SAD Wyeth-Ayerst voluntarily labeled as not recommended for use in pediatric patients in 2003
Serzone (nefazodone)/Bristol-Myers Squibb	1994		Bristol-Myers Squibb voluntarily discontinued sales in 2004 in the United States for commercial reasons
Remeron (mirtazapine)/Organon	1996		Approved for adult MDD

OCD indicates obsessive compulsive disorder; PD, panic disorder; PTSD, posttraumatic stress disorder; PMDD, premenstrual dysphoric disorder; SAD, social anxiety disorder; GAD, generalized anxiety disorder.