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Risk of Suicidality During Antidepressant Treatment of Children and Adolescents

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ABSTRACT

This article will review evidence that led the Food and Drug Administration to issue a black-box warning about the risk of suicidality (suicidal thoughts and behavior) in children and adolescents during treatment with antidepressants. Reanalysis of data from randomized clinical trials of antidepressants in the pediatric population revealed a significantly greater risk of suicidality for drug groups (4%) compared to placebo groups (2%) in a sample of approximately 4,000 subjects. There were no completed suicides. The small but statistically significant risk of suicidality was not restricted to subjects being treated for depression. With respect to efficacy, only three (20%) of 15 antidepressant trials submitted to the FDA for pediatric depression demonstrated superiority of drug over placebo. The essential message of the black-box warning is to remind prescribers and consumers about the importance of monitoring patients closely for adverse behavioral changes during the initiation of (or changes in) antidepressant therapy. Implications of the FDA actions for clinical practice will also be addressed.

INTRODUCTION

Since the introduction of the first antidepressant medications more than 40 years ago, the risk of suicide during drug treatment has been an object of clinical interest. The 1960 textbook[1] *Clinical Psychiatry* contains the admonishment that "With beginning convalescence (following the initiation of treatment with tricyclic antidepressants), the risk of suicide once more becomes serious as retardation fades." In the early 1990s the possible contributory role of antidepressants to suicide was revisited as a new class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs), became available. Teichler and colleagues[2] published an article on the emergence of suicidal ideation during treatment with fluoxetine. Following Food and Drug Administration hearings, considerable public debate, and a series of large scale analyses of clinical

Needs Assessment: The finding of a suicidality signal associated with antidepressant treatment of children and adolescents has received considerable attention but remains controversial. Part of the controversy may stem from misunderstanding of the findings. This topic has enormous clinical significance and merits an in depth review.

Learning Objectives:

- Describe the efficacy of antidepressants in pediatric depression.
- Describe the relative risk of suicidality associated with acute trials of antidepressants in children and adolescents.
- Familiarize with the features of an activation syndrome that might signify adverse behavioral reactions to antidepressants or worsening in underlying condition.

Target Audience: Primary care physicians and psychiatrists.

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data,[3-5] the notion that fluoxetine was responsible for increased suicides was rejected by the scientific community. The more straightforward explanation was to attribute observed suicidal thoughts and behavior to the underlying illness, depression, rather than to its treatment. In 2003, concerns about suicidal behavior surfaced again, this time in the pediatric population being treated with paroxetine or other SSRIs. This time an analysis of the available short-term clinical trials data led to a different conclusion; antidepressants are associated with an increased risk of suicidal thoughts and behavior in a small fraction of children and adolescents.

As recounted by Thomas Laughren, MD, of the FDA,[6] the first suicidality signal appeared during an FDA review of a pediatric supplement for paroxetine. Some adverse events that were initially coded as "emotional lability" by the sponsor were suggestive of suicidality. A subsequent analysis based on the actual narrative account of adverse events suggested increased risk of suicidality with paroxetine compared to placebo in trials for pediatric depression. In June 2003, the Medicines and Healthcare Products Regulatory Agency, the British counterpart to the FDA, banned the use of antidepressants, except fluoxetine, in children and adolescents.7 The FDA equivalent of a ban is a "contraindication," a stronger measure than a black-box warning that was ultimately issued in October 2004.

EVIDENCE EXAMINED

The lead author of this article chaired a joint meeting of the Psychopharmacologic Drug and Pediatric Advisory Committees to the FDA in September 2004 to hear evidence on suicidality during treatment of children with antidepressants.[8] This 27-member panel was composed of experts in psychiatry, pediatrics, statistics, and other disciplines, as well as public representatives. These public deliberations were held over the course of 2 days. The committee reviewed various types of data including rigorous clinical trials, epidemiology studies, and anecdotal reports; however, emphasis was placed on double-blind, placebo-controlled studies submitted to the FDA. Another study funded by the National Institute of Mental Health known as the Treatment for Adolescents with Depression Study (TADS) trial was also entered into the analysis.[9] Together there were 24 acute (≤12-week-long) trials with a total of 4,400 participants, all children and adolescents. The majority of the studies were in major depressive disorder (MDD), but also included trials in anxiety disorders, such as obsessive-compulsive disorder (OCD), generalized anxiety disorder, and social anxiety disorder. The antidepressants studied from 1984–2004 were SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), the serotonin norepinephrine reuptake inhibitor (SNRI) velafaxine, and the atypical agents mirtazapine and nefazodone.

Because these studies used different criteria to define suicidal ideation and behavior, a reclassification of the adverse reports was conducted by suicide experts from Columbia University.[10] The goal was to create a standardized and reliable measure of suicidality (ie, ideation, preparatory actions, and attempts). Reasonably conservative criteria were selected to define this variable. For example, self-injurious actions without intent to die (such as superficial wrist cutting that might be seen in borderline personality disorder) were not included. Identification of suicidality was made blind to drug condition (ie, specific active agent or placebo). The recoded data were then reanalyzed by the FDA and presented to the advisory committee for its opinion and advice. The final decisions rested with the FDA.

Suicide trend data showed a decline in youth suicide rates in the United States following the introduction of SSRIs.[11,12] Although a temporal correlation does not prove a causal relationship, the wider use of antidepressants is one of the more viable explanations. Other factors that could account for this downward trend in youth suicide are earlier recognition and other interventions besides medications (such as psychotherapy) for depression and drug abuse, two leading risk factors for suicide.[13]

Despite the emphasis on hard data, some subjective impressions undoubtedly filtered their way into the minds of the committee members. The prevailing opinion expressed by psychiatrists based on their clinical experience was that an intervention with antidepressants (not just fluoxetine) could be lifesaving in pediatric depression. At the other end of the spectrum were reports during the public testimony portion of the hearing that blamed antidepressants for teen suicides. Some bereaved parents told of behavioral changes (eg, irritability and insomnia) in their sons or daughters that seemed to emerge within days or mere weeks of starting SSRI treatment. A conclusion that the treatment, not the illness, was responsible for these unfortunate deaths is hard to substantiate given the level of the data (eg, several anecdotal cases, no controls, short on clinical details). Nevertheless, to completely ignore these tragic stories and dismiss them as implausible is hard to justify from a public safety perspective.

RESULTS

In aggregate, more patients treated with active antidepressants manifested suicidality than those treated with placebo. This difference was highly statistically significant. The rate of

suicidality was 4% among those on active drug compared to 2% on placebo.[14] Another way of expressing this finding is in terms of "risk difference," defined as the risk in the drug group minus the risk in the placebo group. The overall risk difference for SSRIs in pediatric MDD trials was 2% to 3%.[14] Put differently, out of 100 patients treated, one might expect 2–3 patients to have some increase in suicidality due to short-term treatment with SSRIs beyond placebo treatment of the disorder. Importantly, there were no completed suicides among the 4,400 subjects entered in these clinical trials.

The finding of elevated suicidality with a particular drug was independent of the underlying diagnosis of the patients; suicidality was present in subjects being treated for depression or anxiety disorders. The suicidality signal was not limited to a particular chemical class of antidepressants. Rather, it occurred with SSRIs, the SNRI venlafaxine, and atypical antidepressants. Of note, meaningful statistical inferences could not be drawn from individual trials because the sample sizes and corresponding number of adverse behavioral events were not large enough. That caveat notwithstanding, some numerical differences among individual trials are worth noting. Among the 20 studies in depression or anxiety disorders, three individual trials suggested a protective affect against suicidality (ie, lower rate of suicidality compared to placebo). These studies consisted of a fluoxetine trial in depression, a citalopram trial in depression, and a sertraline trial in OCD.[14] Four trials were neutral with respect to suicidality risk on placebo.[14] The majority, 13 studies, showed an elevated suicidal risk ratio ranging as high as 10.1 times placebo for one venlafaxine trial and 6.6 times placebo for one paroxetine trial.[14]

With respect to efficacy, only three (20%) of 15 antidepressant trials submitted to the FDA for pediatric depression demonstrated superiority of drug over placebo.[14] Fluoxetine showed the most consistent superiority over placebo in studies of pediatric depression. One trial of citalopram was positive in pediatric depression.[14] When the data from two separate sertraline trials were pooled, drug was superior to placebo in pediatric depression.[15] In contrast to outcome in pediatric depression, trials in pediatric OCD with fluoxetine, sertraline, and fluvoxamine were all positive.[16] The tricyclic antidepressant and potent serotonin reuptake inhibitor clomipramine also has been shown efficacious in children with OCD.[17,18] Clomipramine was not a subject of the suicidality analysis that focused on newer generation agents.

LIMITATIONS

Although a detailed discussion is beyond the scope of this review, some shortcomings of data bearing on both suicidality risk and efficacy should be noted. The studies were not designed to assess suicidality as an outcome, so a post-hoc analysis was conducted based on recoding of narrative reports. No long-term trials were available to assess risk of suicidality past the acute trial period, so there is no way to know whether the risk diminishes (as would be expected from clinical experience) or not. The studies examined had varied inclusion and exclusion criteria with respect to several clinical variables of interest including presence or history of suicidality. Such information is important for predicting risk and determining whether observed increases in suicidality represented worsening or emergence of symptoms. Although none of the moderator or mediator variables that were examined affected risk estimates, larger sample sizes would be necessary for a more definitive analysis of predictors. Treatment adherence was typically assessed by pill counts rather than by plasma blood levels. For this reason, the presence of antidepressant could not be confirmed in those cases exhibiting suicidal behaviors. It is conceivable that abrupt medication discontinuation (unbeknownst to the treatment team) could have produced adverse behavioral events including suicidality.[19] Some clinical experts have theorized that increased suicidal ideation was an artifact of medication effects on reporting. According to this interpretation, medication might facilitate verbal communication, unveiling latent suicidal thoughts that pre-dated treatment. This would not explain increased suicidal behaviors.

"ARGUMENTS AGAINST ADOPTING A BLACK BOX INCLUDED THE CONCERN THAT IT WOULD HAVE A CHILLING EFFECT ON PRESCRIBING, DENYING MANY PATIENTS APPROPRIATE TREATMENT."

There are several possible explanations for why so many of these trials failed or were negative for pediatric depression. The failed trials are attributable to a high placebo response rate that, in turn, could reflect diagnostic heterogeneity (eg, social adjustment problems rather than MDD) and/or the potency of placebo for these populations. Because parents were involved in the trials, the added family time and focus on the child's problems might have had salutary effects on outcome. The inability of a drug to separate from placebo even when the placebo response was not unduly high would characterize a study as negative. Apart from the obvious explanation of ineffectiveness, unique attributes of the pedi-

atric supplemental trials could have contributed to negative outcomes. An incentive program was developed whereby the FDA granted 6-month extensions on patents for antidepressants already marketed for adults, provided the manufacturer conducted appropriate trials in children and adolescents (Best Pharmaceuticals for Children Act of 2002).[20] Although this was a well-intentioned program to address a crucial gap in knowledge, the sponsors were not required to prove that their drug was superior to placebo in order to receive patent life extension. Undesirable consequences may have been minimal (rather than optimal) sample size requirements and pressure for rapid enrollment. The quality of these studies may have been compromised in the process. Note, however, that not all studies analyzed for suicidality were submitted under this exclusivity mechanism.

ACTIONS

Based on the evidence presented in September 2004, the advisory committee concluded that antidepressants were associated with an increased risk of suicidality in children and adolescents by a vote of 25 yes, one no, and one abstention. This body unanimously recommended that a warning about this finding should apply to all antidepressants independent of chemical class, including those not included in the analysis or yet on the market. The rationale for this decision is that no chemical class or agent studied seemed free from an association with suicidality. Furthermore, the committee was concerned that if individual agents were exempted, prescription traffic might be steered in their direction in the absence of exculpatory safety data. Other recommendations included developing a medication guide for patients and parents and to conduct further research.

By a split 15 to 8 vote, the advisory committee recommended that the FDA issue a black-box warning for all antidepressants in pediatric patients independent of reason for treatment. This action was the subject of intense debate. Arguments against adopting a black box included the concern that it would have a chilling effect on prescribing, denying many patients appropriate treatment. Others acknowledged this possibility, but thought a black box was necessary to ensure that a dialogue between the prescriber, patient, and parent included alternatives to medication. The outcome of the vote might have been different had the advisory committee realized that the number of new prescriptions being written for antidepressants in children had already begun to decline,[21,22] following an extended period of rapid growth.[23] The FDA adopted the advisory committee recommendations, including the black-box warning. The key elements of the FDA warnings and actions are listed in Table 1.[1,2,24]

TABLE 1

FDA WARNINGS AND ACTIONS ON RISK OF SUICIDALITY AMONG CHILDREN AND ADOLESCENTS TREATED WITH ANTIDEPRESSANTS[1,2,24]

- Pooled analysis of short-term clinical trials in children and adolescent revealed greater risk of suicidal thinking and behavior (suicidality) in those receiving antidepressants compared to placebo.
- The average risk of such events in patients receiving antidepressants was 4% compared to the placebo risk of 2%.
- Evidence of increased suicidality was not limited to subjects with major depression.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- These risks should be balanced with clinical need.
- Development of a Med Guide intended to be distributed to patients and parents (or guardians) to provide background information and to help identify potential side effects.

FDA=Food and Drug Administration.

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POSSIBLE MECHANISMS

Table 2 lists some possible explanations for worsening or emergence of suicidality during antidepressant treatment. At first, the finding of increased suicidality with antidepressants seems counterintuitive. One would have expected more suicidality in the placebo group. That would certainly be the prediction if a drug were more effective than placebo in alleviating the symptoms of depression of which suicidality is a cardinal feature. In a scenario wherein an antidepressant is no more effective than placebo, the rate of suicidality would be expected to be about the same as placebo, not higher

TABLE 2

MECHANISMS PROPOSED TO EXPLAIN WORSENING/ EMERGENCE OF SUICIDALITY DURING ANTIDEPRESSANT TREATMENT

- Progression of underlying depression, reflecting inadequate or ineffective drug treatment
- Energizing phenomenon
- Activation syndrome
- Stage shifts (from depression into mania or mixed state)

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with the active drug. In either situation, ineffectiveness of drug treatment cannot fully explain the findings. There are other problems with attributing the suicidality signal to drug ineffectiveness. Despite three trials showing the efficacy of fluoxetine in pediatric depression,[14] the relative risk of suicidality was still higher in the TADS trial.[9] Furthermore, drug treatment was associated with increased rates of suicidality in positive studies in pediatric OCD.

The alternative explanation is that medication is producing behavioral toxicity in susceptible individuals, some of whom express this as suicidal ideation or behavior. Once suicidality is conceptualized as a side effect, then a higher rate in drug versus placebo groups is no longer surprising. The appearance of a suicidality signal outside trials of MDD also becomes comprehensible. In most clinical trials, even with generally well-tolerated medications, the side-effect rate is higher in drug compared to placebo groups. Suicidality may be an extreme or late manifestation of adverse behavior reactions to antidepressants in some children and adolescents. It seems inconceivable that antidepressants would induce suicidality in the absence of other associated or antecedent behavioral changes. This assumption is at the cornerstone of the FDA warnings that urge frequent and careful monitoring for adverse behavioral changes, not just suicidality.

"IT IS HOPED THAT WITH APPROPRIATE DOSING AND CAREFUL MONITORING, THE RISK OF BEHAVIORAL TOXICITY, INCLUDING SUICIDALITY, MAY BE SIGNIFICANTLY REDUCED"

TABLE 3

FDA VISIT FREQUENCY RECOMMENDATIONS[24]

After starting an antidepressant in a child or adolescent, the patient should see his/her doctor:

- Once a week for the first 4 weeks.
- Every 2 weeks for the next month
- At the end of his/her 12th week taking the drug
- More often if problems develop

FDA=Food and Drug Administration.

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The early clinical observation of an energizing effect by tricyclic antidepressants is inculcated into the training of psychiatrists even today as many new antidepressant agents have appeared on the market.1 The interpretation of this conventional wisdom is that depressed patients (particularly ones with psychomotor retardation) may already be harboring suicidal thoughts but lack the will to act on those impulses; that is, until their energy is boosted during the early phases of antidepressant treatment, before mood has lifted. In this formulation, the antidepressant does not induce suicidality rather it restores drive and the capacity to act on suicidal impulses. The at-risk period is purportedly in the first days or weeks of antidepressant therapy.

Some children may experience an "activation syndrome" characterized by agitation, insomnia, irritability, and other disturbing symptoms[25-27] that if unrecognized could conceivably lead to impulsive actions including suicidality. A similar phenomenon of paradoxical worsening has been observed in adults with anxiety disorders, particularly those with panic disorder.[28,29] Clinicians are well advised to start such patients on lower doses of antidepressants than typically used for initiating treatment in depression. It is commonplace to warn such patients that they might feel worse before they feel better. An adolescent not advised of such untoward effects might misinterpret the event as a sign of deterioration (of their underlying illness) rather than a transient medication side effect. That individual might come to the incorrect conclusion that treatment is futile, and therefore descend further into despair. Combine that aggravated emotional state and cognitive misappraisal with teenage impulsivity, and the result consists of the ingredients for a negative outcome. Child psychiatrists have long recognized that their patients need to have their SSRIs dosed lower and more gradually escalated in order to minimize triggering an activation syndrome.[25,30]

It is axiomatic that all antidepressants are capable of inducing mania in susceptible individuals.[31] Antidepressants are administered with caution to depressed adults with a personal or family history of bipolar disorder out of concern for triggering mania. Perhaps some of the children and adolescents who exhibited suicidality during clinical trials of antidepressants possessed a similar biological vulnerability. Their symptoms may have reflected a state shift induced by the antidepressants.[32] The diagnosis of bipolar disorder in children and adolescents is challenging[33,34] and so one might wonder whether some cases made their way into these trials of depression and anxiety disorders, partially accounting for adverse behavioral reactions, including suicidality.[35] Mixed state mania is associated with high rates of suicidal behavior.[31,36] Compared to the adult literature, however, the evidence for antidepressant-induced mania in children is less consistent.[37]

Individual susceptibility to SSRI side effects may reflect gene-drug interactions. A study in adults found that a polymorphism in the serotonin transporter gene confers a greater risk of side effects to SSRI therapy.[38] Patients who are slow metabolizers at the cytochrome P450 2D6 isoenzyme might have reduced clearance of a drug (eg, paroxetine or fluoxetine), resulting in higher plasma (and brain) levels with a given administered dose.[39] Variants in either pharmacodynamic (eg, serotonin transporter polymorphisms) or pharmacokinetic (eg, slow hepatic biotransformation) handling of an antidepressant may contribute to idiosyncratic reactions to antidepressants. The pharmacokinetic factors can be dealt with by lowering the dose or selecting a different agent. Pharmacogenetic studies are needed to investigate these possibilities in children and adolescents. Genetic testing prior to instituting therapy could then allow a better prediction of which patients are most likely to encounter side effects.

Clinical Implications

The essence of these and earlier warnings by the FDA is to remind prescribers and consumers about the importance of monitoring closely for behavioral changes (eg, "activation syndrome" or state shift into mania) during the initiation of (or changes in) antidepressant therapy. Abruptly stopping antidepressants may cause behavioral problems, exposing the patient to the risk of withdrawal symptoms[40,41] or relapse.[42] It is hoped that with appropriate dosing and careful monitoring, the risk of behavioral toxicity, including suicidality, may be significantly reduced. Since the introduction of fluoxetine and other SSRIs, child psychiatrists have been aware of the activation syndrome and have altered their practice by starting at lower doses, increasing doses more gradually, warning the patient and parent about possible side effects, and frequently monitoring for changes in behavior. These are all elements of the black-box warning meant to underscore a set of practice guidelines that need to be followed by all prescribers.

Table 3 lists the specific visit frequency recommendations that appear in the medication guide developed by the FDA.[24] In some situations (such as geographic or financial barriers) that affect access to care, these requirements may prove onerous. The authors of this article believe that some relaxation of this visit frequency may be made when the patient is also seeing a therapist or counselor. In such cases, the therapist should stay in close communication with the prescriber.

According to the energizing hypothesis (described earlier), the early days or weeks of antidepressant administration correspond to the period of highest risk for suicidality during antidepressant therapy. Some empirical data support this observation. Jick and colleagues[43] conducted a matched case-control study in a base population of nearly 160,000 primary care physicians in the United Kingdom. The relative risk for suicidal behavior and completed suicides was significantly higher for the first 1–9 days of antidepressant treatment compared to after 90 days on medication.[43] The FDA analysis of the extant pediatric clinical data did not reveal similar differences in rates of suicidality when early and late phases of treatment were compared. The sample size may have been insufficient to detect a difference.

There is no universal agreement on what signs and symptoms to include under the rubric of the so-called activation syndrome. Furthermore, there is lack of nosologic consensus on how to distinguish this putative syndrome from akathisia (psychomotor restlessness). Akathisia is usually divided into subjective (inner restlessness and urge to move) and objective components (eg, foot lifting while sitting).[44] For the purposes of this article, the activation syndrome will be broadly defined to include signs and symptoms that might also be manifestations of akathisia or state-shifts into mania. The point is to be vigilant for signs that might reflect adverse behavioral effects of antidepressants. Accordingly, signs and symptoms of the activation syndrome may include agitation, anxiety, panic attacks, irritability, jitteriness, restlessness, hostility, aggressiveness, insomnia, disinhibition, emotional lability, impulsivity, social withdrawal, akathisia (psychomotor restlessness), hypomania, mania, or psychosis (eg, decreased need for sleep, risk-taking behavior, talkativeness, pressured speech, grandiosity, ideas of reference or paranoia).

The aforementioned constellation of symptoms may or may not reflect adverse effects of the drug. Instead, these symptoms may signify worsening or progression of the underlying psychiatric condition and the failure of the drug to prevent this deterioration. Whatever the origin, the concern remains that these signs of instability might be associated with an increased risk of suicidality. Further empirical research is needed to test whether (and how well) the activation syndrome (or its individual components) predicts suicidality.

There may be some clinical parallels between antipsychotic-induced akathisia and antidepressant-induced activation. Although antipsychotics are usually responsible for inducing akathisia, SSRIs have also been implicated in this syndrome.[45,46] Some authors have suggested a connection between akathisia and suicidality.[45,46] The principal lesson from antipsychotic therapy is that motor restlessness must not be mistaken for worsening of the underlying disease and treated with an increased dose of antipsychotic when, in fact, it represents an iatrogenic extrapyramidal syndrome. The correct response is to lower the antipsychotic dose, switch to a different medication, or add a medication (eg, β-blocker) to suppress akathisia.[44]

By the same token, the first thought of the clinician noting increased activation or agitation in a child recently placed on an SSRI should be, "Could these changes represent medication side effects?" If so, the symptoms should be dealt with by lowering or holding the dose rather than by raising the dose. The precept to follow for dosing antidepressants (particularly SSRIs) in children is "start low, go slow."

Deciding whether to recommend a drug treatment or not depends on assessment of both risk and benefit. In the case of adults with depression, the calculation of the risk-to-benefit ratio is more straightforward because the benefit of antidepressants is so well-established both in acute and long-term trials.[47] With the advent of alternatives to the tricyclic antidepressants (eg, SSRIs), tolerability and safety (including risk of death from overdose) have greatly improved.[48,49] Cost effectiveness is another consideration but one that is beyond the scope of this review.[50] The dilemma facing medication treatment in pediatric depression is that apart from fluoxetine (which has an FDA indication in children down to 7 years of age) the available evidence supporting antidepressant efficacy is negative or weak.[51] On the other hand, the preponderance of clinical experience suggests antidepressants are often effective in the long-term management of pediatric depression.[52] The paucity of empirically derived long-term outcome data on antidepressants in children and adolescents marks a major gap in our knowledge.[53]

While acknowledging deficiencies in our database, the risk of suicide from untreated depression seems to outweigh the risk of suicidality (remember this does not equal suicide) ascribed to antidepressants in pediatric trials. In patients ever hospitalized with affective disorders and suicidality, the risk of suicide is 8.6%.[54,55] Suicide is the third leading cause of death in adolescents.[56,57] Reducing the suicide rate has become both a national and state priority.[58] Depression is a major risk factor for suicide in adolescents.[11,59] Other psychiatric comorbidities,[11,60] substance abuse,[11,61] and socioenvironmental[62] circumstances are also associated with elevated suicide risk in children and adolescents. Taking appropriate steps in the management of antidepressants (as discussed earlier) may reduce the incidence and mitigate the magnitude of behavioral side effects. In the final analysis, the clinical condition of the individual case will help determine whether to prescribe or not. In the case of pediatric OCD, the benefits of several SSRIs (fluoxetine, sertraline, and fluvoxamine) and clomipramine are better established.[17,18]

The black-box warning has received tremendous attention from the media, professionals, and consumers. Unfortunately, its ominous-sounding ring seems to have overshadowed its more measured cautionary content. The black box does not constitute a contraindication against antidepressants in the pediatric population. Some special interest groups have reframed the message in ways that advance their own anti-psychiatry agenda.[63] The black box does not say that the risk of suicidality from antidepressants is greater than the risk of suicide from untreated depression. The opposite appears true: depression is the leading risk factor for teen suicide in both boys and girls.[11,59] Post mortem data disclose that the vast majority of youth suicide victims have no detectable levels of antidepressant in their bodies.[64] The black box says to exercise caution while prescribing and to inform the patient and parent about warning signs and alternatives. An alternative that warrants strong consideration is cognitive therapy.[65] The number of new prescriptions for antidepressants in children has fallen.[21,22] Time will tell whether this trend will be beneficial or detrimental to patient welfare. Excessive alarm and misunderstanding about the antidepressant-suicidality controversy may deter appropriate medical treatment of not only depression, but of all pediatric psychiatric conditions. Other ramifications are fueling frivolous lawsuits and driving up the costs of malpractice insurance. The most dreaded unintended consequence of the black-box warning could be the damper it places on new and much needed clinical trials in the pediatric population.

CONCLUSION

The central message of the FDA warnings is to remind prescribers and consumers about the importance of monitoring closely for adverse behavioral changes (especially the so-called activation syndrome) during the initiation of (or changes in) antidepressant therapy in children and adolescents. A small minority of patients (on the order of 2% to 3%) seems prone to suicidality when defined as increased suicidal ideation or behaviors.[14] Future studies of clinical or biological markers may allow a better prediction of which pediatric patients are most liable to show behavioral sensitivity to antidepressants. In the meantime, the decision whether to prescribe antidepressants or not to a child or adolescent should be based on careful weighing of benefit and risk (of both the treatment and the illness) given the facts of the particular case. In principal, this decision-making process is no different from most treatment situations. It is made harder, of course, because we are dealing with a vulnerable population. Additionally, the findings are hard to fathom because they defy the popular impression that SSRIs are harmless. Our gravest deficiency is the paucity of empirical data on long-term outcome with antidepressants in pediatric depression. Most experienced clinicians (including the authors of this study) are convinced that antidepressants often ease the suffering and sometimes spare the lives of children and adolescents afflicted with depression. *PP*

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