Psychopharmacology (2007) 191:87–96
DOI 10.1007/s00213-006-0642-6

REVIEW

Risk of adverse behavioral effects with pediatric use of antidepressants

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Received: 16 May 2006 / Accepted: 6 November 2006 / Published online: 19 December 2006

Abstract
Objectives This article reviews 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.
Results Re-analysis of data from randomized clinical trials of antidepressants in the pediatric population revealed a significantly greater overall (all drugs across all indications) risk ratio for drug 1.95 (95% Cl, 1.28–2.98) compared to placebo in this sample of approximately 4,000 subjects.
Discussion The essential message of the "black box" is to remind prescribers and consumers about the importance of monitoring closely for adverse behavioral changes during the initiation of (or changes in) antidepressant therapy. Possible mechanisms that might account for this phenomenon, particularly the so-called activation syndrome, are discussed.
Conclusion Empirical studies are needed to identify the precursors of suicidality and to predict which individuals are most susceptible to adverse behavioral side effects of antidepressants.

Keywords Children · Adolescents · Antidepressants · SSRIs · Fluoxetine · Obsessive compulsive disorder · OCD · Depression · Activation syndrome · Suicide · Suicidality · Black box · FDA

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The recent controversy surrounding whether antidepressants promote suicidality in some children and adolescents has created a dilemma for clinicians, patients, and parents who must weigh the relative benefits and risks of these agents. Foremost, there is the grave risk of the underlying psychiatric disorder. Suicide is the third leading cause of death in adolescents (Brent et al. 1999; Pfeffer et al. 1991), and reducing the suicide rate has become both a national and state priority (Florida 2005). Depression is a major risk factor for suicide in adolescents (Olfson et al. 2003; Shaffer et al. 1996). Other psychiatric comorbidities (Olfson et al. 2003), substance abuse (Erinoff et al. 2004; Olfson et al. 2003), and socioenvironmental (Gould et al. 1996) circumstances are also associated with elevated suicide risk in children and adolescents. One way of reducing suicide is to identify the factors or conditions that predispose to suicide. To the extent that antidepressants are effective in treating the underlying affective or anxiety disorder, prevention/amelioration of suicidal thinking or behavior (collectively referred to as suicidality) is a reasonable expectation.

However, there are questions about the efficacy of antidepressants in depressed children and adolescents. Only one antidepressant [the selective serotonin reuptake inhibitor (SSRI) fluoxetine] has been proven efficacious for pediatric depression (for pediatric obsessive–compulsive disorder (OCD), more Food and Drug Administration (FDA)-approved options exist). Decision-making about the appropriate circumstances for prescribing antidepressants is further complicated by evidence (reviewed below) that antidepressants may contribute to the risk of suicidality in a small fraction of children and adolescents (who participated in clinical trials for several psychiatric conditions) when compared to placebo treatment. At first, this possibility seems counterintuitive.

In this article, we review the evidence that led the FDA to issue warnings about suicidality during pediatric use of antidepressants and discuss possible mechanisms responsible for this phenomenon. We suggest that induction of activation syndrome by antidepressants in susceptible individuals may confer risk for development of suicidality.

Brief history For more than 40 years, the risk of suicide during antidepressant drug treatment has been the subject of debate. In their textbook, Mayer-Gross et al. (1960) warns 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, namely, the SSRIs, became available. Teicher et al. (1990) published an article on the emergence of suicidal ideation during treatment with fluoxetine. After FDA hearings, considerable public debate, and a series of large-scale analyses of clinical data (Beasley et al. 1992; Khan et al. 2001; Storosum et al. 2001), the notion that fluoxetine was responsible for the increased suicides was rejected by the scientific community. The more straightforward explanation was to attribute observed suicidal thoughts and behavior to the underlying illness and 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 Dr. Thomas Laughren of the FDA (Laughren 2004), 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, British counterpart of the FDA, banned the use of antidepressants, except fluoxetine, in children and adolescents. The FDA equivalent of a ban is a "contraindication", a stronger measure than a "black box" warning that was ultimately issued in October 2004. A move to contraindicate the use of antidepressants (other than fluoxetine) in child and adolescents was not entertained by the FDA advisory panels that deliberated on this issue.

Evidence examined One of the authors (WKG) 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. Although the Committee reviewed various types of data—ranging from rigorous clinical trials to epidemiology studies to anecdotal reports—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 (March et al. 2004). Together, there were 24 acute (up to 16-week-long) trials with a total of 4,582 child and adolescent participants. The majority of the studies were in major depression, but they also included trials in anxiety disorders: OCD, generalized anxiety disorder, and social phobia. The antidepressants studied were SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), the serotonin and norepinephrine reuptake inhibitor venlafaxine, and the atypical agents mirtazapine and nefazodone over the period from 1983 to 2004.

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 (Posner 2004). The goal was to create a standardized and reliable measure of suicidality (i.e., 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, which might be seen in Borderline Personality Disorder) were not included. Identification of suicidality was made blind to drug condition (i.e., specific active agent or placebo). The re-coded data were then re-analyzed by the FDA and presented to the Advisory Committee.

Suicide trend data were presented, which showed a decline in youth suicide rates in the USA after the introduction of SSRIs (Hall et al. 2003; Olfson et al. 2003). Although a temporal correlation does not prove a causal relationship, the wider use of antidepressants is one of the more plausible 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 (IOM 2002).

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. Unfortunately, there is a paucity of published empirical data to support this clinical impression on the long-term efficacy of antidepressants in depressed children and adolescents. 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 (e.g., irritabil-

ity and insomnia) in their son or daughter that emerged within days or a few weeks of starting SSRI treatment and seemed to presage the suicidal act.

Results In aggregate, more patients treated with active antidepressants manifested suicidality (defined as above) than those treated with placebo. This difference was statistically significant. The overall risk ratio for all drugs for all indications was 1.95 (95% Cl, 1.28–2.98). Another way of expressing this finding is in terms of risk difference (RD), defined as the risk in the drug group minus the risk in the placebo group. The overall RD for SSRIs in pediatric major depression trials was 1 to 3% (Hammad et al. 2006). Put differently, out of 100 patients treated, one might expect 2 to 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 4,582 subjects entered in these clinical trials.

Meaningful statistical inferences could not be drawn from individual trials about specific indications or specific agents because the sample sizes and corresponding number of adverse behavioral events were insufficient. That caveat notwithstanding, the finding of elevated suicidality appeared to be independent of the underlying diagnosis of the patients: It was present in subjects being treated for depression or anxiety disorders. Although the suicidality signal did not appear limited to a particular chemical class of antidepressants, 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 (i.e., lower rate of suicidality compared to placebo): a fluoxetine trial in depression, a citalopram trial in depression, and a sertraline trial in OCD (Hammad et al. 2006). Four trials were neutral with respect to suicidality risk on placebo (Hammad et al. 2006). The majority, 13 studies, showed an elevated suicidal risk ratio, reaching as high as 10.1 times placebo for one venlafaxine trial and 6.6 times placebo for one paroxetine trial (Hammad et al. 2006).

With respect to efficacy, only 3 (20%) of 15 antidepressant trials submitted to the FDA for pediatric depression demonstrated superiority of drug over placebo (Hammad et al. 2006). Fluoxetine showed the most consistent superiority over placebo in studies of pediatric depression (Hammad et al. 2006). One trial of citalopram was positive in pediatric depression. When the data from two separate sertraline trials were pooled, drug was superior to placebo in pediatric depression (Wagner et al. 2003). In contrast to outcome in pediatric depression, trials in pediatric OCD with fluoxetine, sertraline, and fluvoxamine were all positive. Clomipramine, a tricyclic antidepressant and potent SRI, also has been shown efficacious in children with OCD (Jermain and Crismon 1990; Leonard et al. 1989); it was not a subject of the suicidality analysis that focused on newer generation agents.

Limitations Important shortcomings of data bearing on both suicidality risk and drug efficacy should be noted. The main outcome variable "suicidality" was a construct formed by post-hoc analyses on recorded spontaneous narrative reports (adverse event reporting). As such, the sensitivity and specificity of this measure within and across trials is uncertain. We have more reason to be confident in the measure's inter-rater agreement, an index of reliability, than in its validity. Prospective ratings of suicidal ideation were available for 17 individual drug trials, which included a depression rating scale with a suicide item score. Meta-analysis for these trials did not reveal a signal for excess suicidality for drug compared to placebo (Hammad et al. 2006). The reason for this divergence is unclear, but could be related to lack of temporal correspondence between scheduled ratings and actual timing of emergence of suicidality, as ascertained by adverse event reporting (Hammad et al. 2006). 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. 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 (unbeknown to the treatment team) could have produced adverse behavioral events including suicidality (Weiss and Gorman 2005). 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 theory would not explain increased suicidal behaviors.

Several explanations are possible 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 (e.g., social adjustment problems rather than major depression), which is a challenge in studies of pediatric depression. Because of the level of parental involvement required for study participation, the placebo condition might have been rendered more potent by the

enhanced family time and focus on the child's problems. Additionally, unique attributes of the pediatric supplemental trials could have contributed to fewer positive outcomes. An incentive program was developed whereby the FDA granted 6-month extensions on patents for antidepressants already marketed for adults, provided that the manufacturer conducted appropriate trials in children and adolescents, the Best Pharmaceuticals for Children Act of the US Congress (2002). Although this is a well-intentioned mechanism to address a crucial gap in knowledge, the sponsors were not required to prove that their drug was superior to placebo to receive patent life extension. Implicitly, the emphasis was more on confirming safety than establishing efficacy. It is conceivable that this softening of the endpoint may have led to less ambitious trials (e.g., lower cost and limited power to detect drug–placebo differences) than would have been the case had the stakes been higher (e.g., beyond 6-month extension) and if drug needed to win over placebo. Note, however, that not all studies analyzed for suicidality were submitted under this exclusivity mechanism. Finally, it is worth noting that the FDA criteria for calling a study "positive" may be more stringent than those used in other quarters. Some studies that did not pass the high bar set by FDA might have otherwise been viewed as positive among the general scientific community.

Recommendations and FDA 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", 1 "no" and 1 "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 of appropriate treatment. Others acknowledged this possibility but thought a "black box" was necessary to ensure that a dialog took place between the prescriber, the patient, and the parent that included alternatives to medication. Perhaps 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 (Murray et al. 2005; Rosack 2005) after an extended period of rapid growth (Delate et al. 2004). The FDA adopted the Advisory Committee recommendations including the "black box" warning. In retrospect, perhaps it would have been better to place emphasis on the risk of a cluster of potentially serious adverse behavioral effects (including suicidal ideation and behavior) rather than on suicidality, an invented term (not found in the dictionary) simplified to suicide in the public eye, regardless of the effort to explain its intended meaning.

Theoretical explanations Table 1 lists some of the explanations for worsening or emergence of suicidality during antidepressant treatment. Initially, the finding of increased suicidality with antidepressants seems counterintuitive. One would have expected more suicidality in the placebo group if drug were more effective than placebo in alleviating depression, the presumed underlying cause of suicidality. However, among three trials that demonstrated efficacy of fluoxetine in pediatric depression, the relative risk of suicidality was still higher with drug in one of them, the TADS trial (Hammad et al. 2006). Despite generally favorable efficacy in pediatric OCD, drug was associated with increased rates of suicidality in several of these trials (Hammad et al. 2006). These disconnects suggest that drug ineffectiveness is insufficient to explain the overall association of drug with risk of suicidality compared to placebo.

The alternative explanation is that medication is producing "behavioral toxicity" (Carlson 2005; Carlson and Mick 2003) 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 vs placebo groups is no longer surprising. The appearance of a suicidality signal outside trials of major depression 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

Table 1 Principal theoretical explanations for worsening/emergence of suicidality during antidepressant treatment

Explanations
Progression of underlying depression, reflecting inadequate or ineffective drug treatment
Energizing phenomenon
Activation syndrome
Akathisia
Stage shifts (from depression into mania or mixed state)
Idiosyncratic reactions (e.g., due to gene–drug interactions)

be an extreme or late manifestation of adverse behavior reactions to antidepressants in some children and adolescents along with some adults (GlaxoSmithKline 2006). 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.

The early clinical observation of Mayer-Gross et al. (1960) 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. The interpretation of this conventional wisdom is that depressed patients (particularly the 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. This possibility cannot be summarily rejected. However, with the notable exception of children with bipolar depression (Mitchell and Malhi 2004), psychomotor retardation is not a common manifestation of pediatric depression.

During the course of SSRI treatment, some children may experience an "activation syndrome" characterized by agitation, insomnia, irritability, brittle mood, and other signs of hyperarousal (Carlson 2005; Go et al. 1998; Guile 1996; Walkup and Labellarte 2001) that, if unrecognized, could conceivably foster suicidality. A similar phenomenon of paradoxical worsening has been observed in adults with anxiety disorders, particularly with panic disorder (Gieseck 1990; Schneier et al. 1990). Clinicians are advised to start such anxiety 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. One can speculate that that individual might come to the incorrect conclusion that treatment is futile and descend further into despair. Academic child psychiatrists have cautioned clinicians about appropriately dosing SSRIs to minimize triggering activation syndrome (Guile 1996; King et al. 1991). Apart from this handful of reports, the scarcity of empirical literature on activation syndrome stands in contrast to the robustness of the clinical lore on this subject. Distinguishing activation syndrome from the energizing phenomena may prove operationally difficult. Conceptually, they are quite different in the way they portray the role of antidepressants. Activation syndrome implies (at least transient) behavioral toxicity, whereas the energizing hypothesis suggests that patients are along the path toward recovery but their mood has yet to respond.

Consensus is lacking on how to distinguish activation syndrome from "akathisia" (psychomotor restlessness). Akathisia is usually divided into subjective (e.g., inner restlessness and urge to move) and objective components (e.g., knee bobbing while sitting; Miller and Fleischhacker 2000). 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 (Akagi and Kumar 2002; Hansen 2001). Some authors have suggested a connection between akathisia and suicidality (Akagi and Kumar 2002; Hansen 2001). An instructive 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 (e.g., beta-blocker) to suppress akathisia (Miller and Fleischhacker 2000). We prefer not to use the term akathisia interchangeably with activation syndrome because the former implies a known neuroreceptor mechanism (e.g., dopamine-receptor blockade) that may or may not apply to SSRIs.

It is axiomatic that all antidepressants are capable of inducing mania in susceptible individuals (Post 2005). 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 (Carlson 2005). The diagnosis of bipolar disorder in children and adolescents is challenging (Biederman et al. 2003; Wagner 2004), 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 (Dilsaver et al. 2005). Mixed state mania is associated with high rates of suicidal behavior (Akiskal et al. 2005; Post 2005). Compared to the adult literature, however, the evidence for antidepressant-induced mania in children is less consistent (Craney and Geller 2003). State-shifts into mania may be recognizable by qualitatively distinct features that include euphoria or grandiosity and hypersexuality (Youngstrom et al. 2005).

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 (Perlis et al. 2003). Patients who are slow metabolizers at the cytochrome P450 2D6 isoenzyme might have reduced clearance of drug (e.g., paroxetine or fluoxetine), resulting in higher plasma (and brain) levels with a given administered dose (Brosen 2004). Variants in either pharmacodynamic (e.g., serotonin transporter polymorphisms) or pharmacokinetic (e.g., slow hepatic biotransformation) handling of an antidepressant may contribute to idiosyncratic reactions to antidepressants. The pharmacokinetic factors can be dealt with by lowering dose or selecting a different agent. Pharmacogenomic studies are needed to investigate these possibilities in children and adolescents. Genetic testing before instituting therapy could then allow a better prediction of which patients are most likely to encounter side effects.

A central lesson of the scientific debate on antidepressants and suicidality is the hazard of extrapolating from psychopharmacologic experience in adults to applications in children. Susceptibility to and nature of SSRI-induced behavioral side effects may be a function of brain maturation and vary according to the age of the patient (Gross et al. 2002). The clinical observation that children are more sensitive than adults to the behavioral effects of SSRIs is not surprising, given pre-clinical studies showing that serotonergic function varies during post-natal development (Gross et al. 2002) and that the serotonin system plays a critical role in emotional maturation (Ansorge et al. 2004). Recent studies in laboratory animals suggest differential behavioral responsiveness to fluoxetine depending on whether the animal is juvenile or adult that, in turn, reflects the developmental stage of the serotonergic system (Taravosh-Lahn et al. 2006). Clinical studies of neurocognitive function have shown that selective inhibition varies across the life span (Bedard et al. 2002).

Characterizing activation syndrome Based on a review of the extant literature, the clinical experience of the authors, and discussions at the FDA hearings, the signs and symptoms that may signal adverse behavioral effects of antidepressants, particularly SSRIs, include irritability, agitation, somatic manifestations of anxiety, panic attacks, restlessness, hostility, aggressivity, insomnia, disinhibition, emotional lability, impulsivity, social withdrawal, conventional akathisia (psychomotor restlessness), odd behavior, hypomania/mania, paranoia, or other psychotic symptoms. The FDA generated a similar list for their Med Guide (2005), which instructs parents to contact their child's healthcare provider immediately if the child exhibits any of the following signs: new or worse anxiety, feeling very agitated or restless, panic attacks, insomnia, new or worse irritability, excitability, acting aggressive, being angry or violent; acting on dangerous impulses, extreme increase in activity and talking, and other unusual changes in behavior or mood (FDA 2005).

At this early stage of descriptive work, it seems reasonable to cast a wide net for activation syndrome. As a first approximation, we propose defining activation syndrome broadly to include this entire constellation of signs and symptoms. This liberal interpretation is done with the understanding that some symptom clusters under this larger umbrella called *activation syndrome* may be better explained as akathisia or a stage shift in mania. We suspect, however, that these two distinct mechanisms (akathisia and mania) will account for a relatively small portion of the variance. In contrast, the remaining uncategorized signs and symptoms may reflect the majority of (i.e., most frequent) adverse behavioral effects observed during SSRI treatment. Whether they are the most important symptoms with respect to promoting suicidality risk is another question that will have to await future study on large patient samples.

How one defines activation syndrome, broadly or narrowly, will determine what constructs are included or excluded. Even excluding akathisia and mania, the constellation of signs and symptoms represented by the appellation activation syndrome may not represent a unitary diathesis. To increase specificity, we can select a discrete set of constructs for which there exist reliable and valid behavioral, neuropsychological, or psychophysiologic measures such as irritability (Leibenluft et al. 2003) or disinhibition/impulsivity (Biederman et al. 1998; Carlson and Mick 2003; Wilens et al. 1998). Examination of these constructs can help point to the possible underlying pathophysiology. For example, irritability can be understood as reactive aggression, and certain behavioral paradigms (e.g., evoking frustration) can help disclose its neurocircuitry (Leibenluft et al. 2003). The phenomenology of irritability matches many of the manifestations of activation syndrome.

Some of the symptoms described under the rubric of activation syndrome 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 better distinguish between behavioral side effects and manifestations of the underlying psychiatric condition.

Underlying neurobiological mechanisms Studies of the effects of acute and chronic administration of SSRIs in laboratory animals may provide insights to the neurobiology of activation syndrome. Electrophysiological studies suggest that chronic SSRI administration (in a time frame

corresponding to the delayed clinical response observed in humans) induces adaptive neuronal changes and a resulting net enhancement in serotoninergic (5-hydroxytryptamine; 5-HT) function (Blier and de Montigny 1998). In contrast, sub-acute administration of SSRIs does not affect net 5-HT function. Increased availability of synaptic 5-HT [secondary to 5-HT transporter (SERT) blockade by the SSRI] is rapidly counterbalanced by a decrease in firing rate, resulting from 5-HT_{1A} autoreceptor activation so that net 5-HT function is neither increased nor decreased (Blier and de Montigny 1998). Thus, the notion that suicidality or activation may reflect disinhibition secondary to diminished 5-HT activity during the first days or 2 weeks of SSRI administration is not consistent with the preclinical literature. However, other acute changes in brain regional 5-HT receptor sensitivity might help explain the phenomenon of activation syndrome. These possibilities include increased sensitivity of 5-HT2 or 5-HT3 receptors (Blier, 2005, personal communication).

Timing of behavioral side effects 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 et al. (2004) conducted a matched case-control study in a base population of nearly 160,000 general practice physicians in the UK. 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 (Jick et al. 2004). 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. However, the sample size may have been insufficient to detect a difference (Hammad, 2005, personal communication). Activation syndrome is typically described as occurring soon after the start of SSRI administration or after dose increases (Walkup and Labellarte 2001). This observation is reflected in the content of the FDA warnings.

More recently, Simon et al. (2006) used a large population-based data set to evaluate the risk of suicide death and serious suicide attempts (i.e., requiring hospitalization) in relation to initiation of antidepressant treatment. In accord with the Jick et al. (2004) study, the risk of a suicide attempt was higher in the first week of antidepressant treatment compared to subsequent weeks (Simon et al. 2006). The authors interpret the progressive decline in suicide attempts following the index prescription as mirroring the time course of expected improvement in depression. They state that the temporal pattern of suicide attempts "appear more consistent with a decline in risk after initiation of treatment than with a medication-induced increase " (Simon et al. 2006). Their data do not rule out precipitation of suicidality by antidepressants in a subgroup of susceptible patients that is otherwise masked by a broader benefit.

Clinical implications 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 (Geddes et al. 2003). With the advent of alternatives to the tricyclic antidepressants—such as the SSRIs—tolerability and safety (including risk of death from overdose) have greatly improved (MacGillivray et al. 2003; Thase 2003). The dilemma facing medication treatment in pediatric depression is that apart from fluoxetine (as an FDA indication in children down to age 7 years), the available evidence supporting antidepressant efficacy is negative or weak (Whittington et al. 2004). On the other hand, the preponderance of clinical experience suggests antidepressants are often effective in the long-term management of pediatric depression (Richmond and Rosen 2005). The paucity of empirically-derived long-term outcome data on antidepressants in children and adolescents marks a major gap in our knowledge (Wagner 2005).

In contrast to pediatric depression, where only fluoxetine has been shown effective, four different antidepressants—the SSRIs (fluoxetine, sertraline and fluvoxamine) and clomipramine (Jermain and Crismon 1990; Leonard and Rapoport 1989)—have proven efficacy in pediatric OCD. For this reason, the overall risk-to-benefit ratio is more favorable for use of SSRIs in OCD compared to depression. Nevertheless, when the OCD and anxiety studies were analyzed in aggregate, the relative risk for suicidality appeared elevated (2.17, 95% Cl, 0.72–6.48; Hammad et al. 2006).

The message of "black box" has been misunderstood by the media and misrepresented by psychiatry watchdog groups. It does not say that the risk of suicidality from antidepressants is greater than the risk of suicide from untreated depression. The opposite appears to be true: The risk of suicide from untreated depression seems to outweigh the risk of suicidality ascribed to antidepressants in pediatric trials. Depression is the leading risk factor for teen suicide in both boys and girls (Olfson et al. 2003; Shaffer et al. 1996). Post-mortem data disclose that the vast majority of youth suicide victims have no detectable levels of antidepressant in their bodies (Leon et al. 2004, 2006). The "black box" says to exercise caution while prescribing and to inform the patient and parent about warning signs and alternatives. Taking appropriate steps in the management of antidepressants may reduce the incidence and

attenuate the magnitude of behavioral side effects that could lead to suicidality. An alternative treatment for depression that warrants strong consideration is cognitive–behavioral therapy (Brown et al. 2005; March et al. 2004). The number of new prescriptions for antidepressants in children has fallen (Rosack 2005). Time will tell whether this trend will be beneficial or detrimental to patient welfare (Ludwig and Marcotte 2005). Unfortunately, excessive alarm and misunderstanding about the antidepressant–suicidality controversy may deter appropriate medical treatment of not only depression but also of all pediatric psychiatric conditions, including those where the benefit-to-risk ratio is more favorable.

Subsequent to the FDA hearings, the Columbia group conducted a matched case-control study (Olfson et al. 2006) to estimate the relative risk of suicide attempt and suicide death in depressed children treated with antidepressants vs those not treated with antidepressants. The cases were drawn from Medicaid beneficiaries from all 50 states who received in-patient treatment for depression, a proxy for severity. In children and adolescents, antidepressant drug treatment was significantly associated with suicide attempts and suicide deaths. In contrast, adults who received antidepressants were not at higher risk of suicide attempts or suicide deaths. These findings support careful clinical monitoring (as recommended by the FDA) during antidepressant treatment of youth with severe depression.

Conclusion A re-analysis by FDA of pediatric clinical trials (N=4,582) in psychiatric conditions found that the relative risk ratio of suicidal ideation and behavior was modestly elevated at 1.95 (95% Cl, 1.28–2.98) when all studies, type of drug, and indications were examined in aggregate. These data revealed that this suicidality signal was not limited to depression: Subjects with OCD and other anxiety disorders also exhibited a higher risk. Although the mechanism responsible for this effect is unknown, induction of an "activation syndrome" (e.g., irritability, disinhibition, restlessness, etc.) may represent an intermediary state change that promotes suicidality. SSRI-induced activation syndrome is well accepted by clinicians and thought to be common, particularly in children and teens. However, there is a dearth of empirical data on the phenomenology and quantification of this putative syndrome. We conceptualize activation syndrome as behavioral toxicity (an adverse event) that occurs relatively independent of the underlying diagnosis, whereas acknowledging that various factors may modify susceptibility and expression (e.g., age, dosing, pharmacogenetics, comorbidity, etc.). Better characterization of activation syndrome and its timing might point to the mechanisms mediating this adverse effect as well as approaches to its mitigation.

Two other mechanisms that might account for antidepressant-induced suicidality are stage-shift and the so-called energizing phenomenon. Individuals with a bipolar disorder diathesis may experience antidepressant-induced mania, representing a specific interaction between the drug and the endophenotype. According to the energizing theory, during the course of antidepressant treatment, energy and motivation might be restored before mood has lifted. In such cases, patients harboring suicidal wishes might now verbalize or act on their thoughts. These manifestations would seem to reflect incomplete response rather than toxicity.

Finally, it is important not to overlook individual cases in which exacerbation or emergence of suicidality may reflect progression of the underlying condition and the need for more aggressive intervention. This may be the most common scenario.

Further empirical research is needed so that we can prospectively identify those individuals at increased risk of behavioral sensitivity during antidepressant therapy. In the meantime, close clinical monitoring during initiation or changes in antidepressants should help reduce the risk of adverse behavioral effects in all children and adolescents. Because of the established association between untreated depression and suicide, the clinician must balance the clinical needs of the individual patient with the liability of antidepressant-induced behavioral toxicity in a minority of patients.

Acknowledgment The authors would like to thank Paula Edge for administrative assistance. Portions of this manuscript were adapted from a previously published article by Goodman WK, Murphy TK, Lazoritz M entitled "Risk of suicidality during antidepressant treatment of children and adolescents" that appeared in Primary Psychiatry 2006, 13(1):43–50. Dr. Goodman is Principal Investigator on NIMH R01 MH078594, "SSRI-induced activation syndrome in pediatric OCD".

Financial disclosure The authors declare the following financial relationships with Industry: Cyberonics—Wayne Goodman (speaker, honoraria paid to employer); Bristol Myers Squibb—Tanya Murphy (research support); PediaMed Pharmaceuticals—Tanya Murphy (research support).

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