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## REVIEW ARTICLE

# The risks and benefits of antidepressant treatment for youth depression

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### Abstract

The U.S. Food and Drug Administration (FDA) has mandated that all antidepressants carry a ‘black box’ warning label indicating that antidepressants increase the risk of suicidality in youth taking these medications. In the U.K., the Medicine and Healthcare Products Regulatory Agency (MHRA) has determined that the balance of risks and benefits favors only the use of fluoxetine in the treatment of depressive illness in children and adolescents. This article reviews the FDA’s analysis linking antidepressant medication use and pediatric suicidality in major depressive disorder, discusses the efficacy of antidepressants in treating depression in children and adolescents, and offers suggestions to aid clinicians, patients, and families in making clinical decisions based on an accurate assessment of the benefits and risks of medication and psychosocial treatments for pediatric depression.

**Key words:** *Antidepressants, adolescents, children, depression, suicidality*

### Introduction

The U.S. Food and Drug Administration (FDA) and the Medicine and Healthcare Products Regulatory Agency (MHRA), the British equivalent of the FDA, have determined that the use of antidepressants slightly increases risk of suicidality (defined as emergent or worsening suicidal thoughts and/or behaviors) in children and adolescents with depression (1,2) and other psychiatric disorders (1). Consequently, in the U.S. the FDA now requires that all antidepressants carry a ‘black box’ warning label indicating that antidepressants increase the risk of suicidality in youth taking these medications (3). In parallel, the FDA has directed prescribing physicians to explain these risks to their patients and their parents and to provide medication guides that include the warning with each new prescription or refill (4). The goal of this article is to help clinicians, patients, and families make rational clinical decisions based on an accurate assessment of the benefits and risks of medication and psychosocial treatments for pediatric depression.

### Is the risk real?

The FDA, in collaboration with a panel of independent experts in adolescent suicidal behavior working with Columbia University, reviewed data from 24 trials comparing antidepressants to placebo, and involving more than 4,400 children and adolescents (1). The majority of trials excluded high-risk participants and no trial was powered to detect a rare event such as suicidality. Large trials randomizing approximately 1.9 million and 220,000 patients, respectively, would be required to detect a 20% decrease in risk of suicide and non-fatal self-harm (5). While no subject in any of these studies committed suicide and very few attempted suicide, the rate of suicidality was 4% in the medication group compared to 2% in the placebo group (odds ratio=1.8, 95% confidence interval (CI)=1.1–2.8). This means that, of every 100 youth treated with SSRIs (selective serotonin reuptake inhibitors), around 2 to 3 per 100 will become suicidal above what would be expected.

The strength of the suicidality signal was very rarely statistically significant within any single trial.

However, the FDA's meta-analysis revealed that SSRIs increased the risk of suicidal thinking or behavior, and this effect was consistent across enough studies to prompt the FDA's Advisory Panel to conclude that this effect, while small, was real.

The FDA's findings persisted when the analyses were restricted to children and adolescents taking SSRIs only for depression. Table I shows that risk of suicidality varied for the 7 drugs examined in placebo-controlled trials of pediatric depression (1,6). In four trials of fluoxetine, including the recent Treatment of Adolescent Depression Study (TADS) (7,8), the overall risk of suicidality was 1.5 (95% CI=0.7–3.2). In two trials of citalopram, the overall risk was 1.4 (95% CI=0.5–3.5). In the combined trial of two mirtazapine studies, the overall risk was 1.6 (95% CI=0.1–38.4). Overall risk ratios exceeded 2.0 in three aggregated trials of paroxetine (RR=2.2, 95 % CI=0.7–6.5) and in the pooled analysis of two trials of sertraline (RR=2.4, 95% CI=0.5–12.4). There were no suicidality events in either trial of nefazadone. Of note, patients taking venlafaxine (Effexor XR) were 8.8 (95% CI=1.1–69.5) times more likely to experience suicidal thoughts or behavior than those who took placebo. *Post-hoc* analyses of venlafaxine *versus* placebo for depression, when restricted to adolescents, showed no significant difference (3% *versus* 1%) in suicide-related events between drug and placebo (Emslie, personal communication).

Several lines of research demonstrate an association between impulsive aggression and suicidal behavior (9,10). The FDA analysis demonstrated that antidepressant treatment was associated with symptoms of treatment-emergent hostility or agitation (RR=1.8, 95% CI=1.2–2.8) (1). No individual trial showed a statistically significant signal for hostility or agitation. However, the overall RR for paroxetine was statistically significant (RR=7.7, 95% CI=1.8–33.0) (1). While the data appeared to reveal a greater risk of suicidality in those medications that showed the greatest increase in hostility, it was not possible to explore the potential link between hostility and suicidality because data on the timing of the latter events was not available (1). It is possible that pediatric SSRI use may be linked with the emergence of suicidality by inducing a mixed bipolar state in those with a bipolar diathesis; through activation and akathisia; disinhibition; experience of withdrawal symptoms due to intermittent non-compliance; or induction of sleep disruption, all of which are known side effects of SSRIs.

The FDA's analysis, while limited to short-term outcome data (4–16 weeks), found that suicidal

### Key messages

- The FDA has established a link between antidepressant medication treatment and pediatric suicidality.
- The overall number needed to treat (NNT) for antidepressants in pediatric depression is 9, whereas the number needed to harm (NNH) with regard to suicidality is 59, meaning that over 6 times more patients will respond favorably to antidepressants than will become suicidal.
- Treatment with antidepressants only makes sense in the context of education, continued clinical monitoring, and a viable safety plan.

adverse events tended to occur early in the course of treatment (1). A recent pharmacoepidemiology study, conducted in U.K. general practices, found the risk for non-fatal suicidal behaviors was especially high during the first month of antidepressant (fluoxetine, paroxetine, amitriptyline, dothiepin) treatment, and elevated for the first 90 days relative to later periods of treatment (11). In recognition of the particularly high risk of suicidality during early treatment, the FDA currently recommends that prescribing physicians see depressed patients weekly during the first month after prescribing an SSRI, and then biweekly for the next two months (4). The FDA provided these recommendations as general guidelines only; high-risk groups (e.g. patients with a family history of bipolar disorder or a personal or family history of suicidal behavior) may need to be monitored much more closely, especially during initial drug therapy. If patients cannot make frequent trips to the physician's office, monitoring of side effects over the phone may be an acceptable alternative.

### *Is there a relation between SSRI use and completed suicide?*

In the FDA analysis, the increased risk of suicidality associated with antidepressant treatment consists mostly of suicidal ideation, with relatively few suicide attempts, and no suicides (1). Pharmacoepidemiological studies, while observational rather than experimental, can provide some perspective on the relationship between SSRI prescription and suicide. If SSRIs pose a significantly increased risk of suicide, then one would expect an increase in suicide rates to correspond with the rapid rise of SSRI use in the pediatric population. In fact, a recent analysis of international panel data

Table I. Rates and relative risk of suicidality and treatment response in antidepressants and placebo: Results from clinical efficacy trials.

Drug	First author (Year)	Suicidality n/N (%)					Response n/N (%)				
		Drug	Placebo	RR	95% C.I.	NNH	Drug	Placebo	RR	95% CI	NNT
<i>Fluoxetine</i>	Simeon <sup>a</sup> (1990)	0/21 (0.0)	1/19 (5.3)	0.30 <sup>b</sup>	0.01–7.02		–	–	–	–	
	Emslie <sup>c</sup> (1997)	2/48 (4.2)	2/48 (4.2)	1.00	0.15–6.81		27/48 (56.3)	16/48 (33.3)	1.69	1.05–2.70	
	Emslie <sup>d</sup> (2002)	6/109 (5.5)	6/110 (5.5)	1.01	0.34–3.03		71/109 (65.1)	54/101 (53.5)	1.22	0.97–1.53	
	March <sup>c</sup> (2004)	9/109 (8.3)	2/112 (1.8)	4.62	1.02–20.92		66/109 (60.6)	39/112 (34.8)	1.74	1.29–2.34	
	Total	17/287 (5.9)	11/289 (3.8)	1.53	0.74–3.16	48	164/266 (61.7)	109/261 (41.8)	1.47	1.24–1.74	6
<i>Paroxetine</i>	Keller <sup>e</sup> (2001)	4/93 (4.3)	1/88 (1.1)	3.79	0.43–33.21		60/90 (66.7)	48/87 (55.2)	1.21	0.95–1.54	
	377 <sup>f</sup> (unpublished)	6/180 (3.3)	2/95 (2.1)	1.58	0.33–7.69		107/177 (60.5)	53/91 (58.2)	1.04	0.84–1.28	
	701 <sup>c</sup> (unpublished)	2/104 (1.9)	1/102 (1.0)	1.96	0.18–21.30		49/101 (48.5)	46/100 (46.0)	1.06	0.79–1.41	
	Total	12/377 (3.2)	4/285 (1.4)	2.15	0.71–6.52	59	216/368 (58.7)	147/278 (52.9)	1.09	0.95–1.26	20
	Wagner <sup>g</sup> (2003)	5/189 (2.7)	2/184 (1.1)	2.43	0.48–12.39	63	130/189 (68.8)	110/187 (58.8)	1.17	1.00–1.36	10
<i>Sertraline</i> <i>Citalopram</i>	94404 <sup>h</sup> (unpublished)	9/124 (7.3)	5/120 (4.2)	1.74	0.60–5.05		–	–	–	–	
	Wagner <sup>i</sup> (2004)	1/93 (1.1)	2/85 (2.4)	0.46	0.04–4.95		32/89 (36.0)	20/85 (23.5)	1.53	0.95–2.45	
	Total	10/217 (4.6)	7/205 (3.4)	1.37	0.53–3.50	77	32/89 (36.0)	20/85 (23.5)	1.53	0.95–2.45	9
	382 <sup>c</sup> (unpublished)	3/80 (3.8)	0/85 (0.0)	7.43 <sup>b</sup>	0.39–141.67		34/68 (50.0)	30/73 (41.1)	1.22	0.85–1.75	
	394 <sup>c</sup> (unpublished)	5/102 (4.9)	0/94 (0.0)	10.15 <sup>b</sup>	0.57–181.04		69/101 (68.3)	56/92 (60.9)	1.12	0.91–1.39	
<i>Mirtazapine</i>	Total	8/182 (4.4)	0/179 (0.0)	8.84 <sup>b</sup>	1.12–69.51	23	103/169 (61.0)	86/165 (52.1)	1.15	0.96–1.39	13
	003–045 <sup>c</sup> (unpublished)	1/170 (0.06)	0/89 (0.0)	1.58 <sup>b</sup>	0.07–38.37	167	93/164 (56.7)	42/85 (49.4)	1.15	0.89–1.48	14
<i>Nefazadone</i>	CN104–141 <sup>c</sup> (unpublished)	0/95 (0.0)	0/95 (0.0)	NC	NC		61/99 (61.6)	40/96 (41.7)	1.48	1.11–1.96	
	CN104–187 <sup>h</sup> (unpublished)	0/184 (0.0)	0/94 (0.0)	NC	NC		–	–	–	–	
	Total	0/279 (0.0)	0/189 (0.0)	NC	NC	NC	61/99 (61.6)	40/96 (41.7)	1.48	1.11–1.96	6
Overall		53/1701 (3.1)	24/1420 (1.7)	1.94	1.22–3.06	59	799/1344 (59.5)	554/1157 (47.9)	1.23	1.15–1.33	9

Note: RR indicates relative risk; CI, confidence interval; NNH, number needed to harm; NNT, number needed to treat; NC, not calculated. Suicidality data are abstracted from Hammad (1). <sup>a</sup> response criterion not stated explicitly; no clinical differences between treated and control groups at either end-point or across study weeks. <sup>b</sup> delta of .5 added to each cell due to zero cell. <sup>c</sup> response criterion, Clinical Global Impressions-Improvement (CGI-I) scale rating of 1 or 2. <sup>d</sup> response criterion,  $\geq 30\%$  decrease in Children's Depression Rating Scale-Revised (CDRS-R) total score from week 0 to endpoint. <sup>e</sup> response criterion, Hamilton Rating Scale for Depression (HAM-D) score  $\leq 8$  or 50% reduction in baseline HAM-D at end of treatment. <sup>f</sup> response criterion,  $\geq 50\%$  reduction in Montgomery Asberg Depression Rating Scale (MADRS) score between baseline and study endpoint. <sup>g</sup> response criterion,  $\geq 40\%$  reduction in adjusted CDRS-R total score; based on pooled analysis of Trials 501001 and 501017. <sup>h</sup> response criterion not available. <sup>i</sup> response criterion, CDRS-R score  $< 28$  indicating full remission.

of SSRI sales and suicide from 1980 to 2000 found that an increase in SSRI sales of one pill per capita corresponded with a 2.5% reduction in the suicide rate, an association that was more pronounced for older adolescents and younger adults than for children (12). A limitation of the use of SSRI sales data in this study was the availability of sales data at the national level only, which did not allow for an examination of SSRI sales and suicide risk disaggregated by population subgroups such as children and adolescents. A study in the U.S. of children and adolescents aged 10 to 19 years, found a significant inverse relationship for changes in regional rates of antidepressant medication treatment and changes in regional suicide rates (13). For each one percent increase in the use of SSRIs among adolescents, there was a decrease of 0.23 suicides per 100,000 adolescents per year. A propensity-adjusted study in the U.S. of more than 24,000 paid health insurance claims for adolescents who were newly diagnosed with major depressive disorder (MDD) found that treatment with SSRIs was not significantly associated with risk of suicide attempt (14). Treatment with any antidepressant for at least 6 months was also found to significantly reduce the risk of suicide attempt compared with antidepressant treatment for <8 weeks (hazard ratio=0.34, 95% CI=0.21–0.55) (14). Moreover, there may be other factors involved in the decline in the adolescent suicide rate in the United States, such as greater awareness of adolescent depression and more restrictive firearms laws (15). On the other hand, a study in Australia of adolescents ≥ age 15 years and adults found concurrent increases in antidepressant use and young suicide (15–24 years) (16). Moreover, a recent nested case-control study in the United Kingdom of 146,095 newly depressed patients who were prescribed SSRIs or tricyclics found some evidence of an association between SSRIs and non-fatal self-harm in patients aged 18 years and younger (adjusted OR=1.59, 95% CI=1.01–2.50) (17).

### How efficacious are antidepressants in treating pediatric depression?

It appears there is a publication bias insofar as published trials of SSRIs in the treatment of childhood and adolescent depression have generally overestimated benefits while understating risk (18,19). To address these limitations, we include in this report both published and unpublished pediatric depression trials identified in the MHRA and FDA reports, data from the recent TADS trial, and efficacy data from a recent review of the use of

antidepressants in treating pediatric depression (see Table I) (1,8,20).

*Fluoxetine (Prozac).* Of all antidepressants, only fluoxetine has received FDA approval to treat depression in children and adolescents under the age of 18. As Table I shows, the evidence supporting efficacy of SSRIs in treating youth depression is strongest for fluoxetine, for which there are three positive clinical trials, including the landmark TADS study, which compared cognitive therapy, fluoxetine, the two treatments combined, and placebo for adolescent depression (8,21,22). The study by Simeon et al. did not reveal a significant difference between fluoxetine and placebo, but response rates during acute treatment were not reported (23). In all three positive studies, the Clinical Global Impressions-Improvement (CGI-I) response rate (much or very much improved) for antidepressant was 52%–61% versus 33%–37% for patients treated with placebo.

*Sertraline (Zoloft).* Sertraline was studied in 2 parallel-designed, concomitantly conducted, multicenter, double-blind, randomized, placebo controlled trials that were pooled for analysis (24). In the pooled analysis, 69% of the patients receiving sertraline were considered responders, defined as ≥40% decrease in the adjusted CDRS-R total score, compared with 59% of those receiving placebo, a difference of 10% (Table I). There were no differences between drug and placebo when each trial was examined separately (2).

*Citalopram (Celexa).* Two studies have been conducted evaluating the efficacy of citalopram in treating pediatric depression (Table I). One published paper showed a 12% difference between drug and placebo in response (defined as a score of ≤28 on the Children's Depression Rating Scale-Revised (CDRS-R), although the difference in response on the CGI-I was not significant (47% versus 45%) (25). The unpublished study of citalopram for adolescent depression was negative, and had a very high dropout rate, and, atypically for most pediatric trials, involved both inpatients and outpatients (2,20).

*Paroxetine (Paxil).* Paroxetine was studied in three trials (1 published, 2 unpublished). The published study (26) was negative on the primary outcome measure, a Hamilton Rating Scale for Depression (HAM-D) ≤8 or 50% reduction in baseline HAM-D at the end of treatment, but positive on several secondary outcome measures, including the CGI-I.

Two unpublished studies were both negative (Table I) (data available at <http://www.gsk.com/media/paroxetine.htm>) (2).

*Venlafaxine (Effexor XR)*. Mandoki and colleagues conducted the only published trial of venlafaxine treatment in pediatric depression (27). However, cognitive-behavioral therapy (CBT) was administered to all subjects making the absence of a medication effect difficult to interpret. Two unpublished trials of venlafaxine have found no evidence of efficacy for the drug in comparison to placebo (Table I) (2). A re-analysis of the data stratified by age showed that medication was superior to placebo for adolescents but not for children (28). Children treated with venlafaxine had an adjusted mean decrease of -22.7 points on the primary efficacy variable compared with -24.0 for the placebo group ( $P=0.53$ ). Adolescents treated with venlafaxine had an adjusted mean decrease of -24.4 points on the primary efficacy variable compared with -19.9 for the placebo group ( $P=0.02$ ) (28).

*Nefazadone (Serzone)*. There has been one positive trial of nefazadone in treating pediatric depression, which was presented in scientific meetings (29,30), but not published (Table I). Nefazadone was taken off the market last year amid rare reports of hepatic failure being associated with its use. Despite this, the FDA determined that the drug was not withdrawn from sale for reasons of safety or effectiveness (31).

*Mirtazapine (Remeron)*. There have been two unpublished trials of mirtazapine (pooled for analysis), neither of which found evidence of efficacy (Table I) (2).

### Is the benefit of prescribing SSRIS worth the risk?

One useful method for describing the magnitude of treatment effects is the 'number needed to treat' (NNT). The NNT is defined as the number of patients who would need to be treated with an experimental drug or therapy to achieve one additional favorable outcome (32), and is calculated by taking the inverse of the drug-placebo difference of degree of response. The closer the NNT is to 1 the greater the treatment effect (33). Analogously, the number needed to harm (NNH) is the number of patients needed to treat to cause one additional person to have an adverse event (32). We focus on drug-placebo differences because they are most

relevant to the FDA analyses and for addressing the question of the positive and negative impact of SSRIs. The question of the relative safety and efficacy of alternative medical (e.g. tricyclic antidepressants (TCA)) and psychosocial treatments is an important one, for which there are insufficient data. Only one trial compares SSRI directly to TCA (26), and one to cognitive behavioral therapy (CBT) (8). In both studies, SSRI showed superior efficacy to alternative treatment (8,26).

Using the primary response criterion from each individual trial, the overall drug-placebo difference in the three positive fluoxetine trials is 19.6%, so that the NNT is  $1/0.196=6$ . In contrast, the incidence of suicidality in the fluoxetine trials is 5.9% *versus* 3.8%, meaning that the analogous number needed to harm (NNH) is 48 ( $1/0.021$ ), so that approximately 8 times more subjects experienced significant improvement in their depression than had incident or worsened suicidality.

With respect to sertraline, for which there are two trials, the drug-placebo difference in the pooled analysis is 10% (69% vs. 59%), yielding a NNT of 10 (24). In contrast, the drug-placebo difference in incident suicidality is 2.7% *versus* 1.1%, yielding a NNH of 63. Thus, 6 times more patients treated with sertraline benefited by taking the medication than had incident or worsened suicidality.

With regard to the other antidepressants, it is difficult to estimate the risk-benefit ratio due to the number of unpublished trials. For instance, with regard to citalopram, one published trial (25) found a drug-placebo difference in response of 12% (36% *versus* 24%), yielding a NNT of 9, and a drug-placebo difference in incident suicidality of 1.3% *favoring citalopram* [RR=0.46, 95% CI=0.04-4.95]. However, the unpublished citalopram trial did not demonstrate efficacy and had a NNH of 33 (1,2). Similarly, for paroxetine, two unpublished trials were negative (2).

Both depression and suicidal ideation and behavior convey markedly increased risks of suicide in adolescents of about the same order of magnitude, so that a favorable ratio of the NNT/NNH would suggest that the benefits outweigh risks. This is most clear in the case of fluoxetine, which has three published trials with consistent efficacy results that show that 8 times more patients will be helped rather than harmed. Since the data are most consistent in fluoxetine, it is logical to use this agent as a first-line antidepressant treatment. However, the FDA analysis revealed that in TADS the rate of suicidal events in patients treated with fluoxetine was 4.6 times higher than patients receiving pill placebo (8.3% *versus* 1.8%) (6). Moreover, only 60% of those

treated with fluoxetine will respond, meaning that other antidepressants will need to be considered for which there is some evidence of efficacy that outweighs the risk of incident suicidality, such as sertraline and citalopram. With respect to sertraline, the drug-placebo difference in treatment response was modest and significant only in the pooled analysis (24). Since there is only one positive study to date that supports the use of citalopram in pediatric depression (25), additional replication studies are indicated. The risk-benefit profile of paroxetine does not favor its use in treating pediatric depression, consistent with the recommendation made by the MHRA (2). The risk-benefit profile does not favor use of venlafaxine as a first-line agent, although the drug may have a role in treating adolescents with treatment resistant depression (28). Studies of adults have shown the superiority of venlafaxine to active medication and placebo for patients who have already failed to respond to one SSRI (34–37) and among patients with concomitant depression and anxiety (38), with no differences in the rates of adverse events and side effects.

#### *Strengths and limitations*

A strength of our approach to examining the likelihood of youth being helped *versus* being harmed by antidepressant medications is that we include both published and unpublished data, thus reducing problems of publication bias. In addition, we used only the primary clinical measure of response from each individual trial.

A limitation of our approach is that individual data are not available, and so we cannot examine subject level characteristics that might predict response. Moreover, there was heterogeneity in investigator's choice of outcome variables, which limits generalizability. Finally, we did not include older antidepressants (e.g. TCAs, monoamine oxidase inhibitors (MAOIs)) in our review, as the FDA analysis focused only on the newer classes of antidepressants. Ideally, a risk-benefit analysis would address these limitations, consider the efficacy and safety of available treatment alternatives, and examine longer follow-up periods.

#### **Are there effective alternatives to medications?**

Many patients with a first episode of mild to moderate depression respond to education and support. Two specific psychotherapeutic approaches for which there are studies supporting efficacy for adolescent depression are cognitive behavioral therapy (CBT) and interpersonal therapy

(IPT) (39–41). CBT focuses on helping depressed patients recognize distorted patterns of thinking that contribute to their depressed moods, and to change behavior patterns that reinforce those moods (42,43). IPT conceptualizes depression as occurring in the context of an interpersonal matrix, arising from lack of support, interpersonal discord, loss, or role transition, and helps arm patients with the interpersonal awareness and skills to interrupt and change dysfunctional relationship patterns that tend to perpetuate depressive symptoms (44).

Although cognitive-behavioral therapy (CBT) appears to be more effective than some other psychosocial treatments for depression (39,45), the only study that compared therapy to medication found CBT inferior to fluoxetine therapy (8). It is hard to reconcile the results of these studies with the TADS findings, but the difference in outcome could be accounted for by greater severity of depression in the TADS trial, possible positive expectations of the TADS subjects *vis a vis* medication, and difference in the style and delivery of CBT in TADS *versus* other trials (46). While there is growing evidence supportive of IPT as a treatment for moderate depression in adolescents, IPT has never been compared to medication (40,41). The initial use of psychotherapeutic approaches prior to use of antidepressants may be a reasonable alternative for depressed youth, a family history of bipolar disorder, given the high risk of induction of mania or a mixed state (47).

The evidence base for treatment of prepubertal depression is less well developed than is our knowledge about the treatment of adolescent depression. There are no empirically validated psychotherapeutic treatment approaches for this population, and, while the results of some trials are supportive of the use of antidepressants for prepubertal depression (e.g. fluoxetine, citalopram, sertraline), others are not (e.g. venlafaxine). Clearly, additional research is needed to determine the most efficacious treatments for prepubertal depression.

#### **How can physicians best manage depression in their child and adolescent patients?**

It is important for physicians to develop a collaborative partnership with parents and patients through education and shared decision-making. Physicians have a responsibility to educate the family about depression as an illness, about how to monitor symptoms of depression and to recognize signs of suicidality, and of the benefits and risks of medication and psychotherapy. In anticipation of the high risk for suicidality in depressed patients regardless

of treatment approach, a safety plan should be developed with the adolescent and family about how to anticipate, mitigate, and communicate about increased suicidality. The safety plan includes an agreement from the patient to keep him or herself safe, and to contact a responsible adult if suicidal urges become too strong to resist. The clinician or a proxy must be available 24 hours a day, so that emergencies can be dealt with expeditiously.

Education, support, and either CBT or IPT may be more appropriate than antidepressant medications for patients with milder depression. The benefits of antidepressant treatment may outweigh the risks for patients with more severe, recurrent, or chronic depression. Often, the patient or family does not wish to engage in psychotherapy, in which case, even for moderate depression, medication is a reasonable alternative. Regardless of the choice of initial treatment, the therapeutic contract should carefully define symptomatic and functional goals, a timetable for reaching those goals, a discussion of potential side effects of antidepressants that may be related to incident suicidality (e.g. irritability, hostility, disinhibition, agitation, and hypomania), and a framework for reviewing alternative treatment options if the first treatment fails to deliver.

## Conclusions

The FDA analysis demonstrates that there is a small but statistically significant increased risk of suicidality associated with antidepressant treatment, and physicians have a duty to fully inform patients and their families about this side effect of medication as part of a discussion about benefits and risks (1,4). SSRIs may increase the risk of irritability, agitation, akathisia, disinhibition, withdrawal (in those who are non-compliant) or induction of a mixed state particularly in those who have or are predisposed to develop bipolar disorder, any of which may precipitate suicidality. Especially for those with moderate to chronic or severe depression, many clinicians posit that the benefits of antidepressants outweigh the risks. The balance of benefits and risks favors fluoxetine, and provides some support for the use of sertraline and citalopram. However, treatment with antidepressants only makes sense in the context of education, continued clinical monitoring, and a viable safety plan. Evidence for the continuity between suicidal ideation and suicidal behavior comes from both case-control and prospective, longitudinal follow-up studies (48–50). Untreated depression is associated with significant morbidity and a high risk of completed and attempted suicide, a risk that is much greater than the risk of suicidality due to treatment with an SSRI.

Consequently, any decisions about the benefits and risks of both medication and psychotherapy for pediatric depression should take into consideration that, untreated, depression is a potentially fatal illness.

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