In Debate

Selective Serotonin Reuptake Inhibitors and Suicidality: A Guide for the Perplexed

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The rate of suicidal adverse events is elevated around 2-fold in drugs, relative to placeboes, in clinical trials of antidepressants in children, adolescents, and young adults.[1,2] Since the FDA's black box warning in 2003–2004, there has been a decline in the prescription rate of antidepressants, with no compensatory increase in referrals for psychotherapy in the United States.[3] Families, patients, and clinicians are uncertain about how to balance the benefits and risks of antidepressants. In this brief review, the clinical significance of suicidal events is discussed along with the factors that may increase or attenuate the risk, possible explanations for this phenomenom, the benefits and risks of antidepressants, the public health implications of a decline in the use of SSRIs, and recommendations for clinicians.

Suicidal adverse events are treatment-emergent increases in suicidal ideation or an actual suicide attempt. In more than 4300 participants in pediatric antidepressant clinical trials, there have been no deaths by suicide, and most of these events were increases in suicidal ideation, rather than actual suicide attempts. The actual risk difference for the occurrence of an event is not large. While the FDA initially reported a risk difference of 2%, a more recent re-analysis included more recently conducted trials found a risk difference of only 0.9%, which translates to a NNH of 121.[1,2] Moreover, during the period of time when the rate of SSRI prescriptions was increasing, youth suicide rates were declining.[4] One cannot necessarily infer a causal relation between the increase in the use of SSRIs in adolescents and a decline in the adolescent suicide rate. However, if antidepressants were associated with an increased risk for suicide, one would have expected an increase in adolescent suicide, which clearly was not the case.

The nature of assessment for suicidal events has also been questioned. In most clinical trials, suicidal events are not surveyed systematically, but are reported spontaneously. In fact, in the subset of clinical trials that had systematic assessment, there was no difference between medication and placebo regarding systematically assessed suicidal ideation.[2] However, other reports have shown similar rates of events, whether using usual adverse event reporting methods or by deriving the occurrence of events from systematically assessed measures of self-reported suicidal ideation. [5,6]

Predictors of suicidal adverse events include previous suicidal behaviour and higher baseline levels of suicidal ideation, anger, and irritability.[5] In the Treatment of Adolescent Depression Study,[6] the rate of suicidal events was lower in the combination of antidepressant and CBT than in medication alone; however, in other clinical trials of more severely or chronically depressed youth, no protective effect was found for combination treatment.[6,7] No relation has been established among dosage, adherence pattern, medication type, and risk for events, and while some promising pharmacogenetic findings have been reported, there is currently no clinical applicability of these findings.

Several hypotheses, all unproven, have been advanced to explain the increased rate of suicidal events in antidepressant-treated patients, compared with those on placebo. These have included induction of akathisia, disinhibition, increasing energy of the patient to the point where he or she can actually make an attempt, induction of mania or a mixed state, or withdrawal from medication as a result of nonadherence, with induction of dysphoria and suicidality. The adage of suicidal behaviour coming as a consequence of improvement in mood is not consistent with data showing a high correlation between severity of suicidal ideation and severity of depression; further, most reported suicidal events were not attempts, but were increases in suicidal ideation. The induction of a mixed state can certainly lead to suicidal ideation and behaviour; however, while the risk of a suicidal event is higher in adolescents than in children, the risk of mania after treatment with an antidepressant is higher in younger children. Finally, it is hard to reconcile the hypothesis of withdrawal symptoms as a cause of suicidal events in light of similar rates of suicidal events in youth

treated with fluoxetine as in other, more rapidly metabolized antidepressants.

To compare the benefits and risks of antidepressants, one needs to compare the number of people who benefit from an antidepressant with the number who experience a suicidal event. For anxiety-disordered youth, in whom the effects of antidepressants are much stronger than in depression (NNT = 3), nearly 50 youth benefit from antidepressants for every one who experiences a suicidal adverse event.[1] For youth with depression, the NNT is 10, whereas the NNH is 121, indicating that 12 times as many youth will benefit from an antidepressant for the treatment of depression as will experience a suicidal event. The effect size for antidepressant treatment of depression increases with increasing severity of depression, owing to a lower placebo response rate; however, suicidal events are also more likely to occur in those who are more severely depressed. It is up to each family, patient, and clinician to determine what ratio between NNT and NNH constitutes an acceptable risk–benefit ratio for the treatment of depression. It is unclear if the addition of CBT to antidepressant treatment is actually protective against suicidal events; however, because its addition appears to result in a more complete and more rapid response, this may be one way to improve the benefit-to-risk ratio. Also, given that the half-lives of many antidepressants are shorter in youth than in adults, current practice may not be providing a sufficient dose to obtain an optimum clinical response.

Since the announcement of the black box warning from the FDA, there has been a decline in prescriptions for SSRIs in children and adolescents, especially in the primary care sector. According to one study, there has also been a decline in the rate of diagnosis of depression and no compensatory increase in referral for psychotherapy, which may reflect therapeutic nihilism on the part of practitioners.[3] Several studies have documented a correlation between increases in SSRI sales and prescriptions and a corresponding decline in the youth suicide rate. Educational activities designed to increase primary care physicians' recognition of depression and proper use of antidepressants have been shown to decrease the suicide rate, particularly in women, for whom mood disorders are especially salient regarding suicidal risk.[8]

Abbreviations used in this article

CBT	cognitive–behavioural therapy
FDA	Food and Drug Administration
NNH	number needed to harm
NNT	number needed to treat
SSRI	selective serotonin reuptake inhibitor

There are also studies showing a positive association between the use of antidepressants in youth and both attempted suicide and deaths by suicide.[9] However, the peak incidence for initiation of antidepressant treatment for adolescents is immediately after a suicide attempt.[10] Therefore, people with a past history of an attempt, who are most likely to make another suicide attempt, are also more likely to receive antidepressants, which could lead to incorrect inferences about the causal direction between suicidal behaviour and treatment with antidepressants.

In summary, it appears that there is an association between the use of antidepressants and the occurrence of suicidal adverse events. Based on most extant data, there is no association with deaths by suicide. Further, most reported suicidal adverse events involve new-onset, or worsening suicidal ideation, rather than actual suicidal behaviour. Pharmacoepidemiologic studies show that widespread use of antidepressants in youth may be protective against deaths by suicide, and certainly do not find an increased risk of deaths by suicide. Case–control studies that find an association between medication use and suicidal behaviour may confound the reason for the initiation of the medication with the outcome. Many more depressed youth benefit from antidepressants than are harmed by these agents, and the risk–benefit ratio is even more favourable for those with anxiety disorders. The risk–benefit ratio for the treatment of pediatric depression with an antidepressant can be improved by using a combination of psychotherapy and medication, using an adequate dose of medication, and by closely monitoring for changes in suicidal ideation. Given that many suicidal events occur early in treatment, interventions that accelerate the pace of response, such as triiodothyronine augmentation or the addition of CBT, as well as so-called front-loaded interventions to create a safety plan to reduce suicide risk, may be effective in reducing the risk of suicidal events.

An open discussion with patients and families about the benefits and risks of antidepressants, placed in the context of the modest seriousness of most suicidal adverse events, along with careful monitoring for clinical response and suicidal ideation, is the recommended approach to be taken by clinicians confronting a depressed child or adolescent. For the family and child who have concerns about medication, beginning with psychotherapy is a good alternative and the preferred approach if the patient has milder symptoms of depression. Among those youth with more severe depression, the fastest and most complete response occurs with antidepressant treatment in combination with psychotherapy. The patient and family should also be educated about the morbidity and mortality associated with untreated depression and that the best prevention against suicide is to restore the patient to normal functioning as soon as possible.

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