Effect of antidepressants on suicide risk in children and adolescents

AUTHORS: C Scott Moreland, DO, Liza Bonin, PhD
SECTION EDITOR: David Brent, MD
DEPUTY EDITOR: David Solomon, MD

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Literature review current through: **Oct 2023.**
This topic last updated: **Aug 31, 2022.**

INTRODUCTION

There is concern that selective serotonin reuptake inhibitors (SSRIs) and other antidepressants may increase the risk of suicidal ideation and behavior in children, adolescents, and adults younger than 25 years [1-4]. In early 2004, the US Food and Drug Administration (FDA) in the United States asked manufacturers of a number of antidepressants to make labeling changes to include a warning about a possible increased risk of suicidal ideation or behavior, particularly at the initiation of therapy or at the time of dose changes [5]. After further analysis, in October 2004, the FDA directed manufacturers of all antidepressants (including tricyclic antidepressants and monoamine oxidase inhibitors) to include a warning stating that antidepressants may increase the risk of suicidal ideation and behavior in children and adolescents [6].

Establishing the causal association is difficult because of the clear associations between severe depression and suicide and between severe depression and the need for antidepressant therapy. Because suicide is uncommon, it also is difficult to demonstrate the negative, which is that antidepressants do not cause suicide. Risk factors for suicidal behavior in children and adolescents are discussed separately. (See "Suicidal behavior in children and adolescents: Epidemiology and risk factors", section on 'Psychiatric disorder'.)

This topic discusses the evidence regarding antidepressants and the risk of suicide in children and adolescents. The use of antidepressants in adolescent depression is discussed separately, as is the association between antidepressants and suicide risk in adults. (See "Pediatric unipolar

depression and pharmacotherapy: Choosing a medication" and "Effect of antidepressants on suicide risk in adults".)

EVIDENCE OF ASSOCIATION

Overview — Evidence for and against an association between antidepressant therapy and suicidal thoughts and/or behaviors in children, adolescents, and young adults comes from randomized trials [7-11], observational studies [12-14], and population-based studies comparing the rates of suicide and antidepressant use over time [15-19]. Each of these study designs has limitations in demonstrating a causal association [20,21]:

- Suicide is rare in randomized, controlled trials of antidepressants. Thus, individual trials typically lack the power to detect a relationship between antidepressants and suicidal ideation or behavior.
- Observational studies can more easily detect rare events such as suicide. However, causality is difficult to establish because of the association between severe depression and the use of antidepressants.
- Population-based studies have examined rates of antidepressant use and suicide over time. These studies have generally found lower rates of suicide with increasing rates of antidepressant use [15-19]. Accordingly, the consensus has been that increases in prescribing likely yield lower rates of suicide. However, rare antidepressant-induced suicides could be masked by secular trends [22]. In addition, the use of newer antidepressants (eg, selective serotonin reuptake inhibitors) may be a marker for better overall quality of health care [19]. Thus, it is not clear that increased rates of antidepressant prescribing are the cause of decreasing rates of suicide [22].

Randomized trials — Randomized trials of antidepressants in children and adolescents were not designed primarily to determine whether these antidepressants increase suicidal behavior [23]. Most of the trials excluded subjects with suicidal ideation and did not have enough power to detect rare adverse events such as suicide deaths. Suicidal ideation and behavior were not methodically assessed as prespecified outcomes in earlier studies; rather, suicidal ideation and behavior were spontaneously reported as adverse events and were not uniformly defined [10]. More recent studies have systematically evaluated suicidal ideation and behavior in pediatric antidepressant trials, prompted partly by the US Food and Drug Administration's (FDA) concern of a lack of standardized language to define, monitor, and clinically assess suicidal behavior [24-26]. One study (n = 334 patients) found that suicidal ideation and behavior were detected less

often by spontaneous reporting, compared with systematic assessment (9 versus 21 percent of patients) [25].

In addition, patients in randomized trials who are assigned to treatment with active drug often have more side effects, which may have led to increased contact with study personnel and a greater opportunity to report suicidal ideation and behavior (ascertainment bias) [27]. Most of the reported suicidal events were suicidal thoughts, rather than suicidal behavior.

Systematic reviews of randomized trials, subject to the limitations described above, have yielded different conclusions about the association between antidepressants and increased risk of suicidal ideation and behavior, as illustrated in the two subsections below. In many instances, the reviews conducted meta-analyses that pooled results from trials in patients with different disorders, such as unipolar major depression, anxiety disorders, and obsessive-compulsive disorder.

Evidence of an increased risk

- The FDA convened an advisory panel to reexamine analyses regarding suicidal thoughts and behaviors and antidepressants in children and adolescents. The advisory panel's combined analysis of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medications in more than 4400 children and adolescents being treated for unipolar major depression and other psychiatric disorders yielded the following results [11]:
    - Seventy-eight patients (2 percent) experienced adverse events representing suicidal ideation or behavior, collectively termed suicidality; adverse events were reports made by the research clinician if a patient or parent spontaneously shared thoughts about suicidality [28].
    - Among the adverse events that were reported, patients on antidepressant medication had an increased risk of suicidality during the first few months of treatment compared with those on placebo (4 versus 2 percent).
    - In 17 trials, standardized forms were used to ask each patient about suicidality at each visit. The data revealed that medication neither increased the suicidality that was present before treatment, nor induced suicidality in patients who were not thinking about suicide at the start of the study. Over the course of treatment, all studies combined showed a slight reduction in suicidality.
    - No completed suicides occurred during any of the trials.

The FDA advisory panel concluded that there was a small increased risk of suicidal thoughts or behavior in children taking antidepressants compared with placebo (risk ratio 2.0, 95% CI 1.3-3.0) [11]. The risk appeared to be greatest in the first few weeks after initiating therapy [11,29].

- A meta-analysis of 27 trials (n >5300 youth) found a small increased risk of suicidal ideation or behavior in patients taking antidepressants than placebo (0.7 percent; 95% CI 0.1-1.3) [30]. The number needed to harm was 143, meaning one additional episode of suicidal ideation or behavior occurred with antidepressants for every 143 youth taking antidepressants and every 143 youth taking placebo. The investigators concluded that the benefits of antidepressants far outweighed the risks of suicidal ideation/behavior.

- A meta-analysis of 17 trials (n >3200 children and adolescents) compared antidepressants (selective serotonin reuptake inhibitors [SSRIs], mirtazapine, or venlafaxine) with placebo and found that suicidal ideation or behavior occurred in more patients who received antidepressants (risk ratio 1.58, 95% CI 1.02-2.45) [31]. The authors estimated that this translated to an increase in suicidal events of approximately 1.5 percent, in contrast to an increase in remission of 6.8 percent; thus, the rate of remission was 4.5 times greater than the rate of suicidal ideation and behavior.

- A network meta-analysis included 34 randomized trials that evaluated 14 different antidepressants in pediatric patients with acute major depression (n >5000); the study used direct comparisons between two drugs or between a drug and placebo, as well as indirect comparisons of the drugs through their relative effect with a common comparator (typically placebo) [32]. The study found that the risk of suicidal ideation or behavior was greater with venlafaxine than placebo, duloxetine, escitalopram, fluoxetine, imipramine, or paroxetine.

Evidence of no increased risk

- The American College of Neuropsychopharmacology Task Force report on SSRIs and Suicidal Behavior in Youth reviewed 15 trials (n >2000) regarding the safety and effectiveness of five antidepressants (citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine) [10]. The rate of suicidal ideation and behavior was similar between those treated with antidepressants and placebo, and there were no completed suicides.

- Analysis of FDA summary reports of randomized trials of nine second-generation antidepressants found 77 suicides among 48,277 patients [7]. Rates of suicide based on patient exposure years were similar among those receiving an SSRI (0.59 percent [95% CI 0.31-0.87 percent]), a different antidepressant (a combination of the newer

antidepressants being studied and the older antidepressants used in the active control arms of the studies) (0.76 percent [95% CI 0.49-1.03 percent]), and placebo (0.45 percent [95% CI 0.01-0.89 percent]).

- A meta-analysis of patient-level data from four randomized trials (708 children and adolescents with unipolar major depression) found that the risk of suicidal thoughts and behavior was comparable for fluoxetine and placebo [33].

- A review identified seven randomized trials published since 2007 that compared antidepressants with placebo for unipolar major depression (total number of youth not reported); in each trial, the rate of suicidal ideation/behavior with active drug and placebo was comparable [24].

Observational studies — Observational studies have yielded inconsistent results regarding the association of antidepressants with suicidal behavior. Differences in results may be due at least partially to study methods, such as adjusting the analyses for potential confounding factors:

- A meta-analysis of eight observational studies (n >200,000 patients) found that exposure to selective serotonin reuptake inhibitors (SSRIs) in adolescents with moderate or severe depression was associated with an increased risk for attempted or completed suicide (OR 1.9, CI 1.5-2.4) [14]. However, adolescents who received treatment with SSRIs may have been more severely depressed and at greater risk of suicide than those who did not receive SSRIs (confounding by indication).

- A subsequent retrospective study used an administrative claims database to examine the use of antidepressants and the number of suicide attempts that occurred before and after the FDA issued its warnings about a possible increased risk of suicidal ideation and behavior due to antidepressants [34]. The dataset included a cohort of children and adolescents aged 10 to 17 years (n >1 million), and the analyses used psychotropic drug poisonings as a proxy for suicide attempts. The study found that in the second year (2006) after the warnings, use of antidepressants declined by 31 percent, whereas psychotropic drug poisonings increased by 22 percent. It is worth noting that psychotropic poisonings may reflect substance abuse rather than suicidality.

- Another subsequent study used administrative databases to identify youth ages 5 to 17 years with new episodes of depression (n >200,000), who were followed for up to 180 days [27]. The analyses compared the frequency of self-harm (suicide attempts and self-inflicted injury) in patients who were either treated or not treated with antidepressants, and included adjustments for potential confounding due to patient characteristics that change over time (eg, demographics, prior self-harm, comorbid conditions, and psychiatric

hospitalization) and can affect the probability of receiving an antidepressant and the outcome of treatment. Although the initial unadjusted analyses found that antidepressant treatment was associated with an increased risk of self-harm, the adjusted analyses did not.

Observational studies suggest that in children and adolescents, the risk of suicide attempts associated with selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors appears to be similar across different medications [35]. As an example, a retrospective study using an insurance claims database and medical records identified more than 38,000 youth who were treated with fluoxetine, citalopram, escitalopram, paroxetine, sertraline, or venlafaxine, including 419 patients with medically treated suicide attempts [36]. After adjusting for the propensity to receive a particular antidepressant as well as factors such as age, mental health diagnoses, and use of psychotropic medications, the analyses showed that the rate of suicide attempts for users of fluoxetine was comparable to the rate for each of the other antidepressants. However, the risk of suicide attempts was elevated in patients treated with multiple antidepressants concurrently, compared with patients who were treated with fluoxetine alone (relative risk 1.7, 95% CI 1.1-2.6). This elevated risk may reflect increased severity of depression rather than a drug effect.

In addition, relatively high starting doses of antidepressants prescribed for children and adolescents appear to be associated with suicidal behavior. An observational study used an insurance claims database of depressed patients aged 10 to 24 years (n >39,000), and compared the incidence of suicide attempts in patients who started SSRIs at modal (eg, fluoxetine 20 mg or sertraline 50 mg per day) or higher than modal doses [37]. The analyses included propensity score matching to balance the two groups with regard to observed potential confounders (eg, depression severity and previous self-harm). The risk of deliberate self-harm was two-fold greater in patients who initiated treatment at the higher dose (hazard ratio 2.2, 95% CI 1.6-3.0). This corresponded to approximately one additional suicide attempt for every 130 patients who started treatment with each regimen. Despite propensity score matching, it is possible that patients started at higher doses were at greater risk for suicidal behavior due to a history of treatment nonresponse or treatment response only at higher doses [38]. In addition, the study did not address the risk of suicidal behavior associated with dose escalation conducted in line with clinical guidelines (eg, fluoxetine 10 mg for one week, then fluoxetine 20 mg for 3 weeks, and then increase only in patients who do not respond).

RECOMMENDATIONS OF VARIOUS GROUPS

In response to concerns about the increased risk of suicidality with antidepressant therapy, various regulatory and clinical groups have taken a closer look at the data, and based upon their conclusions, made recommendations regarding the use of antidepressants in children and adolescents.

FDA black box warning — In 2004, the US Food and Drug Administration (FDA) directed manufacturers of antidepressants (table 1) to revise the labeling of their products to include a boxed warning and expanded warning statements about the risks of suicidality in children and adolescents being treated with these drugs (table 2) [6,39]. In May 2007, the FDA extended the warning to include adults younger than 25 years [21,40]. (See "Effect of antidepressants on suicide risk in adults".)

The FDA also updated the medication guide and product labeling to remind health care providers that depression and certain other serious psychiatric disorders are themselves the most important causes of suicide [41].

The warning applies to any and all use of antidepressant drugs in children and adolescents. The warning requires any clinician prescribing antidepressant medication to clearly warn the patient and his/her family about the potential risks associated with these medications. In addition, the FDA has determined that all patients receiving these medications should be given a Patient Medication Guide (MedGuide) to advise them of the risk and precautions that can be taken (table 3) [42]. MedGuides are intended to be distributed by the pharmacist with each new prescription or refill of antidepressant medication.

Other groups — Other regulatory and clinical groups have come to differing conclusions regarding the safety and efficacy of antidepressants in children, as illustrated below.

- The United Kingdom's Medicines and Healthcare Products Regulatory Agency found only fluoxetine to have a favorable risk-benefit profile [43]. It recommends against the use of citalopram, escitalopram, paroxetine, sertraline, fluvoxamine, and venlafaxine for the treatment of unipolar major depression in children [43].

- The American College of Neuropsychopharmacology (ACNP) Task Force on SSRIs and Suicidal Behavior in Youth concluded that, because depression is one of the largest risk factors for suicide, diagnosis and treatment of depression in children and adolescents require urgent attention [44]. The Task Force found that among the antidepressants, only fluoxetine has demonstrated strong statistical evidence of efficacy. The Task Force also concluded that, based on the FDA meta-analysis, selective serotonin reuptake inhibitors (SSRIs) and other antidepressants are associated with a small increase in the risk of suicidality. However, other lines of evidence (eg, population-based studies comparing the

rates of suicide and antidepressant use over time [15-19], toxicology studies of completed suicides [45,46], and cohort studies [47,48]) indicated a possible beneficial effect of antidepressant therapy on the risk of suicide. The Task Force recommends the continued use of fluoxetine as an effective and readily available treatment for major depression in children and adolescents.

- The American Academy of Child and Adolescent Psychiatry (AACAP) supported the conclusions of the ACNP Task Force. The AACAP Work Group recommended that its members continue to treat depression with all of the effective means available. Effective treatment, based on available research, includes treatment with an antidepressant only, an antidepressant with CBT, or CBT alone. The AACAP supports a combined treatment approach as the most efficacious [28,49].

  Fluoxetine has the most evidence of efficacy and is considered the first-line medication [28]. However, because 30 to 40 percent of patients may not respond to fluoxetine and others will be unable to tolerate it because of side effects, alternative medications are often necessary; other SSRIs are most appropriate. In the Treatment of Resistant Depression in Adolescents randomized trial, patients who had not responded to initial treatment with an SSRI showed comparable reduction in symptoms when treated with fluoxetine, citalopram, or venlafaxine [50]. The treating clinician, in conjunction with the patient and family, must determine the best treatment option for the individual patient.

- The Society for Adolescent Medicine strongly supports the appropriate use of antidepressant medications in the treatment for adolescents with depression [51]. When using such medications, the risk of suicidality must be balanced with the clinical need.

MONITORING FOR SUICIDALITY

Patients who are treated with antidepressants must be closely monitored by the clinician and family. Details of monitoring, including frequency and parameters, are discussed separately. (See "Pediatric unipolar depression and pharmacotherapy: General principles", section on 'Monitoring'.)

IMPACT OF THE FDA ADVISORY

Integrated claims data from national managed care plans in the United States were used to evaluate patterns of diagnosis and treatment of depression in children and adolescents before and after the US Food and Drug Administration (FDA) advisory on risk of suicidality with

selective serotonin reuptake inhibitors (SSRIs) in 2004 [34,41,52-54]. Between 1999 and 2004, the rates of diagnosis of new episodes of pediatric depression and of treatment with SSRIs were increasing. After the FDA advisory, there was a reversal in both of these trends, without evidence of a significant increase in other treatment modalities. In addition, care and treatment of children and adolescents with depression shifted from generalists to psychiatrists.

The aforementioned studies did not evaluate the possible underlying causes of the shifts in diagnosis of depression and prescribing of antidepressants for children and adolescents. One possibility is that the original increase in depression rates and use of antidepressants in children reflected over-diagnosis and misuse of medication. If this is correct, then the decrease after the FDA warnings is an appropriate outcome. Alternatively, current practice could reflect a substantial problem with under-diagnosis and undertreatment of depression.

What is clear is that since the FDA warnings, general practitioners are diagnosing less pediatric depression and prescribing fewer antidepressants to children and adolescents [41,52,53]. While psychiatrists are treating slightly more youth depression, it is not enough to compensate for the observed decline in primary care. The observed rates of diagnosis after the FDA advisory (0.3 to 0.5 percent) are substantially lower than previously published incidences of child (0.4 to 2.5 percent) and adolescent depression (0.4 to 8.3 percent) [52]. It is still too soon to know the impact and meaning of these trends on the treatment and prognosis of depression in children and adolescents. Some studies show that five years from the FDA Advisory, the initial decline in SSRI prescriptions for children and adolescents has reversed, whereas another study shows the decline is ongoing. Continued monitoring and studies are needed [34,55,56].

According to the United States Centers for Disease Control and Prevention (CDC), 1985 suicides occurred among children and adolescents aged 10 through 19 years in 2004, compared with 1737 in 2003 [57,58]. This was the first increase in the suicide rate in this age group in more than ten years. Similarly, in the Netherlands, the suicide rate in children and adolescents increased by 49 percent between 2003 and 2005; during the same time period, SSRI prescriptions for children and adolescents decreased by 22 percent [59].

Similar results were found in a 2008 Canadian study which examined data 9 years before and 2 years after Health Canada's regulatory warning on prescribing antidepressants to children and adolescents (which occurred in June 2003, 4 months before the FDA's October warning). Suicide deaths in children and adolescents increased significantly by 25 percent, corresponding to a significant decrease in antidepressant prescriptions of 14 percent [60]. In addition, changes were found in treatment that was not directly targeted by the warning: antidepressant prescriptions for young adults (18 to 24 years) decreased significantly, as did follow up visits for depression for children, adolescents, and young adults.

The black box warning was intended to bring attention to and close monitoring of antidepressants in children and adolescents, not to decrease the amount of prescriptions and/or treatment for depression. The apparent unexpected effect of the regulatory actions on clinician's prescribing practices is a cause for significant concern, particularly in the context of evidence that antidepressant treatment in children and adolescents is beneficial [61].

The debate concerning risk for suicidality with antidepressants compared to the risk of suicide in untreated or undertreated depression has significant consequences. Beyond working to clarify the nature of the relationship between suicide and antidepressants, systemic monitoring of the consequences of regulatory warnings is an ongoing need. Approximately two-thirds of children and adolescents with a mental disorder do not receive adequate treatment [62]. Anything that significantly interferes with access to care should be a cause for concern.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Depression in children and adolescents (Beyond the Basics)" and "Patient education: Depression treatment options for children and adolescents (Beyond the Basics)")

SUMMARY

- There appears to be a slightly increased risk of suicidal thoughts and behaviors (but not completed suicide) among a small group of children and adolescents who are treated with antidepressant medications compared with placebo. However, the evidence is inadequate to conclusively establish this association. (See 'Evidence of association' above.)

- The US Food and Drug Administration (FDA) has directed manufacturers of antidepressants (table 1) to include a boxed warning label regarding the increased risk of suicidality (table 2), thus requiring the prescribing clinician to discuss the warning with the patient and family. In addition, all patients receiving antidepressants should be given a Patient Medication Guide (MedGuide) to advise them of the risk and precautions that can be taken (table 3). (See 'FDA black box warning' above.)

- When considering the use of antidepressants in children and adolescents, the risk of antidepressant-related suicidality must be weighed against the benefits of treatment and the long-term risk of suicide in untreated depression. When considering this balance, the consensus among most mental health specialists is that the benefits of antidepressant therapy outweigh the risks. The ratio of response to suicidal events is approximately 11:1, and for remission to suicidal events is 4.5:1 (See 'Other groups' above and 'Randomized trials' above.)

- Children and adolescents who are treated with antidepressants should start on low doses and be closely monitored by clinicians and families for increasing suicidal thoughts or behaviors. (See "Pediatric unipolar depression and pharmacotherapy: General principles", section on 'Monitoring'.)

Topic 1225 Version 25.0

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