Effect of antidepressants on suicide risk in adults

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INTRODUCTION

Antidepressants are efficacious for treating depressed patients, especially patients who are severely ill and may be at greater risk for suicide [1,2]. However, all antidepressants in the United States carry a warning that they are associated with an increased risk of suicidality in adults age 18 to 24 years during initial treatment (generally the first one to two months) [3]. Suicidality includes suicidal ideation, action to prepare for an attempt, attempt or nonfatal self-harm, or death. The warning also applies to children and adolescents.

This topic reviews whether antidepressants affect the risk of suicidality in adults. The effect of antidepressants on suicide risk in children and adolescents, risk factors and management of suicidality in adults, and the pharmacology and use of antidepressants to treat depression are discussed separately.

- (See "Effect of antidepressants on suicide risk in children and adolescents".)
- (See "Suicidal ideation and behavior in adults".)
- (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)
- (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

BACKGROUND

In 1990, concerns were first raised about antidepressants precipitating suicidality (ie, suicidal ideation, action to prepare for an attempt, attempt or nonfatal self-harm, or death). At that time, case reports described patients who developed intense suicidal ideation during treatment with fluoxetine, a selective serotonin reuptake inhibitor [4]. The manufacturer of fluoxetine subsequently performed a meta-analysis of 17 randomized trials (3065 patients with major depression) and found that the pooled incidence of the combined outcome of preparatory acts, nonfatal self-harm, or death did not differ significantly between patients who received fluoxetine or placebo (0.3 versus 0.2 percent) [5]. In addition, baseline suicidal ideation improved significantly more with fluoxetine than placebo (72 versus 55 percent).

Concerns about antidepressants and suicidality reemerged in 2003 when the US Food and Drug Administration (FDA) issued an advisory in response to numerous reports of suicidal ideation, suicide attempts, and suicide deaths in clinical trials of antidepressants in pediatric patients with unipolar major depression [3,6]. In 2004, the FDA reexamined data from pediatric randomized trials of the antidepressant drugs bupropion, citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine. The analyses suggested an increased risk of suicidal ideation, preparatory acts for self-harm, or nonfatal self-harm occurring during the first weeks of treatment with an antidepressant, compared with placebo. As a result, the FDA elevated the advisory and issued a warning regarding emergence of suicidality in children and adolescents starting antidepressant treatment [3,7].

The FDA issued an advisory in 2005 about suicidality in adults treated with antidepressant drugs [3]. In 2007, the FDA extended the 2004 warning about antidepressant drugs and suicidality to include adults age 18 to 24 years and all antidepressant drugs. The warning issued in 2007 did not advise against the prescription of antidepressants for approved indications, including depressive and anxiety disorders. Instead, the warning emphasized that:

- Patients 18 to 24 years of age should be informed about the risk of developing suicidality during initial antidepressant treatment (generally the first one to two months).
- Clinicians should monitor patients closely during initial antidepressant treatment.
- Depression and certain other serious psychiatric disorders are themselves associated with an increased risk of suicidality.

Although the risk of suicidality posed by antidepressants remains in question, there is no doubt about the risk of suicidality in untreated depressed patients [8]. As an example, an

observational study of 186 depressed patients followed for up to 38 years found that 14 percent committed suicide, which was 27 times greater than the rate in the general population; treatment with an antidepressant was associated with a lower rate of suicide mortality. [9].

There is no evidence that more frequent contact between clinicians and depressed patients reduces the risk of suicide attempt or suicide death. However, there is evidence that fewer symptoms of depression occur in patients who receive follow-up care, compared with patients who do not [10]. Advisories and warnings about the need for more frequent monitoring do not seem to have increased the low rate of follow-up care during antidepressant treatment [11].

EVIDENCE REVIEW

There is no clear evidence that treatment of depressed patients with antidepressant drugs increases the average risk of suicidality (ie, suicidal ideation, action to prepare for an attempt, attempt or nonfatal self-harm, or death) [8,12]. However, there may be an age-specific effect, such that antidepressants may raise the risk of suicide attempts (nonfatal self-harm) or preparatory acts in patients age 18 to 24 years during the first several weeks of treatment, yet have no effect upon patients age 25 to 30 years, and may lower the risk in patients 31 years and older. It is not known whether there are other sociodemographic or clinical factors associated with risk of suicidality in patients treated with antidepressants. In addition, it is not known whether specific antidepressant drugs differ in their risk of suicidality, or how polypharmacy affects the risk.

Several methodologic issues make it difficult to answer the question of whether antidepressants cause suicidality. The associations between depression and use of antidepressants and between depression and suicidality potentially confound the results of studies that examine the association between antidepressants and suicidality [13]. Another issue is the reliability of classifying certain events or behavior as suicide attempts [14]. (See 'Methodologic issues' below.)

Three types of studies have examined the association between antidepressants and suicidality. In order of quality, these are [15]:

- Randomized trials (including meta-analyses)
- Observational studies (including meta-analyses)
- Ecological studies (these use community-level, epidemiologic data rather than individual-level data)

Randomized trials

Suicide deaths — Three independent analyses combined data from placebo-controlled efficacy trials of various antidepressants to examine risk of suicide death during antidepressant treatment [16-18]. Each analysis found no evidence for higher or lower risk of suicide death during acute-phase treatment with antidepressants compared with risk during treatment with a placebo.

- A meta-analysis of 342 randomized trials (40,826 patients) found no significant difference in suicide deaths for patients treated with a selective serotonin reuptake inhibitor (SSRI) compared with patients treated with placebo (0.04 versus 0.04 percent) [17].
- A meta-analysis of 207 randomized trials (40,028 patients) found no significant difference in suicide deaths for patients treated with an antidepressant compared with patients treated with placebo [18].
- A secondary analysis of 48,277 depressed patients found no significant difference in suicide deaths for patients treated with an SSRI, a non-SSRI antidepressant, or placebo (0.15 versus 0.20 versus 0.10 percent) [16].

It should be noted that the data used in these analyses were often overlapping, rather than independent.

New onset of suicidal behavior — Five re-analyses of data from randomized trials suggested that treatment with antidepressants was associated with an increased risk of nonfatal self-harm (attempt) or preparatory acts, compared with placebo [17,19-22]. The increased risk appeared to reside primarily in patients under the age of 25 years.

- Two meta-analyses (n >40,000 and 36,000 patients) focused on SSRI antidepressants and found that the risk of nonfatal self-harm was 1.6 to 2.3 times higher during the first weeks of SSRI treatment compared with treatment with placebo [17,19].
- A meta-analysis (372 trials, n >99,000 patients) found that the relative odds of nonfatal self-harm and preparatory acts varied by age. Compared with the risk during placebo treatment, the risk of nonfatal self-harm and preparatory acts during antidepressant treatment was [20]:
  - More than twice as high in patients under age 25 years (absolute difference approximately 4 per 1000 patients)
  - Approximately equal in patients age 25 to 64 years

- Approximately half as high in those age 65 or more years (absolute difference approximately 3 per 1000 patients)

- A meta-analysis of 70 trials (n >18,000 patients) compared antidepressants (duloxetine, fluoxetine, paroxetine, sertraline, or venlafaxine) with placebo on the outcome of suicidality, which included suicide, suicide attempt or preparatory behavior, intentional self-harm, and suicidal ideation [22]. The results indicated that suicidality varied by age:

  - Among adults (age ≥18 years), suicidality was comparable in patients who received antidepressants and placebo (odds ratio 0.8, 95% CI 0.5-1.3).

  - Among children and adolescents, antidepressants doubled the risk of suicidality (odds ratio 2.4, 95% CI 1.3-4.3).

Given the higher frequency of suicide attempts than suicide deaths, these analyses had adequate statistical power to detect effects of treatment with antidepressants overall or with a commonly used class of drugs (such as SSRIs). It appears that there is no difference in risk of suicide attempts among different classes of antidepressants. (See 'Differences among antidepressant classes' below.)

The analyses did not have adequate power to either detect or exclude even relatively large effects of individual antidepressant drugs. In addition, data from these trials could not be used to examine the effect of antidepressants on reducing baseline nonfatal self-harm or preparatory acts, because patients with such behavior were typically excluded from such trials.

New onset of suicidal ideation — Among patients with no suicidal ideation at the start of treatment, antidepressants do not increase the incidence of suicidal ideation:

- A pooled analysis of four randomized trials (n = 1399 patients with unipolar major depression) found that in patients with no suicidal ideation at baseline, new onset of suicidal thoughts was comparable with vilazodone and placebo (9 and 10 percent) [23].

- A pooled analysis of three randomized trials (n = 1374 patients with generalized anxiety disorder) found that in patients with no suicidal ideation at baseline, new onset of suicidal thoughts was comparable with vilazodone and placebo (4 and 6 percent) [23].

- A pooled analysis of four randomized trials (n = 1603 patients with unipolar major depression) found that in patients with no suicidal ideation at baseline, new onset of suicidal thoughts was comparable with levomilnacipran and placebo (11 and 9 percent) [24].

Reduction of existing suicidal ideation — Among patients with suicidal ideation at the start of treatment, antidepressants reduce suicidal thoughts and behavior:

- A meta-analysis of patient level data (37 randomized trials, 8477 adult and geriatric patients with unipolar major depression) compared fluoxetine (modal dose 20 mg per day) or venlafaxine (modal dose range 75 to 150 mg per day) with placebo [25]. The risk of suicidal thoughts and behavior over 12 weeks decreased more with active treatment than placebo; the effect appeared to be mediated by decreases in depressive symptoms.

- An eight-week randomized trial compared paroxetine (mean dose 39 mg per day) with placebo in 173 patients with unipolar major depression and found that suicidal ideation improved more with paroxetine, and the effect was clinically large [26].

Suicidality — The composite outcome of suicidality includes suicidal ideation, preparatory act, nonfatal self-harm or attempt, or death. Randomized trials indicate that antidepressants do not increase the risk of suicidality in adults. In a meta-analysis of 32 randomized trials (n >8,000 adults) that compared duloxetine, fluoxetine, paroxetine, sertraline, or venlafaxine with placebo, suicidality was comparable for active treatment and placebo (odds ratio 0.8, 95% CI 0.5-1.3) [22].

Suicidality and age — New onset of suicidality (suicidal ideation, preparatory act, nonfatal self-harm or attempt, or death) was evaluated in separate meta-analyses of randomized trials in adults as well as children and adolescents. Taken together, the findings showed a convincing trend of increasing risk in younger age groups, and decreasing risk in older adults (figure 1) [8,12]. The pattern is striking, though in itself does not constitute proof:

- Children and adolescents (odds ratio 2.22, 95% CI 1.40-3.60)
- Age 18 to 24 years (odds ratio 1.55, 0.91-2.70)
- Age 25 to 30 years (odds ratio 1.00, 0.60-1.69)
- Age 31 to 64 years (odds ratio 0.77, 0.60-1.00)
- Age ≥65 years (odds ratio 0.39, 0.18-0.78)

Studies of individual drugs show a similar trend of increasing risk with younger age. As an example, a meta-analysis of 61 randomized trials (14,911 adult patients with various psychiatric disorders) found that suicidality did not differ significantly between paroxetine compared with placebo (0.9 versus 1.1 percent of patients) [27]. However, a separate analysis of adults age 18 to 24 years found a nonsignificant, twofold increase in suicidality with paroxetine compared with placebo (2.6 versus 1.3 percent of patients; odds ratio 2.0, 95% CI 0.8-4.8). By contrast, the analysis of adults age 25 to 64 years found a nonsignificant decrease in suicidality with

paroxetine compared with placebo (0.8 versus 1.1 percent of patients; odds ratio 0.7, 95% CI 0.5-1.0).

Methodologic issues — The evidence available for examining whether antidepressants cause suicidality in adults is imperfect [15]. The highest quality of existing evidence consists of meta-analyses of data from secondary analyses of randomized efficacy trials.

The question about whether antidepressants precipitate suicidality should ideally be answered with placebo-controlled trials specifically designed to address this issue. However, no such trials exist and it would not be feasible to assign depressed patients to a long-term placebo arm. Instead, we must rely upon secondary analyses of trials designed to evaluate clinical efficacy and medical adverse events. Our ability to answer the question with these analyses is restricted by certain factors. First, patients at high risk for suicide attempts are typically excluded from such trials (limiting external validity or generalizability) [15]. Thus, data from such trials are limited in their capacity to detect change in suicidality and, in addition, cannot address the patients about whom we are most concerned. A second limitation of existing trials is that assessments were not designed to identify emergence or worsening of suicidal ideation. Consequently, reanalyses of those data depend on post-hoc classification of measurements intended for a different purpose. Third, although most trials involved patients with depression, some trials involved other psychiatric illnesses, such as anxiety disorders. Fourth, trials were short-term in duration, lasting approximately six to eight weeks.

Suicide deaths are relatively rare events in randomized trials, and there were typically fewer than 100 completed suicides for all drugs and placebo combined in the meta-analyses. Although the analyses included hundreds of trials and tens of thousands of patients, statistical power to detect differences in suicide mortality rates was modest. Thus, none of the analyses could rule out relatively large (ie, three- or fourfold) increases or decreases in risk of suicide mortality during antidepressant treatment compared with placebo. In addition, randomized trials will most likely never have sufficient statistical power to examine suicide mortality with specific antidepressant drugs.

Observational studies — Observational (cohort and case-control) studies suggest that treatment of depressed patients with an SSRI is associated with fewer suicide attempts or suicide deaths, compared with no treatment with an antidepressant [28-32]. In addition, symptom severity and the rate of suicide attempts appear to be higher during the time period preceding antidepressant treatment, compared with post-treatment.

Suicide death or attempt — Many observational studies suggest that antidepressants are not associated with an increased risk of suicidal behavior in adults [29,32,33]:

- A retrospective study of an administrative claims database in the United States examined suicide attempts in patients with a new episode of depression who were treated with antidepressants (n >100,000) or were not treated with antidepressants (n >200,000) [34]. After adjusting for the probability (propensity) to receive antidepressants, based upon potential confounding factors such as depression severity, history of suicide attempt, and comorbid general medical and psychiatric diagnoses, the analyses found that suicide attempts were comparable for the treated and untreated groups.

- A 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 US Food and Drug Administration (FDA) issued its warnings about a possible increased risk of suicidal ideation and behavior due to antidepressants [35]. The dataset included a cohort of young adults age 18 to 29 years (n = 1.4 million). Psychotropic drug poisonings was used as a proxy for suicide attempts. The study found that in the second year (2006) after the warnings, use of antidepressants declined by 24 percent, whereas psychotropic drug poisonings increased by 34 percent. It is worth noting that psychotropic poisonings may include accidental overdoses as well as suicidality.

- A meta-analysis of eight observational studies (n >250,000 depressed patients treated with an SSRI) found that use of an SSRI was associated with a decreased risk of suicide death or attempt, compared with no antidepressant treatment in controls (odds ratio 0.6, 95% CI 0.5-0.7) [28]. The protective effect was larger in patients age 65 years or more (odds ratio 0.5).

- Data from multiple health care systems, which studied depressed patients treated with antidepressants (n >70,000 [29], n >110,000 [31], and n >50,000) [34], all found the same pattern: suicide attempts were higher in the month before starting antidepressant medication and declined after starting medication.

Methodologic problems — Relative strengths and weaknesses of large observational studies are opposite those of randomized trials. Data from large population-based samples increase statistical power and maximize generalizability. However, nonrandom assignment of treatments introduces bias and threatens internal validity, especially if treatment decisions (such as the decision to prescribe an antidepressant or the choice of specific antidepressant) are influenced by clinical characteristics related to risk of suicidality. As an example, SSRIs are safer in overdose than tricyclic antidepressants, and clinicians may thus be more likely to prescribe SSRIs to patients who present with suicidality.

Ecological studies — Ecological studies used community-level, epidemiologic data to examine whether variation in rates of antidepressant use (either between areas or over time) were associated with variation in suicide deaths. Most studies found that higher rates of antidepressant use were associated with lower rates of suicide death [36-39]:

- A cross-sectional analysis of county-level data from the United States found that use of either an SSRI or other antidepressant (nefazodone, mirtazapine, bupropion, or venlafaxine) were each associated with lower suicide mortality [36].
- An increase of antidepressant use by 161 percent over a seven-year period in a district of Sweden was accompanied by a 36 percent decrease in the rate of suicide death [39].
- Analyses of time trends prior to the FDA warnings found that increasing rates of antidepressant use in England and Japan were accompanied by declines in suicide mortality [37,38].
- In a study that examined antidepressant prescribing rates and suicide rates across 29 European countries, increased use of antidepressants was associated with decreased suicides [40].

However, other ecological studies have found that antidepressant use was not associated with suicide rates [41].

These ecological studies cannot determine whether differences in suicide deaths are the direct result of differences in antidepressant use or whether differences in antidepressant use are simply a marker for other “true” causes of lower suicide rates (such as better recognition and treatment of depression).

Several observational studies have focused upon the effects of FDA safety advisories on antidepressant prescribing and suicidal behavior. These studies have generally found that safety advisories and the accompanying publicity were followed by decreases in rates of depression diagnosis and antidepressant prescribing, especially among adolescents and young adults [35,42-44]. Some studies also found evidence for increased rates of suicide attempts or psychotropic drug poisoning [35,44]. All of this research, however, is more relevant to policy questions regarding safety warnings than to the true causal relationship between starting antidepressant treatment and subsequent suicidal ideation or behavior. Whether or not antidepressant drugs sometimes precipitate suicidal ideation or behavior, policy changes (such as safety warnings) can have both intended and unintended consequences.

Differences among antidepressant classes — Concern about antidepressants and suicidality were first raised in regard to the SSRI fluoxetine [4], and the FDA warning about antidepressants and suicidality initially focused upon SSRIs and bupropion, mirtazapine, nefazodone, and venlafaxine [7]. The warning now extends to all antidepressants. Although a few observational studies suggest that some antidepressants are associated with higher rates of suicide deaths and attempts [45,46], most randomized trials and observational studies suggest that there is no difference in risk of suicidality among different classes of antidepressants, including SSRIs, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other antidepressants (bupropion, mirtazapine, and nefazodone) [5,16]:

- A meta-analysis of randomized trials found that the risk of nonfatal self-harm was comparable for SSRIs and tricyclic antidepressants [19].
- Multiple observational studies from different countries have found that different classes of antidepressants are associated with a comparable risk of suicide attempts and deaths [47-51]. One observational study using electronic health records data found that the risk of self-harm was greater in patients starting treatment with mirtazapine, trazodone, or venlafaxine, compared with patients starting treatment with citalopram [45]. However, another records-based study, which used propensity scoring to account for observed potential confounders, found that self-harm was comparable across individual drugs as well as drug classes [34].

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".)

SUMMARY

- The US Food and Drug Administration issued a warning in 2007 that patients age 18 to 24 years should be informed about the risk of becoming suicidal during initial treatment with any antidepressant drug, that clinicians should monitor patients closely during initial antidepressant treatment, and that depression and certain other serious psychiatric disorders are themselves associated with an increased risk of suicide. The warning does not advise against the use of antidepressants for approved indications, including depressive and anxiety disorders. (See 'Background' above.)

- There is no clear evidence that antidepressant treatment of depressed patients increases the risk of suicidality (suicidal ideation, action to prepare for an attempt, attempt or nonfatal self-harm, or death) in adults. Randomized trials suggest that antidepressants may possibly reduce suicidality; some observational and ecological studies show an association between greater antidepressant use and decreased suicide attempts and suicide deaths. (See 'Evidence review' above.)

- Available evidence strongly suggests an age-specific effect of antidepressants and risk of suicidality. Among young adults (and children and adolescents), onset of suicidality is significantly greater compared with placebo, during at least the first few weeks of antidepressant treatment. The absolute difference is approximately four patients per 1000. However, the same evidence shows no detectable effect of antidepressant treatment on suicidality in middle-aged adults, and suggests a protective effect (lower risk of suicidality with antidepressant medication than with placebo) among older adults. (See 'Suicidality and age' above.)

- The small risk of suicidality in young adults associated with antidepressants needs to be balanced against the clear risk of suicidality associated with depressive syndromes. (See 'Background' above.)

- Randomized trials and most observational studies suggest there is no difference in risk of suicidality among different classes of antidepressants, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other antidepressants. Available evidence is not adequate to determine the risk associated with a specific antidepressant drug. (See 'Differences among antidepressant classes' above.)

- Based upon our review of the evidence and our clinical experience, we believe it is prudent for clinicians to warn young depressed adults starting any antidepressant about the possible emergence of suicidality, to encourage all patients to quickly contact their clinician if they suffer new onset or worsening suicidality, and to evaluate any patient with suicidality every one or two weeks. In addition, all patients initiating antidepressant therapy should receive follow-up within two to four weeks. (See 'Background' above.)

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