REVIEW

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Antidepressant-Induced Suicidality: An Update

Roy R. Reeves[1,2] & Mark E. Ladner[1,2]

1 G.V. (Sonny) Montgomery VA Medical Center, Jackson, MS, USA
2 University of Mississippi School of Medicine, Jackson, MS, USA

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Correspondence
Roy R. Reeves, D.O., Ph.D., VA Medical Center – Mental Health (11M), 1500 E. Woodrow Wilson Drive, Jackson, MS 39216, USA.
Tel.: 601-368-4159;
Fax: 601-364-1395;
E-mail: roy.reeves@va.gov

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Evidence suggests that antidepressant treatment may in some cases result in worsening depression and increased risk of suicidality in pediatric and adolescent patients. The United States Food and Drug Administration requires that antidepressants carry a black box warning regarding such a risk in patients up to age 24. Many studies of antidepressant-induced suicidality among adults have also reported an increased risk, while several other investigations involving that population have not supported such a finding. This article provides an update of the controversy surrounding antidepressants as a potential cause of suicidal ideations or behavior. Antidepressant-induced suicidality appears to be an uncommon occurrence but also a legitimate phenomenon. Close monitoring and a follow-up care should be provided for patients after initiation of a new antidepressant.

Introduction

Depression is a common, often serious, disorder and one of the most common reasons for suicide. Antidepressants are commonly accepted as a standard of treatment for depression [1]. Although a large *meta*-analysis showed a mean medication versus placebo improvement of only about 2 HAM-D points [2], critical objections cannot disprove their positive overall effects against depression [3]. The medications may also affect personality distinct from the effect on depression [4].

However, antidepressants can increase the risk of suicidal thoughts and behavior in certain patients under certain conditions. Consequently, use of antidepressant medication and the risk of suicidality has become an issue of concern. In the United States the Food and Drug Administration (FDA) has been actively involved in providing guidelines and warnings related to the use of these medications. In 1991, the organization held a public meeting to address concerns about abnormal behavior in patients treated with fluoxetine. Attendees described suicidal behavior in acquaintances shortly after they had started taking the medication [5]. In March 2004, the FDA issued a Public Health Advisory to monitor patients being treated with antidepressants, and to strengthen the labeling of 10 commonly prescribed antidepressants regarding worsening of depression and emergence of suicidal thoughts [6]. In September 2004, the FDA required a black box warning related to increased risk of suicidality in pediatric patients for all antidepressant drugs, and in 2007 extended the warning to include patients up to age 24. Similar warnings have been issued by European agencies.

A large body of research has resulted from investigation of the effects of antidepressants. Findings have not been fully conclusive, and at times, contradictory, regarding the risk of suicidality during treatment with antidepressants. The authors of this article previously published a discussion of antidepressant-induced suicidality and its implications for clinical practice [7]. The present review is an update of recent findings related to this controversial topic.

Case Reports of Antidepressant-Induced Suicidality

The phenomenon of antidepressant-induced suicidality is well illustrated by the 2008 case report [8] of a man

who developed chronic posttraumatic pain and became depressed. He was treated with imipramine, then escitalopram, without side effects. Then his antidepressant was changed to duloxetine 30 mg/day. Within 4 days he became irritable and restless and had insomnia and difficulty in concentrating. Over the next 10 days his depression worsened. He "did not want to live like that" and lacerated both radial and popliteal arteries, nearly dying. The rapid changes in his condition concomitant with initiation of duloxetine suggested that the medication caused or significantly contributed to his suicide attempt.

Suicidal behavior secondary to antidepressant usage has been described with many other antidepressants. Over two decades ago Akiskal and Mallya [9] described a group of outpatients treated "overzealously" with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors who developed an agitated depression characterized by excitatory symptoms, including panic and suicidality. In 1988, Damluji and Ferguson [10] described patients with worsening depression, some with suicidal ideations, concurrent with treatment with desipramine, amoxapine, nortriptyline, or trazodone. Teicher et al. [11] described the emergence of suicidality with fluoxetine treatment in six patients and their publication was followed by several other reports of fluoxetine-induced suicidal behavior [12–14]. There have also been case reports of what appeared to be antidepressant-induced suicidality with other antidepressants, including paroxetine [15] and sertraline [16].

Evidence for and against Antidepressant-Induced Suicidality

Several investigations related to antidepressant-induced suicidality refute the risk of the occurrence of such a phenomenon, but others suggest that the risk of suicidal behavior does increase in certain patients during antidepressant treatment. The consensus of experts appears to agree with the latter point of view. One of the first investigations refuting the risk of antidepressant-induced suicidality was a *meta*-analysis of clinical trials data pooled from 17 double-blind studies conducted by the marketer of fluoxetine (Eli Lilly & Co, Indianapolis, Indiana, USA), which concluded that fluoxetine was not associated with increased risk of suicidal behavior [17]. A 2000 *meta*-analysis of the FDA database of studies of seven antidepressant drugs involving 16,639 patients [18] revealed annual rates of suicide and attempted suicide of 0.4% and 2.7% with placebo, 0.7% and 3.4% with active comparitors, and 0.8% and 2.8% with investigational antidepressants, respectively. Rates of attempted and completed suicide did not differ significantly among placebo- and drug-treated groups. A study of suicidal behavior among patients starting depression treatment with medication or psychotherapy showed that patterns of suicide attempt were not specific to medication and were consistently higher before starting antidepressants than afterward [19]. Another investigation involving 82,825 acute-phase antidepressant treatment episodes during a 10.5-year period [20] showed approximately one in 1000 risk of serious suicide attempt and one in 3000 of suicide, representing no significant increase in risk of suicidality after starting treatment.

A *meta*-analysis by Gunnell et al. of 477 British randomized controlled trials (over 40,000 individuals) of serotonin selective reuptake inhibitors (SSRIs) compared with placebo reported 16 suicides and 172 episodes of nonfatal self-harm, with the conclusion that increased risk of suicide and self-harm caused by SSRIs could not be ruled out, but larger trials with longer follow-up are required to assess the balance of risks and benefits fully [21]. Among 15,390 Finnish patients hospitalized after a suicide attempt, the current use of any antidepressant was associated with an increased risk of attempted suicide, but a decreased risk of completed suicide [22]. A large *meta*-analysis [23] assessing data from all manufacturer-sponsored short-term randomized controlled trials of nine commonly used antidepressants in patients with major depressive disorder and various anxiety disorders (259 trials, 51,000 patients) also concluded that antidepressants were not associated with an increased risk of suicide. Recently, a prospective study of inpatient antidepressant treatment [24] performed in 12 psychiatric hospitals (1014 patients) of the German research network on depression and suicidality reported a rather low suicide rate of 13.44 per 1000 patient years.

However, other investigations suggest that antidepressants may increase the risk of suicidal behavior, particularly among pediatric and adolescent patients. For example, data from 4582 patients in 24 placebo-controlled trials concluded that the use of antidepressant drugs was associated with a modestly increased risk of suicidality in pediatric patients [25]. An analysis of 27 trials of SSRIs, nefazodone, venlafaxine, and mirtazepine in participants younger than age 19 also showed increased risk (although antidepressants appeared to be beneficial) [26]. Several adult studies also suggested an increased risk of suicidal behavior. Data from 1.2 million elderly Ontario residents showed that initiation of SSRI therapy was associated with an increased, although low, risk of suicide during the first month of therapy [27]. A study of 159,810 users of amitriptyline, fluoxetine, paroxetine, and dothiepin [5] showed an increased risk of suicidal behavior during the first month of treatment, especially during the first 9 days. A review of 702 randomized

controlled trials from Medline and the Cochrane registry involving 87,650 patients documented an association between suicide attempts and the use of SSRIs [28]. Recently, a *meta*-analysis by Stone et al. [29] of 342 double-blind randomized placebo-controlled trials (99,231 adults assigned to antidepressants or placebo) found that risk of suicidality associated with use of antidepressants was strongly age-dependent. Compared with placebo, the increased risk for suicidality and suicidal behavior among adults under age 25 approached that seen in children and adolescents.

The net effect appeared to be neutral on suicidal behavior but possibly protective for suicidal ideations in adults aged 25–64, and to reduce the risk of both suicidality and suicidal behavior in those over 65.

Potential Mechanisms for Antidepressant-Induced Suicidality

How antidepressants might induce suicidality is not definitely known [30,31]. The findings of increased suicidality with antidepressants seem counterintuitive and progression of underlying depression reflecting ineffective drug treatment could be an initial consideration. However, in many clinical trials demonstrating their efficacy, antidepressants were associated with increased rates of suicidality. Thus, drug ineffectiveness is insufficient to explain an association of antidepressants with risk of suicidality compared to placebo. Several mechanisms (many of which have been concisely reviewed by Teicher [30]) have been postulated through which antidepressants may induce suicidal behavior [10,30,31]. Two primary pathways were initially postulated: in one model antidepressants may energize suicidal patients to act on their impulses; in the other antidepressants may produce a worsening of depressive symptoms leading to the emergence of suicidal thoughts or actions. Other pathways were subsequently proposed.

Antidepressants may rapidly energize an anergic patient before reversing their depressed mood such that a potentially suicidal patient may remain depressed but be provided with enough energy to act on preexisting suicidal ideations [31]. This may occur when some antidepressants produce uneven temporal resolution of symptoms. For example, symptoms such as psychomotor retardation and lethargy may be improved while depressed mood and feelings of guilt persist, resulting in a precarious condition. One explanation for this might be that certain depressed patients (particularly those with psychomotor retardation) might already be harboring suicidal thoughts, but lack of will to act on these impulses until their energy is increased during the early phase of antidepressant treatment before mood has improved [32]. An activation syndrome with agitation, insomnia, and irritability may also occur during the course of SSRI treatment [33].

The risk of elevation of mood by antidepressants in patients with bipolar disorder is well known. Unrecognized bipolar patients who are depressed may be misdiagnosed as having uncomplicated depression and may be at risk for development of mania when given an antidepressant, and known bipolar patients may experience elevated mood if not provided an adequate dosage of a mood stabilizer. Mixed mood states with a combination of depressive symptoms, increased energy, and increased impulsivity represent a potentially dangerous condition with increased risk of suicide [30]. Thus, a possible mechanism for antidepressant-induced suicidality could be induction of mania or hypomania in such patients. However, although theoretically feasible, overall data thus far do not support an increase in suicidality in bipolar patients exposed to antidepressants [34].

Jitteriness and akathisia may occur in some patients taking antidepressants. Akathisia is a sensation of intense restlessness that occurs primarily in patients taking antipsychotic drugs, and may sometimes result in patients becoming severely agitated or suicidal. Akathisia with suicide attempt has been described in eight patients taking fluoxetine [14]. Jitteriness sometimes seen in susceptible individuals taking TCAs may represent a mild form of akathisia. It has been suggested that more serious states of akathisia are more likely to occur with antidepressants with dopaminergic effects or high potency SSRIs than with other antidepressants [30,35]. However, a recent review of 107 articles by Sinclair et al. [36] concluded that an antidepressant-induced jitteriness/anxiety syndrome remains poorly characterized and the effect of the syndrome on suicide rates has not been evaluated.

In a small percentage of patients, depression may paradoxically worsen with antidepressant treatment in some cases leading to the occurrence of suicidal thoughts or actions [37]. In 1989, Baldessarini estimated [38] that, in general, a given antidepressant will produce a favorable response in about 70% of patients and most of the remainder will show no significant effects; however, a small percentage will worsen. A recent study found [24] that emergence, worsening, and improvement of suicidal ideations occurred in 3.2%, 14.74%, and 90.79% of hospitalized patients treated with antidepressants, respectively. In some instances worsening of depression may lead to the emergence of suicidality, as evidenced by a number of case reports [8,11–13,15,39,40]. Damlugi and Fergusson [10] estimated that worsening of depression occurred in about 1% of patients. An investigation of 554 subjects randomly assigned to 12 weeks of treatment with

imipramine or sertraline showed higher rates of 7.1% of all patients (8.6% of premenopausal women; 4.5% and 5.9% of postmenopausal women and men, respectively [41]. Although not a common occurrence, the possibility of an antidepressant increasing depressive symptoms obviously may pose a clinical dilemma for clinicians.

Worsening of depression in some cases may be related to the existence of many different clinical subtypes [42]. Three of the DSM-IV symptoms of major depression may show opposite changes (weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation), being broad enough to include very different types of depression. However, there are no means of defining these subtypes. Recent publications [43,44] have suggested new definitions for agitated or mixed depression based on the coexistence of a major depressive episode and hypomanic symptoms such as psychomotor agitation, intense inner tension, and racing or crowded thoughts. The authors suggested that when these types of states are treated with antidepressants, adverse outcome with increased agitation, psychotic symptoms, and increased risk of suicide might be induced.

In theory, antidepressants that may be stimulating could cause insomnia and thereby create an additional stressor and increased risk for some patients. Sleep disturbances are associated with increased risk for suicide [45] and suicidal ideations during depression are frequent in patients with insomnia compared to patients without insomnia. Patients with depression and insomnia score high on the Beck Scale for Suicidal Ideation compared with patients without insomnia [46]. Another possible construct involves the effect of antidepressants on cerebral electrical activity. Struve et al. [47] reported a strong association between paroxysmal Electroencephalography (EEG) abnormalities and suicidal and assaultive behavior, and hypothesized that EEG disturbances may lead to increased vulnerability to impairments in impulse control, and thereby to increased risk of suicidality. A study [48] of quantitative EEG parameters as predictors of changes during SSRI treatment in major depressive disorder showed that left-right asymmetry of combined theta and alpha power correlated significantly with changes in suicidal ideation from baseline. Thus, it is conceivable that, by inducing changes in cerebral electrical activity, antidepressants may enhance suicidal tendencies in some patients.

Soloff et al. [49] reported that almost half of borderline personality disorder patients treated with any antidepressant showed increased depression and suicidality. Certain patients in this population may respond differently to different antidepressants and be at risk for antidepressant-induced suicidality. The mechanism by which this might occur is unclear. It has also been postulated that some patients who do not suffer from borderline personality disorder may experience antidepressant-induced borderline reactions that include emergence of uncharacteristic aggression, self mutilation, and suicidality [30], again by an unknown mechanism. Patients with panic and anxiety disorders seem to be particularly susceptible to antidepressant-induced jitteriness and may also be more vulnerable to antidepressant-induced suicidality [50].

The neurobiological mechanisms underlying increased suicidality concurrent with antidepressant treatment are poorly understood. Abnormalities of neurotransmission have been implicated in the occurrence of depression and suicide, so neurotransmitters and/or neuroreceptor changes are likely to be involved in suicidal behavior concomitant with antidepressant treatment. The serotonergic (5-hydroxytryptamine; 5-HT) system has been studied the most extensively. Suicidality has been associated with a serotonin deficit independent of psychiatric diagnosis, and an increased number of $5HT_{1A}$ and $5HT_2$ receptors have been found in the prefrontal cortex of suicide victims [51], which could be expected to produce receptor sensitivity. Acute changes in brain serotonin receptor sensitivity might help explain the phenomenon of activation [32].

Electrophysiological studies in laboratory animals suggest that chronic SSRI administration induces adaptive neuronal changes and a resulting net enhancement in serotonergic function [52]. In contrast, subacute administration of SSRIs does not affect net 5-HT function. Increased availability of synaptic 5-HT secondary to serotonin transporter blockade by an SSRI is rapidly counterbalanced by a decrease in the firing rate resulting from $5\text{-}HT_{1A}$ autoreceptor activation so that net serotonergic function is neither increased or decreased [52]. These findings are consistent with the risk of suicidality being greatest early in antidepressant treatment.

Activity of the serotonin system might also be involved in the explanation for the observation that children are more sensitive than adults to the behavioral effects of SSRIs. Serotonin function varies during human development. Susceptibility to SSRI-induced behavioral side effects may be a function of brain maturation and vary according to the age of the patient [53].

Animal and postmortem studies have demonstrated that antidepressants increase central brain-derived neurotropic factor (BDNF) and activate the BDNF-tyrosine kinase receptor B (TrkB), which plays an important role in their therapeutic mechanisms. Several possible mechanisms related to this pathway have been proposed to account for antidepressant-induced suicidality [54]. Possibilities include (1) acute reduction of BDNF by antidepressants; (2) dose-dependent effects of antidepressants on central BDNF levels; (3) age-related

effects of antidepressants on BDNF expression; (4) overexpression of truncated TrkB or underexpression of full-length TrkB; (5) dysfunction of the TrkB pathway; and (6) antidepressant-induced mania secondary to increased central BDNF levels. Further exploration of these hypotheses is needed to elucidate the role of BDNF and TrkB in treatment-emergent suicidality.

Genetic factors may play a role in individual susceptibility to the effects of serotonin on suicidal behaviors. It has been found that a polymorphism in the serotonin transporter gene confers an increased risk of side effects to SSRI treatment [55]. Patients with slower hepatic biotransformation via cytochrome P450 2D6 isoenzyme might have reduced clearance of certain SSRIs, resulting in higher levels following a dose of medication [56]. These factors may contribute to idiosyncratic responses to antidepressants, including suicidality.

A *meta*-analysis of data from the Treatment of Adolescent Depression Study showed a significant correlation between the relative risk for suicidal behavior and antidepressant half life, particularly with fluoxetine, the antidepressant with the longest half life [57]. Exactly how antidepressant half life might be a contributing factor to treatment-emergent suicidal behavior is unclear, however. A number of other potential mechanisms for antidepressant-induced suicidality remain unexplored. Of particular interest would be the role of other subtypes of serotonin receptors and receptors for other neurotransmitters such as norepinephrine.

Are SSRIs More Likely to Induce Suicidal Behavior Than Are TCAs?

Another area of controversy involves the question of whether SSRIs place patients at a greater risk for suicidality than do other antidepressants such as TCAs. Altogether several *meta*-analyses are consistent to the extent that most of them do not find any differences between the risk of suicidal behavior with modern antidepressants/SSRIs compared to placebo or treatment with standard antidepressants, mostly TCAs [58]. Notably, an analysis by Jick et al. [5] using the UK General Practice Research Database from 1993 to 1999 showed a similar risk among users of amitriptyline, fluoxetine, and paroxetine compared with the risk among users of dothiepin. However, a *meta*-analysis by Fergusson et al. [28], which included the largest number of studies addressing this issue, documented an association between suicide attempts and the use of SSRIs. The increased risk was explained by a higher number of suicide attempts, while there was no actual increased suicide risk. Another relatively large *meta*-analysis by Gunnell et al. [21] found "weak evidence" that SSRIs could induce a risk of suicide attempts. Thus, the exact comparative risk is difficult to define. However, any potential induction of suicidality of SSRIs compared to TCAs may be compensated for by a much lower risk of a fatal outcome of a suicide attempt with an SSRI compared to a TCA [58].

Should Clinicians Alter Their Practice of Prescribing Antidepressants?

In spite of conflicting findings among studies, it may be seen that antidepressants may result in increased suicidal ideations in certain vulnerable persons, particularly early in the course of treatment. The risk in adults is less than that in children and adolescents. Still, an actual increase in *completed* suicide related to antidepressant treatment has not been conclusively demonstrated [59]. If antidepressants do increase the risk of suicide in some patients, the number of additional deaths would appear to be small because ecological studies have generally found that suicide mortality has declined (or at least not increased) as SSRI usage has increased [60]. For the patient population as a whole, there is reasonable evidence that antidepressants are able to reduce suicidal ideations and suicidal behavior in depressed patients [1] and benefits of antidepressants appear to be greater than risks from suicidal ideations and attempts [28].

Nevertheless, regulatory agency warnings have had a notable impact upon antidepressant prescribing patterns. In the United States from 1994 to 2004, diagnosis of depression in pediatric patients increased from 3 to 5 per 1000, but after the FDA advisory the rate decreased back to 1999 levels. The proportion of patients receiving no antidepressants increased to three times the rate predicted by the preadvisory trend [61]. Decreases in antidepressant prescribing have been associated with increases in rates of suicidality in children and adolescents [62]. Pediatric policies appear to have had an adverse effect on adult prescribing with the rate of diagnosed depression 7.7% lower after the advisory than would have been expected on the basis of the preadvisory historical trend. Adults with depression who did not receive an antidepressant increased from an average of 20% before the policy to an average of 30% [63]. The apparent impact on prescribing patterns has resulted in some arguing that the FDA overreacted to the analysis of the pediatric antidepressant trials with resultant unintended consequences [64]. Not all studies have demonstrated a negative impact, however. An ecological study of young people in the UK [65] concluded that the noticeable reduction in antidepressant prescribing following regulatory action in 2003 to restrict the use of SSRIs in persons under

age 18 did not seem to have been associated with changes, either favorable or unfavorable, in suicidal behavior in that population.

A decrease in antidepressant prescribing under these conditions may be a reason for concern because a valuable modality for the treatment of depression may be in danger of underutilization. But clearly, clinicians should not stop prescribing antidepressants when they are indicated. The World Psychiatric Association consensus statement recommends that risks of suicidality with antidepressants have to be balanced against the well-known beneficial effects of the medications [66]. Perhaps the matter may be best summarized by Moller's statement that, "The ongoing discussion about suicidality-inducing effects should not prevent physicians from prescribing SSRIs and other antidepressants to their patients if they are clinically indicated. However, they should take into account potential risks and manage them by good clinical practice" [58].

What precautions then should be taken to prevent complications in the rare patient who might exhibit suicidal behavior as a result of antidepressant treatment? Obviously, a number of biologic and psychosocial factors must be considered and clinical vigilance, regular clinical follow-up, and supportive therapeutic relationship with physicians and mental health professionals are essential ingredients for suicide prevention. One of the first mandates for physicians is *primum no nocere*—first do no harm. Psychiatrists should try to identify vulnerable individuals and develop effective prevention strategies to avoid iatrogenic precipitation of antidepressant-induced suicidality. Before initiating treatment with an antidepressant, clinicians should carefully review the patient's past psychiatric history and assess any family history of mental illness, including mood disorders and any suicide attempts among relatives. Past suicidal behavior by the patient, particularly any behavior representing adverse events that may have occurred as a result of previous antidepressant treatment, should be assessed. Patients should also be screened to determine whether they might have unrecognized bipolar disorder. Before prescribing an antidepressant, clinicians should educate patients and their families or other caregivers to watch for signs of worsening depression or suicidality, and be instructed to report such symptoms immediately if they occur [6].

When antidepressant treatment is initiated it is important to monitor patients, especially at the beginning of treatment or when the dose is increased or decreased. The FDA initially recommended that pediatric and adolescent patients have visits once a week during the first month of treatment, every 2 weeks during the second month, and a visit at 3 months [67], but later modified its recommendations to make them less specifically prescriptive of weekly in person visits. Additional studies need to be conducted to provide detailed guidelines for all patients. Regardless, careful monitoring should be considered. Particular attention should be given to patients with abrupt changes in symptoms and those developing symptoms that were not part of their presentation prior to the initiation of treatment. It is important to remember that worsening symptoms could be due to the underlying disease or might be a result of drug treatment, and that activating symptoms (e.g., irritability, impulsivity, anxiety, insomnia, agitation, hostility, akathisia, hypomania, and mania) could indicate increased suicidal risk.

The management of patients who do exhibit suicidality secondary to antidepressant treatment should involve a careful evaluation of suicide risk, including the presence of a plan of self-harm and the availability of a method to carry out such a plan (e.g., guns in the home). If there appears to be a risk of suicide, hospitalization should be seriously considered. In some instances the dose of an antidepressant may need to be decreased or the medication discontinued; this should be determined on an individual basis for each case. If antidepressants are to be stopped, some authorities recommend tapering instead of abrupt discontinuation [6]. Starting a different antidepressant is also a case by case decision, and when done would obviously require careful monitoring.

In conclusion, the benefits of antidepressants outweigh their risks and the judicious use of these medications can serve to effectively treat and actually protect depressed patients from suicide [68]. However, appropriate precautions and monitoring must be exercised to avoid the increased risk of suicide in an apparently small, but real, number of patients. Additional information on FDA recommendations on antidepressant use in children, adolescents, and adults may be obtained at www.fda.gov/cder/drug/antidepressants/default.htm.

Conflict of Interest

The authors have no conflict of interest.

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