Review Article

Association between antidepressant drugs and suicidal behavior: A review

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ABSTRACT

Antidepressant drugs provide relief to depressed patients. However, they have been historically blamed to cause worsening or an emergence of suicidal behavior. This has been a keen concern in recent years, especially in the pediatric population. There have been many studies regarding this issue and evidences have been equivocal. Several mechanisms of action for the suicidal behavior have been proposed. Clinical characteristics suggestive of vulnerable patients have been identified. The current review is an attempt to gather available evidence to help the clinician to arrive at an appropriate treatment decision while weighing the risk-benefit ratio of prescribing antidepressant drugs.

Key words: Antidepressants, Monitoring, Suicidal behavior, Vulnerable patients

INTRODUCTION

Suicide is a significant public health issue. An estimated 804000 suicide deaths occurred worldwide in 2012, representing an annual global age-standardized suicide rate of 11.4 per 100 000 population (15.0 for males and 8.0 for females). Furthermore, for every completed suicide; there is more than 10-fold number of non-fatal suicide attempts, and as many as almost one tenth of individuals worldwide, report having had suicidal ideation over their lifetime. The risk is about eightfold during a major depressive episode compared to periods of full remission. Although antidepressant drugs provide depressed patients with undeniable relief, their ability to induce suicidality has been of recent concern. The crucial point is whether antidepressants increase suicidality over and above what is caused by the underlying disorders, such as major depression. This review is an attempt to gather evidence suggesting that antidepressants amplify or induce suicidality; its associated mechanisms and finally weigh the risk of emergence of suicidal tendencies against the benefits of antidepressants.

HISTORY BEHIND THE ISSUE

In the early 1960s, case reports linked imipramine with the worsening of irritability or aggression. Eventually patients with worsening depression, some with suicidal ideations, concurrent with treatment with desipramine, amoxapine, nortriptyline, or trazodone were described.[1] Moreover, an emergence of suicidality with fluoxetine treatment was described by various researchers. Over the next decade, other case reports and studies surfaced including other selective serotonin reuptake inhibitors (SSRIs) like paroxetine among depressed children.[2] Subsequently, higher risk of "possibly suicide-related" events in trials with paroxetine involving depressed children was found resulting in a labeling change contraindicating paroxetine in pediatric major depressive disorders.[3] An FDA advisory was issued in October 2003, indicating that preliminary data suggested an increased risk of suicidality. By October 2004, the FDA had completed a review of 24 trials involving more than 4400 children and adolescents concluded that these medications had a two-fold (4% versus 2%) increased risk for suicidal

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behavior or ideation. The FDA called for a "black box warning" on antidepressant use in children and adolescents in September 2004.[4] In 2007, based on studies of eleven antidepressants in more than 77,000 patients, the FDA extended the warning to include patients up to age 24.

CONFUSION SURROUNDING THE DEFINITION OF SUICIDAL BEHAVIOR AND SUICIDALITY

In most proposed definitions suicide is considered as a fatal act of self-injury (self-harm) undertaken with more or less conscious self-destructive intent, however, vague and ambiguous. The most basic and significant obstruction in defining any correlation between suicide and antidepressant has been a lack of uniformity in defining suicidal behavior. Suicidality is a term brought in wide use after FDA analyses and has come to mean suicidal ideation (passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior), intent (self-injurious behavior associated with some intent to die, preparatory actions toward imminent), attempt or behavior (person takes steps to injure self but is stopped by self or other, intent to die is either stated or inferred). The relationship between terms suicidal ideation, attempts, and completed suicide is unclear and occurrence of one has no predictive value for other. The lack of uniformity of definitions across the studies thus makes generalization of their findings difficult to validate.

PROPOSED MECHANISMS FOR ANTIDEPRESSANTS INDUCING SUICIDAL TENDENCIES AND THEIR CRITICISMS

Several means are possible for antidepressant drugs to cause emergence and/or exacerbate suicidal tendencies. Postulated mechanisms and their criticisms are discussed below:

Energising role of antidepressants

It was observed that during initial treatment with tricyclic antidepressant (TCAs), the risk of suicide once more becomes serious as retardation fades. Analyses of community clinical practice databases substantiate this observation, especially during the first 9 days. However, single drug fatalities occurred most often in patients taking the mixed amine uptake inhibitors amitriptyline and dothiepin thereby undermining the hypothesis that selective noradrenergic uptake inhibitors would energize patients.[5]

Paradoxical worsening of depression

A given antidepressant will generally produce a favorable clinical response in the recipients, but a small percentage will worsen. It was estimated that about 1% of 800 patients treated in their practice showed a paradoxical response to antidepressants, with a marked worsening of depression, and de novo emergence of suicidal ideation.[1] Similar observations has been reported by others.[6] Serotonin uptake inhibitors have been known to produce "bilaterally-symmetric" adverse effects (e.g., anorexia vs. hyperphagia, hypersomnia vs. insomnia), due to the complexity of the serotonin system.

Under treatment of depression

There is substantial literature suggesting that many suicide victims with major depressive disorder are inadequately treated.

Akathisia

Akathisia is an intense state of inner agitation and restlessness that is often provoked by antipsychotic drugs. It has been reported to have resulted in suicidal states in some patients. Although serious states of akathisia have been reported in patients receiving high potency SSRIs and or antidepressants with dopaminergic effects, they are not well known for this effect. Another related but vague concept put forth recently is of "activation syndrome" which comprises of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, even hypomania, and mania.[7] However, they are treatments of choice for panic.

Manic or mixed states

Several studies suggest that TCAs and MAOIs substantially increase the rate at which bipolar patients switch from depression into mania. Dysphoric and mixed states are associated with a significantly a higher risk of suicide. But, no valid systematic data exist on the relative propensity of different antidepressant agents to induce mixed states.

Insomnia or disturbances in sleep architecture

A study of patients who eventually committed suicide indicated that one of the most outstanding features of their clinical picture was sleeplessness. Antidepressants, particularly those that are stimulating can potentially enhance risk if they induce insomnia. The relationship between alterations in sleep

architecture and suicidal tendencies has also been put forth. However, many of these studies focused on possible trait differences rather than state differences.

Obsessive suicidal preoccupation

Development of violent suicidal preoccupations during treatment with fluoxetine. But also no statistical association between the use of fluoxetine and the emergence of substantial suicidal ideation in OCD population.[8]

Alterations in electroencephalogram (EEG) activity

The earliest pioneering studies on physiological determinants of suicide reported a strong positive association between paroxysmal EEG disturbances and suicidal ideation.[9] The authors hypothesized that the paroxysmal EEG disturbances may have led to enhanced vulnerability to impairments in impulse control and planning (ability to reject suicidal thoughts).

Genetic basis

A possible biologic basis for SSRI-related suicidal ideation in patients who had received initial treatment with citalopram for depression has also been explored.[10] These researchers found that two high-risk allele markers within the *GR1K2* (first intron on chromosome 6) and *GR1A3* (chromosome X) genes, were associated with treatment-emergent suicidal ideation independent of citalopram dose. These findings have been replicated in patients from the Munich antidepressant response signature project.

EVIDENCE THAT ANTIDEPRESSANTS INDUCE SUICIDALITY

There are systematic investigations that support the existence of antidepressant-induced suicidality. Many case-control studies, randomized controlled trial (RCT) and currently numerous reviews and meta-analyses are available as in Tables 1-4.

EVIDENCE THAT ANTIDEPRESSANTS REDUCE SUICIDALITY

Antidepressants as a group are well-established for reducing the severity of depressive symptoms, improvement in mood, motor retardation and also the associated negative cognitions including suicidal behavior. Proposed mechanisms by which antidepressants act to reduce suicidality include their pro-serotonergic as well as pro-catecholaminergic properties which confers efficacy against depression and enhancement of serotonergic tone by agents such as SSRIs should also reduce features of impulsivity and aggression potentially linked with violent or suicidal behavior. Many studies have been done establishing the benefits of antidepressant in reducing suicidality. Summary of such studies shown in Tables 5-8.

Safety warnings about antidepressants and widespread media coverage decreased antidepressant use, and there were simultaneous increases in suicide attempts among young people. Some studies found no evidence that treatment with antidepressants elevated the risk of suicidality. Instead, treatment reduced the risk and provided a protective effect. In a unique kind of evidence the variation in the SSRI sales and suicide mortality using data from 26 countries for up to 25 years was studies and conclusion reached that an increase in SSRI sales of 1 pill per capita (12% of 2000 sales levels) reduces suicide by 5%.[32] In yet another unique study the exposure to antidepressants in suicides was estimated both by prescriptions antemortem and by toxicology post-mortem. This study supported the notion that antidepressants prevent suicide in youth and contradicts the rationale for the "black box." The researchers argued that truly suicidal persons might have been denied antidepressants, or abstained from them, due to the "black box" and then committed suicide because of untreated depression.[33]

EVIDENCES FOR NEUTRAL EFFECTS OF ANTIDEPRESSANTS ON SUICIDALITY

About Tables 9-11 reveals trials where the antidepressants have been shown to be equivocal in their efficacy in reducing suicidal risk.

The difference in various studies right from protective effect to induction of suicide can be best explained by varied population under study, different outcome variables measured, various statistical methods employed and different antidepressant group studied.

DIFFERENTIAL RISK BETWEEN VARIOUS ANTIDEPRESSANTS

Like the whole issue of suicidality and antidepressant, the differential risk between various antidepressants is also equivocal. A positive association between TCA prescription and suicide rate was observed.[38] Further, it has been proposed that that a switch from TCAs to SSRIs as first line treatment for depression may prevent 300-450 overdose deaths a year. Comparison of 226,866 veterans on SSRIs, new-generation non-SSRI antidepressants (bupropion, mirtazapine, nefazodone,

Table 1: Meta-analyses

Sample source	Study design	Size	Diagnosis	Medication	Clinical outcome
Fergusson *et al*., 2005	Meta-analytic review of 702 RCTs	87,650	Depression	SSRIs/TCAs/ other Antidep	A significant increase in the number of suicide attempts (odds ratio 2.28) for patients receiving SSRIs compared with placebo.[11]
Stone *et al*., 2009	Meta-analysis of 372 double blind RCTs	99,231	Depression, other psychiatric disorders, and non-psychiatric disorders	SSRIs/SNRIs, other modern antidepressants, TCAs and other antidepressants	In non-psychiatric indications, SB and SI were extremely rare. In psychiatric indications, risk was associated with age. For age <25 odds ratios was 1.62-0.79 for those aged 25-64, and 0.37 for those aged ≥65. Risk of suicidality with antidepressants is strongly age dependent.[12]

RCT: Randomized controlled trial, SSRIs: Selective serotonin reuptake inhibitors, SNRI: Serotonin and norepinephrine reuptake inhibitors, TCA: Tricyclic antidepressant

Table 2: RCT

Sample source	Study design	Size	Diagnosis	Medication	Clinical outcome
Abbott, 2003	Placebo controlled trial	1385	Depression in children and Adolescents	Paroxetine versus placebo	Non-significantly more suicidal thoughts and behaviors (without completions) in patients taking paroxetine (25 of 738 patients) than placebo (8 of 647 patients).[2]
Aursnes *et al.* 2005	Review of 16 randomized controlled placebo	NA	Depression	Paroxetine versus placebo	Recommendation of restrictions to be extended to include usage by adults.[6]

RCT: Randomized controlled trial

Table 3: Epidemiological studies

Sample source	Study design	Size	Diagnosis	Medication	Clinical outcome
Jick *et al.* 1995	Nested case-control study	172598	Depression	Dothiepin, amitriptyline, clomipramine, imipramine, flupenthixol, lofepramine, mianserin, fluoxetine, doxepin, and trazodone	143 people committed suicide. People recieving high doses were at risk. Rates of suicide were higher in patients who received fluoxetine.[13]
Martinez *et al.* 2005	Nested case-control study	146095	Depression	TCAs, SSRIs and other antidepressants including mirtazapine, reboxetine	1968 cases of non-fatal self-harm and 69 suicides. The risk of non-fatal self-harm for people prescribed SSRIs versus users of TCA for those aged 18 or younger was high (1.59) but no association was apparent in other age groups.[14]
Tiihonen *et al.* 2006	Cohort study in Finland with mean follow-up of 3.4 years	15390	Depression	RR of completed suicides, suicide attempts leading to hospitalization, and overall mortality during TCA, SSRI and SNA treatment versus no antidepressant use was calculated	Fluoxetine use was associated with a slightly lower, and Venlafaxine use with a slightly higher risk of suicide than no antidepressant use. Mortality was substantially (31-41%) lower during the use of any antidepressants than control.[15]
Juurlink *et al.* 2006	Population-based case-control study	1.2 million residents 66 years of age and older from 1992 to 2000	Depression	SSRI/TCAs/SNRI except MRTZ	1,329 suicide cases. Initiation of SSRI is associated with an increased risk of suicide (odds ratio: 4.8) during the 1st month of therapy. The absolute risk is low.[16]
Seemuller *et al.*, 2009	Naturalistic prospective study	*n*=1014	Depression	Not specified	The rate of suicides and emergence and worsening of suicidal ideation comparable to various RCTs. No definite conclusions about compounds due to design of study.[17]

RCT: Randomized controlled trial, SSRIs: Selective serotonin reuptake inhibitors, SNRI: Serotonin and norepinephrine reuptake inhibitors, TCA: Tricyclic antidepressant

and venlafaxine) and TCAs found that suicide attempt rates were lower among patients who were treated with antidepressants than among those who were not, with a statistically significant odds ratio for SSRIs

Table 4: Trend studies

Sample source	Location	No. of suicide	Antidepressant-related deaths	Trend for prescriptions (antidepressant)	Clinical outcome
Isacsson *et al.*, 1994	Sweden	3400	542	Not assessed	Toxic concentrations of antidepressants were found in only 190 cases (5.6%). Most depressed patients who commit suicide are not taking antidepressants immediately before death. Therapeutic failure may be a greater problem with antidepressants than toxicity.[18]
Morgan *et al.*, 2004	England	46,747	3,987 deaths involving TCAs and 430 with SSRIs	Increasing	Increased antidep prescription was associated with a fall in suicide rates and fall in fatal poisoning involving TCAs suggesting a change in preference high-risk patients.[19]

TCA: Tricyclic antidepressant, SSRIs: Selective serotonin reuptake inhibitors

Table 5: Meta-analysis

Sample source	Study design	Size	Diagnosis	Medication	Clinical outcome
Montgomery *et al.* (1995)	Series of meta-analyses of double-blind, parallel-group efficacy studies lasting up to 6 weeks	4,507	Depression	Paroxetine versus placebo or active comparator	Fewer new suicidal thoughts and reduction in suicidal ideation with paroxetine versus placebo in all analyses; 2.8-fold fewer suicides with paroxetine versus active comparator; 5.6-fold fewer suicides with paroxetine versus placebo.[20]
Letizia *et al.* (1996)	Meta-analysis of double-blind, randomized, placebo-controlled, parallel-group trials	3,828	Depression	Fluvoxamine versus placebo	Greater reduction in suicidal ideation (P=0.01) and less worsening of suicidal ideation (P<0.01) with fluvoxamine versus placebo; no difference in emergence of suicidal ideation.[21]
Beasley *et al.* (2000)	Seta-analysis of double-blind, parallel-group efficacy studies	4,016	Depression	Fluoxetine versus placebo versus active comparators	Fluoxetine superior to placebo in reducing baseline levels of suicidal ideation.[22]
Bridge *et al.*, 2007	Meta-analysis of 27 trials of pediatric MDD	NA	MDD, OCD, or non-OCD anxiety disorders	Selective serotonin reuptake inhibitors, nefazodone, venlafaxine, and mirtazapine	There was increased risk difference of suicidal ideation/suicide attempt across all trials the pooled risk differences were not statistically significant.[23]

Table 6: RCT

Sample source	Study design	Size	Diagnosis	Medication	Clinical outcome
Georgotas *et al.* (1987)	7-week trial, double-blind, randomized, placebo-controlled	75	Depression	Nortriptyline versus phenelzine versus placebo	Reduction from baseline suicidality with nortriptyline (within 2 weeks) or phenelzine (within 3 weeks) versus placebo (P<0.05).[24]
Muijen *et al.* (1988)	6-week trial, double-blind, randomized, placebo-controlled	81	Depression	Fluoxetine versus mianserin versus placebo	Greater improvement on suicidality item of the MADRS in subjects who took fluoxetine versus placebo at week 7 (P<0.01).[25]

RCT: Randomized controlled trial

and tricyclics and weaker, non-significant effect was observed for non-SSRIs. The risk within individual classes of antidepressants has been studied with the conclusion that prescriptions for SSRIs and other new-generation non-SSRI antidepressants, e.g., nefazodone, mirtazapine, bupropion, and venlafaxine are associated with lower suicide rates.[38]

In an observational study Mirtazapine, venlafaxine, and trazodone were associated with the highest rates of suicide and attempted suicide or self-harm. However, the findings may reflect indication biases and residual confounding from the severity of depression and differing characteristics of patients prescribed these drugs.

Table 7: Epidemiological study

Sample source	Study design	Size	Diagnosis	Medication	Clinical outcome
Angst *et al.* (2002)	Naturalistic study of patients who were followed prospectively for 34-38 years	406	Major depressive disorder, bipolar disorder	Any medications (including antidepressants, neuroleptics, and lithium)	Reduction in mortality due to suicide among those who had been treated with antidepressants versus untreated patients (P=0.04).[26]
Angst *et al.* (2005)	Naturalistic study of patients who were followed prospectively for 40-44 years (1963-2003)	406	Unipolar depression, bipolar disorder	Any medications (including antidepressants, neuroleptics, and lithium)	11.1% of the 406 patients had committed suicide. Suicide rates were highest among Dep patients and lowest among manic patients. Prospectively, the suicide rate decreased over the 44 years' follow-up. Lithium, neuroleptics and antidepressants reduced suicides significantly. Long-term treatment also reduced overall mortality, and combined treatments proved more effective than mono-therapy.[27]
Simon *et al.*, 2006	Population-based study from 1992 to 2003. (n=65103)	31 suicide deaths 76 serious suicide attempts	Depression	Bupropion, citalopram, FXT, fluvoxamine, MRTZ, nefazodone, PXT, sertraline, escitalopram, and venlafaxine	One in 3,000 treatment episodes, and risk of serious suicide attempt is approximately one in 1,000 do not indicate a significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs.[28]

Table 8: Trend studies

Sample source	Location	No. of suicide	Antidepressant-related deaths	Trend for prescriptions (antidepressant)	Clinical outcome
Isacsson (2000)	Sweden for 1978-96	NA	-	Increasing	Five-fold increase in the use of antidepressants might reduce Swedish suicide rates by 25%.[29]
Hall *et al.*, 2003	Australia for 1991-2000	National rate	-	Increasing	National rates of suicide did not fall significantly, the higher the exposure to antidepressants the larger the decline in rate of suicide.[30]
Milane *et al.*, 2006	United States for 1960-2002	Suicide rates 13.7 per 100,000 gradually declined to 10.4 in 2000	-	Fluoxetine prescriptions increased from 2,469,000 to 33,320,000	Decrease in expected suicide mortality of 33,600 individuals.[31]

Some studies found similar rates of deliberate self-harm for depressed patients who initiate treatment with either an SSRI or a serotonin and norepinephrine reuptake inhibitors (SNRI) suggesting that physicians need not weigh differential suicide risk when deciding which class of antidepressant to prescribe. Similar evidence has been noted for SSRI and SNRI antidepressants in children also.

CLINICAL CHARACTERISTICS OF VULNERABLE PATIENTS

The FDA in 2004 has listed such warning symptomatologic correlates as psychomotor agitation, panic, insomnia, irritability, aggressiveness, and impulsivity, and in addition, urged screening for personal and family history for bipolar disorder.[4] Other researchers have also concluded that irritability, psychomotor agitation and racing/crowded thoughts were the major predictive clinical characteristic for emergent suicidality. Increased risk may be more likely in patients aged 30 or younger and those who experienced a psychosocial stressor prior to the suicide attempt.

In a naturalistic study of inpatients with a major depressive episode five clinical factors for the emergence of suicidal ideation were determined: Age (with higher risk at age <45 years), treatment resistance, the number of hospitalizations, presence of akathisia and comorbid personality disorder.[17]

Table 9: Meta-analysis

Sample source	Study design	Size	Diagnosis	Medication	Clinical outcome
Tollefson *et al.* (1993)	Combination of 2 meta-analyses of randomized controlled trials: (1) 17 North American studies; (2) 46 international studies	5,655	Major depressive disorder	Fluoxetine versus placebo or tricyclic comparator	No significant differences between groups in rates of suicidal acts or emergence of SI in the separate meta-analyses; less emergent SI for fluoxetine versus placebo in "worldwide analysis" (P=0.03); reduction from baseline SI with fluoxetine versus placebo in North American and worldwide analyses (P<0.001).[34]
Khan *et al.* (2000)	Metaanalytic review of FDA databases for suicidal acts during registration trials with new antidepressants	19,639	Depression	SSRI (sertraline or paroxetine) versus other antidepressant (nefazodone, mirtazapine, or bupropion) versus Placebo	No significant differences found between those who received any of these active agents versus placebo; numerically fewer attempts or completions occurred with subjects taking placebo.[35]

SSRIs: Selective serotonin reuptake inhibitors

Table 10: RCT

Sample source	Study design	Size	Diagnosis	Medication	Clinical outcome
Beasley *et al.* (1992)	Combination of 22 double-blind, randomized, placebo-controlled trials	355	Obsessive-compulsive disorder	Fluoxetine versus placebo	No differences in the emergence of SI or acts; no reduction from baseline SI.[8]
Tanum *et al.* (2000)	Cumulative report of data from open-label and controlled trials	2,530	Depression	Reboxetine (n=1,503) versus placebo or active comparator (n=1,027)	Suicide attempts or completions occurred in 0.26% with reboxetine versus 0.56% with placebo; formal statistical comparisons not reported.[36]

RCT: Randomized controlled trial

Table 11: Epidemiological studies

Sample source	Study design	Size	Diagnosis	Medication	Clinical outcome
Leon *et al.* (1999)	Prospective, naturalistic data from NIMH collaborative depression study	643	Depression	Fluoxetine (n=185) versus other antidepressants (unspecified; n=226) versus no medication (n=232)	Non-significant trends favoring the prevention of suicide attempts or completions with either fluoxetine or other antidepressants compared to no treatment.[37]

MANAGING PATIENTS ON ANTIDEPRESSANT EMERGENT SUICIDALITY

A careful assessment of patients, education of patients and caregivers, and monitoring and follow-up care is clearly indicated when treatment with an antidepressant is undertaken:[3]

- Patients should be carefully screened for bipolar disorder before being started on antidepressants
- Patients and their caregivers or healthcare providers should be educated to be watchful of worsening depression, emergence of suicidality, and activation symptoms, and to report any changes at the beginning of treatment or after any change in dose
- Start with a low dose of antidepressant for several days
- Schedule a follow-up appointment at the end of the initial consultation
- If the patient's depression worsens or suicidality emerges with an antidepressant, consider stopping or changing the antidepressant therapy
- Assess the mechanism of emergent suicidality and treat/attend it accordingly
  - o Rule out co-morbid substance intake
  - o Activation symptoms or syndrome:
    - stoppage (preferably tapered)/lowering the dose
    - adjunctive medicine like clonazepam,
    - propranolol (for akathisia).
  - o Identification of manic/mixed state:
    - Mood stabilizer
    - Antipsychotics.
- If antidepressant medication needs to be discontinued, it should be tapered rather than stopped abruptly

- Consider augmenting pharmacotherapy with psychotherapy (cognitive behavioral therapy/dialectical behavior therapy)
- Consider the need for electroconvulsive therapy, lithium, and clozapine as proven antisuicidal agents.

SPECIAL POPULATION

Children and adolescents

Evidence in the young population has been equivocal. No association between use of SSRIs and likelihood of suicide attempt was found using both child and adult person-level data from a large-scale insurance claims database. However, a nested case-control study of 146,095 individuals receiving the first antidepressant prescription for treatment of depression found a greater risk of nonfatal self-harm among youths receiving SSRIs compared with those receiving tricyclics.[14] The serotonin/norepinephrine reuptake inhibitor venlafaxine had the highest risk of suicidality in the FDA analysis of pediatric RCTs.[39]

Old age

One study found that their datawas consistent with the FDA's finding that in adults older than 25 years SSRI are protective against suicide.

In medical illness

A large and consistent body of literature suggests that TCAs may have specific beneficial effects in the following: Peptic ulcer disease, irritable bowel syndrome, muscle contraction headache, migraine headache prophylaxis, urinary incontinence in adults, insomia, chronic pain syndromes, chronic pelvic pain, chronic low back pain, rheumatic pain, fibrositis and fibromyalgia syndromes, and neuropathic pain. Many common illnesses are independently associated with an increased risk of suicide in the elderly. The risk is greatly increased among patients with multiple illnesses.[40]

A review found evidence that antidepressants, cause improvement in depression in patients with a wide range of physical diseases significantly more frequent than either placebo or no treatment.

Limitations of the studies

The below limitations of RCTs have been noted:

- Assessment of overall suicide risk or the ratio of suicide attempts to completed suicides in the study group, could not be fully done since much of these data were missing
- Clinical trial participants are not identical to routine clinical samples of depressed patients
- Length of participation of patients in clinical trials is generally shorter than in general clinical practice
- Routine clinical practice is also usually associated with higher doses of medication as well as the use of other medications
- As RCTs are designed to primarily identify clinical efficacy, there are limitations on the gathering of exhaustive data on unwanted side effects
- Selection of patients for an RCT generally excludes patients who are at risk for suicide
- Because of the pressures against the use of placebo in RCTs, as well as cost considerations, there is a trend to having unbalanced groups with fewer subjects in the placebo and control arms. This results in reduced power and the need for larger numbers of patients in the studies.

Thus, there are limitations to extrapolating the findings to all depressed patients.

The results of FDA's meta-analysis could be explained by ascertainment bias, whereby patient suicidality is more likely to be noted in medical record reviews of patients (children or adults) randomly assigned to an active medication condition compared with placebo controls, due to increased contact with medical staff because of increased side effects in general with an active medication compared with placebo. Similarly, suicide attempts may also be subject to ascertainment bias in that overdoses of placebo may not be identified by study staff.

It has also been reported that adverse event reporting system used by the FDA is a passive reporting system and is, therefore, subject to numerous sources of selection bias, over- and under-reporting. Most notable among these are:

- A lack of a denominator indicating the population at risk for a particular drug-AE interaction
- Lack of control or comparison groups
- Recall bias of patients and reporters
- Poor case documentation in the reports
- Large amounts of missing data on patient characteristics
- Media sensitivity, and
- Substantial under-reporting.

Other limitations of the studies are summarized below:

- Emergence of suicidality may simply be due to underlying psychopathology

- Some investigators did not factor in deliberate self-harm in the attribution of patients in their study. If these patients had been screened as not being actively suicidal at the onset of a trial, they were nevertheless still at higher risk subsequently. This type of susceptibility bias was very much present in the Leon *et al*. study in 1999
- A common deficiency in many studies of the treatment of the depression is a consideration of unipolarity or bipolarity. The latter is readily missed for a number of reasons but because the condition is not uncommon and requires adapted treatment with mood stabilizers, a greater risk of suicide may appear in these patients than in undertreated patients
- Increased regional antidepressant medication treatment is linked to a higher suicide rates. Communities with high rates of suicide (and presumably high rates of severe psychiatric illnesses) may simply tend to use more antidepressant medications than communities with low rates of suicide
- Moreover, the suicidal tendencies item of the Hamilton depression scale for Depression has been used as the instrument for quantification. It is not meant to clearly discriminate and quantify the nuances of suicidality
- Confounding by indication, whereby patients are selected for a particular treatment depending upon their diagnosis, or the severity of their medical condition, may lead to erroneous conclusions of a treatment resulting in an adverse outcome. Instead, factors such as age, gender, suicidal ideation and depression itself appeared to be the primary risk factors for these outcomes.

The current study was also subject to limitations. The most important one was that due to confusion in the definition of various suicidal terminologies; there might be inaccurate values in incidents of suicidal behavior.

CONCLUSION

Since antidepressant drug treatments were introduced, there has been an argument whether the use of antidepressant is safe or not. Studies have given evidences both for and against the possibility of treatment-emergent or worsening suicidal behavior. Further, the mechanisms of causation have also been debated over and still remain inconclusive. However, these studies carry many limitations from the description of the problem to the methodology involved. Appropriate assessment of potential risky clinical features, close monitoring, regular follow-up, early recognition of warning signs and judicious use of adjunct medications and appropriate psychotherapy is more likely to reduce overall risks. To date the evidence for antidepressant-induced suicide is not that robust to deter the prescription of antidepressants and the benefits of prescribing them far outweigh the risks.

REFERENCES

1. Damluji NF, Ferguson JM. Paradoxical worsening of depressive symptomatology caused by antidepressants. J Clin Psychopharmacol 1988;8:347-9.
2. Abbott A. British panel bans use of antidepressant to treat children. Nature 2003;423:792.
3. Culpepper L, Davidson JR, Dietrich AJ, Goodman WK, Kroenke K, Schwenk TL. Suicidality as a possible side effect of antidepressant treatment. J Clin Psychiatry 2004;65:742-9.
4. Food and Drug Administration. FDA Public Health Advisory: Worsening Depression and Suicidality in Patients Being Treated with Antidepressant 2004. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161696.htm. [Last accessed on 2015 Jun 20].
5. Montgomery SA, Pinder RM. Do some antidepressants promote suicide? Psychopharmacology (Berl) 1987;92:265-6.
6. Aursnes I, Tvete IF, Gaasemyr J, Natvig B. Suicide attempts in clinical trials with paroxetine randomised against placebo. BMC Med 2005;3:14.
7. Harada T, Sakamoto K, Ishigooka J. Incidence and predictors of activation syndrome induced by antidepressants. Depress Anxiety 2008;25:1014-9.
8. Beasley CM Jr, Potvin JH, Masica DN, Wheadon DE, Dornseif BE, Genduso LA. Fluoxetine: No association with suicidality in obsessive-compulsive disorder. J Affect Disord 1992;24:1-10.
9. Struve FA, Klein DF, Saraf KR. Electroencephalographic correlates of suicide ideation and attempts. Arch Gen Psychiatry 1972;27:363-5.
10. Laje G, Paddock S, Manji H, Rush AJ, Wilson AF, Charney D, *et al.* Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. Am J Psychiatry 2007;164:1530-8.
11. Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, *et al.* Association between suicide attempts and selective serotonin reuptake inhibitors: Systematic review of randomised controlled trials. BMJ 2005;330:396.
12. Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, *et al.* Risk of suicidality in clinical trials of antidepressants in adults: Analysis of proprietary data submitted to US Food and Drug Administration. BMJ 2009;339:b2880.
13. Jick SS, Dean AD, Jick H. Antidepressants and suicide. BMJ 1995;310:215-8.
14. Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, *et al.* Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: Nested case-control study. BMJ 2005;330:389.
15. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry 2006;63:1358-67.

16. Juurlink DN, Mamdani MM, Kopp A, Redelmeier DA. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. Am J Psychiatry 2006;163:813-21.
17. Seemüller F, Riedel M, Obermeier M, Bauer M, Adli M, Mundt C, *et al.* The controversial link between antidepressants and suicidality risks in adults: Data from a naturalistic study on a large sample of in-patients with a major depressive episode. Int J Neuropsychopharmacol 2009;12:181-9.
18. Isacsson G, Holmgren P, Wasserman D, Bergman U. Use of antidepressants among people committing suicide in Sweden. BMJ 1994;308:506-9.
19. Morgan OW, Griffiths C, Majeed A. Association between mortality from suicide in England and antidepressant prescribing: An ecological study. BMC Public Health 2004;4:63.
20. Montgomery SA, Dunner DL, Dunbar GC. Reduction of suicidal thoughts with paroxetine in comparison with reference antidepressants and placebo. Eur Neuropsychopharmacol 1995;5:5-13.
21. Letizia C, Kapik B, Flanders WD. Suicidal risk during controlled clinical investigations of fluvoxamine. J Clin Psychiatry 1996;57:415-21.
22. Beasley CM Jr, Koke SC, Nilsson ME, Gonzales JS. Adverse events and treatment discontinuations in clinical trials of fluoxetine in major depressive disorder: An updated meta-analysis. Clin Ther 2000;22:1319-30.
23. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, *et al.* Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: A meta-analysis of randomized controlled trials. JAMA 2007;297:1683-96.
24. Georgotas A, McCue RE, Friedman E, Cooper TB. Response of depressive symptoms to nortriptyline, phenelzine and placebo. Br J Psychiatry 1987;151:102-6.
25. Muijen N, Roy D, Silverstone T, Mehmet A, Christie M. A comparative clinical trial of fluoxetine, mianserin and placebo in depressed patients. Acta Psychiatr Scand 1988;78:384-90.
26. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: Follow-up over 34–38 years. J Affect Disord 2002;68:167-81.
27. Angst J, Angst F, Gerber-Werder R, Gamma A. Suicide in 406 mood-disorder patients with and without long-term medication: A 40 to 44 years' follow-up. Arch Suicide Res 2005;9:279-300.
28. Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. Am J Psychiatry 2006;163:41-7.
29. Isacsson G. Suicide prevention – A medical breakthrough? Acta Psychiatr Scand 2000;102:113-7.
30. Hall WD, Mant A, Mitchell PB, Rendle VA, Hickie IB, McManus P. Association between antidepressant prescribing and suicide in Australia, 1991-2000: Trend analysis. BMJ 2003;326:1008.
31. Milane MS, Suchard MA, Wong ML, Licinio J. Modeling of the temporal patterns of fluoxetine prescriptions and suicide rates in the United States. PLoS Med 2006;3:e190.
32. Ludwig J, Marcotte DE, Norberg K. Anti-depressants and suicide. J Health Econ 2009;28:659-76.
33. Isacsson G, Ahlner J. Antidepressants and the risk of suicide in young persons – Prescription trends and toxicological analyses. Acta Psychiatr Scand 2014;129:296-302.
34. Tollefson GD, Fawcett J, Winokur G, Beasley CM Jr, Potvin JH, Faries DE, *et al.* Evaluation of suicidality during pharmacologic treatment of mood and nonmood disorders. Ann Clin Psychiatry 1993;5:209-24.
35. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: An analysis of the Food and Drug Administration database. Arch Gen Psychiatry 2000;57:311-7.
36. Tanum L. Reboxetine: Tolerability and safety profile in patients with major depression. Acta Psychiatr Scand Suppl 2000;402:37-40.
37. Leon AC, Keller MB, Warshaw MG, Mueller TI, Solomon DA, Coryell W, *et al.* Prospective study of fluoxetine treatment and suicidal behavior in affectively ill subjects. Am J Psychiatry 1999;156:195-201.
38. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and rate of suicide. Arch Gen Psychiatry 2005;62:165-72.
39. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63:332-9.
40. Juurlink DN, Herrmann N, Szalai JP, Kopp A, Redelmeier DA. Medical illness and the risk of suicide in the elderly. Arch Intern Med 2004;164:1179-84.

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