Topical review

Suicidal ideation and behavior associated with antidepressant medications: Implications for the treatment of chronic pain

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

1. Introduction

Antidepressant medications have a prominent role in the treatment of chronic pain. For patients with neuropathic pain, tricyclic antidepressants (TCAs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been recommended as first-line treatments; selective serotonin reuptake inhibitors (SSRIs) and bupropion are generally considered third-line treatments because of inconsistent or unreplicated clinical trial results [1,6,7]. For treatment of fibromyalgia, it has been recommended that various antidepressants reduce pain and often improve function and should therefore be considered [5]. Randomized clinical trials (RCTs) of duloxetine, an SNRI, have shown efficacy in chronic low back pain and osteoarthritis, and have provided the basis for its approval by the US Food and Drug Administration (FDA) to treat chronic musculoskeletal pain [38].

The use of antidepressants for analgesic effects when treating chronic pain—and for antidepressant effects in patients with co-morbid depression—makes it important to consider the evidence regarding associations between these medications and suicidal ideation and behavior (SIB) [24,39]. After conducting a meta-analysis, the FDA issued a black box warning in 2004 regarding an increased risk of suicidal ideation and behavior in children and adolescents treated with all antidepressants [35]. The European Medicines Agency reviewed SSRIs and SNRIs and issued similar warnings in 2005 [8]. To determine whether these warnings should be extended to adults, the FDA conducted another meta-analysis [36], which led to an expanded warning that included young adults 18 to 24 years old [37].

In considering associations between antidepressant use and SIB, it is important to recognize that individuals with chronic pain are at increased risk for SIB. For example, the odds of attempted suicide are approximately 2 times higher in the presence of chronic pain [17], and the prevalence of suicidal ideation appears to range from approximately 20% to 25% [26,34] to as high as 48% in fibromyalgia patients [3]. In addition, depression—a well-established risk factor for SIB—is a very common co-morbidity in individuals with chronic pain that undoubtedly contributes to their increased risk of SIB [2,27].

The objective of this article is to review recent research examining associations between antidepressants and SIB in adults. Several studies outside the search criteria were included that also specifically addressed antidepressants and SIB in adults. Separate searches were performed to identify guidances and other unpublished materials from FDA and EMA.

2. Methods

A Medline search was performed exploding the MESH search terms “antidepressants” and “suicide,” and a PubMed search was conducted using the same terms as well as individual classes of antidepressants. We selected for emphasis those articles that were generally recent (ie, 2005 and after) and involved associations between antidepressants and SIB in adults. Several studies outside the search criteria were included that also specifically addressed antidepressants and SIB in adults. Separate searches were performed to identify guidances and other unpublished materials from FDA and EMA.

3. Results

On the basis of the literature search, 5 meta-analyses and 6 cohort or case-control studies were selected as most relevant to evaluating antidepressant-associated risks of SIB; these studies are summarized in Table 1. None of these studies specifically focused on SIB outcomes in patients with chronic pain, and only 2 specified that chronic pain patients were included [4,33].

The FDA examined 372 RCTs of 11 newer antidepressants in adults to evaluate associations with SIB using an approach similar to their analysis of children and adolescents [33]. Treatment
<table>
<thead>
<tr>
<th>Study</th>
<th>Indications for AD treatment</th>
<th>Sample</th>
<th>Research design</th>
<th>Outcomes</th>
<th>Key results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpenter et al. [4]</td>
<td>Any indication (including 1 fibromyalgia trial)</td>
<td>14,911 Adult patients (mean age = 41 y)</td>
<td>Meta-analysis of 57 paroxetine RCTs and 4 long-term extension studies</td>
<td>SIB</td>
<td>No significant differences for SIB between paroxetine and placebo across all indications. Greater suicidal behavior in paroxetine vs placebo-treated patients with MDD (OR = 6.7; 95% CI = 1.1–149.4; P = .058) and in those aged 18–24 years regardless of condition (OR = 2.4; 95% CI = 0.9–7.3; NS)</td>
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<tr>
<td>Ferguson et al. [10]</td>
<td>Any indication</td>
<td>87,650 Patients (in 91% of the trials, mean age &lt;60 y)</td>
<td>Meta-analysis of 702 RCTs of SSRIs</td>
<td>Completed suicide, suicide attempts</td>
<td>Significant increases in fatal/nonfatal suicide attempts in patients treated with SSRIs vs placebo (OR = 2.28; 95% CI = 1.14–4.55; P = .02) and SSRIs vs therapeutic interventions other than TCAs. The difference between SSRIs and TCAs was not significant</td>
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<td>Gibbons et al. [12]</td>
<td>Depression</td>
<td>226,866 Veterans (mean age = 59 y)</td>
<td>Cohort study; before and after AD treatment, no AD treatment</td>
<td>Suicide attempts</td>
<td>Suicide attempt rates were lower with SSRI and TCA treatment than no AD. Suicide attempt rates were higher before vs after starting treatment with SSRIs and non-SSRIs; for SSRIs, this effect was significant for all ages except 18–25 y SIB decreased over time for adults treated with fluoxetine or venlafaxine vs placebo, but the difference was not significant for youths treated with fluoxetine (MMLE = 0.081; P = .17)</td>
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<tr>
<td>Gibbons et al. [13]</td>
<td>Depression</td>
<td>9,185 Patients (7,517 adult, 960 geriatric, 708 youth)</td>
<td>Meta-analysis of 20 fluoxetine and 21 venlafaxine RCTs</td>
<td>SIB</td>
<td>No evidence that SSRIs increased the risk of suicide or suicidal ideation, but there was an increased risk of self-harm (OR = 1.57, 95% CI = 0.99–2.55)</td>
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<tr>
<td>Gunnell et al. [15]</td>
<td>Any indication</td>
<td>52,503 Adult patients</td>
<td>Meta-analysis of 477 RCTs of SSRIs</td>
<td>SIB</td>
<td>Number of suicide attempts decreased from 39 in the 6 months before AD treatment to 20 during treatment. Suicide ideation was reduced from 47% at baseline to 14% or less after 3 weeks</td>
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<td>Mulder et al. [21]</td>
<td>Depression</td>
<td>72 Young adult patients (18–24 y); 123 adult patients (24–65 y)</td>
<td>Prospective cohort study</td>
<td>SIB</td>
<td>In adults, antidepressant treatment was not significantly associated with completed suicide (OR = 0.90, 95% CI = 0.52–1.55) or suicide attempts (OR = 1.10, 95% CI = 0.86–1.39), but these associations were significant in children and adolescents</td>
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<td>Olsson et al. [22]</td>
<td>Depression</td>
<td>607 Adult patients (19–64 y); 271 child and adolescent patients (6–18 y)</td>
<td>Case-control study</td>
<td>Completed suicide, suicide attempts</td>
<td>For completed suicides, unadjusted and adjusted HRs for venlafaxine vs citalopram were 2.44 (95% CI = 1.12–5.31) and 1.70 (95% CI = 0.76–3.80); for venlafaxine vs fluoxetine were 2.85 (95% CI = 1.37–5.94) and 1.63 (95% CI = 0.74–3.59), and for venlafaxine vs dothiepin were 2.54 (95% CI = 1.07–6.02) and 1.31 (95% CI = 0.53–3.25)</td>
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<td>Rubino et al. [28]</td>
<td>Depression or anxiety</td>
<td>219,088 Adult patients (18–89 y)</td>
<td>Cohort study</td>
<td>Completed suicide, suicide attempts</td>
<td>Outcome rates ranged from 4.41/1000 PY to 9.09/1000 PY, with most events occurring in the 6 months after treatment initiation. There was no meaningful variation in the risk of suicide and suicide attempts by type of antidepressant</td>
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<td>Schneeweiss et al. [29]</td>
<td>Depression</td>
<td>287,543 Adult patients (≥18 y)</td>
<td>Cohort study with propensity score adjustment</td>
<td>Completed suicide, hospitalization for self-harm</td>
<td>Risk of a suicide attempt was highest in the month before starting an AD, fell by more than one-half in the month after starting medication, and then declined progressively</td>
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<td>Simon et al. [30]</td>
<td>Any indication</td>
<td>82,285 Episodes of AD treatment in patients aged 5–105 y (mean age = 44 y)</td>
<td>Cohort study</td>
<td>Completed suicide, suicide attempts requiring hospitalization</td>
<td>For suicidal behavior (ie, completed, attempts, and preparatory acts), the ORs were 2.30 (95% CI = 1.04–5.09) for ages &lt;25 y, 0.87 (95% CI = 0.58–1.29) for ages 25–64 y, and 0.06 (95% CI = 0.01–0.58) for those aged ≥65 y. Analyzing age as a continuous variable, the OR for suicidal behavior declined at the rate of 4.6% per year of age (P = .001), which was steeper than for suicidal ideation</td>
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<td>Stone et al. [33]</td>
<td>Any indication (including trials of neuropathic pain, fibromyalgia, migraine)</td>
<td>99,231 Adult patients (mean age = 43 y)</td>
<td>Meta-analysis of 372 RCTs submitted to the FDA</td>
<td>SIB</td>
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**Abbreviations:** AD, antidepressant; CI, confidence interval; FDA, United States Food and Drug Administration; MDD, major depressive disorder; MMLE, marginal maximal likelihood estimate; NS, not significant; OR, odds ratio; PY, person years; RCT, randomized clinical trial; SIB, suicidal ideation or behavior; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
indications were depression, other psychiatric disorders, and non-psychiatric disorders, and 99,231 subjects randomized to antidepressants or placebo were rated using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) [25]. Analyses demonstrated that patients 18 to 24 years old had an increased risk of SIB with antidepressants that approached the risk previously seen in children and adolescents (odds ratio \( \text{OR} = 2.3 \), 95% confidence interval \( \text{CI} = 1.04–5.09 \)). For patients 25 to 64 years old, the effect was neutral for suicidal behavior, whereas SIB was decreased in those 65 years and older who were administered antidepressants. When the data were analyzed by type of antidepressant, no significant differences were found. These results provided the basis for expanding the FDA warning to include young adults treated with any antidepressant [37]. Of note is the smaller nonpsychiatric group of patients—which included patients diagnosed with painful diabetic peripheral neuropathy and other types of neuropathic pain, fibromyalgia, and migraine—in which no completed suicides occurred and the rates of suicidal ideation were comparable in subjects administered antidepressants versus placebo.

Several other analyses of SIB in RCTs of antidepressants have also been conducted. Ferguson et al. [10] examined 345 RCTs of SSRIs that had information regarding fatal or nonfatal suicide attempts and reported significantly higher odds ratios for suicide attempts for SSRIs compared to placebo (OR = 2.28, 95% CI = 1.14–4.55) and to interventions other than TCAs; the difference between SSRIs and TCAs was not significant. A meta-analysis of 477 RCTs of SSRIs submitted by pharmaceutical companies to the UK's Medicines and Healthcare Products Regulatory Agency found no evidence that SSRIs increased the risk of suicide [15]; for nonfatal self harm, however, the authors reported “weak evidence” of increased risk with SSRIs (OR = 1.57, 95% CI = 0.99–2.55).

Although an overall increased risk of SIB was not found in a meta-analysis of 61 paroxetine RCTs [4], a greater incidence of suicidal behavior was associated with paroxetine in patients with major depression (OR = 6.7, 95% CI = 1.1–149.4). A re-analysis of 20 fluoxetine and 21 venlafaxine RCTs found that SIB decreased over time for adults randomized to fluoxetine or venlafaxine versus placebo [13].

To determine whether antidepressant classes (ie, TCAs, SSRIs, SNRIs, and other agents) are associated with different risks of suicide and self-harm, a cohort study used propensity score analyses to control for confounding by indication [29]. The outcomes were similar when SSRIs were compared to other agents, and the authors concluded that their results supported the FDA's decision to treat all antidepressants alike for SIB warnings. In a cohort study, venlafaxine was associated with higher risks of suicide and suicide attempts compared with citalopram, fluoxetine, or dothiepin [28]. However, venlafaxine-treated patients had more severe depression—which could reflect use in treatment-refractory depression [32]—and their risk of suicide was substantially reduced in adjusted analyses.

In veterans with depression, treatment with SSRIs or TCAs was associated with significantly lower suicide attempt rates compared with no antidepressant treatment, and SSRI treatment significantly reduced suicide risk in all patients except those 18 to 25 years old, possibly because of their smaller numbers [12]. In health plan patients and in a case-control study of children and adults, antidepressant treatment was not associated with completed suicide or suicide attempts in adults [22,30], but it was associated with increases in children [22]. In outpatients with psychiatric disorders, suicide attempts and ideation decreased after treatment initiation, although 22% of patients experienced treatment-emergent SIB [21].

4. Conclusions

Suicide is a relatively rare event, occurring in approximately 1 million people worldwide each year. Because this relative scarcity makes suicide difficult to study, a variety of research designs have been used to evaluate the effect of antidepressants on SIB [14]. Unfortunately, the results of these studies are inconsistent. This lack of consistency may be accounted for by several factors, including differences in research designs (eg, meta-analyses of RCTs vs cohort studies), conditions treated, and how confounding by indication was addressed, which is particularly important when examining SIB. In addition, there were differences in how SIB was classified and assessed. Some studies examined only suicide attempts, whereas others included suicidal ideation or related behaviors such as preparatory acts and self-injurious behavior without intent to die. Although several studies used the C-CASA [25] to classify SIB, a variety of other approaches have been used for the classification and assessment of SIB [19,20]. To increase the comprehensiveness and comparability of SIB assessments in clinical trials, the FDA recently released a revised draft guidance [39] that recommends evaluating SIB using the 11 categories included in the Columbia Suicide Severity Rating Scale (C-SSRS) [24], which has been translated into more than 100 languages.

The FDA expanded warning included all antidepressants, because the risks of SIB did not differ significantly in their analyses [33], and there was little evidence of differences among antidepressants in the other studies that we reviewed. This could be due to limited statistical power; given the differences among antidepressants in postulated mechanisms of action, the possibility that these medications may confer different risks of SIB requires additional investigation.

Perhaps most importantly from the perspective of chronic pain treatment, the studies that we reviewed examined patients treated with antidepressants for a considerable number of different conditions. Not surprisingly, the majority of studies focused on major depression and other psychiatric disorders, and relatively few studies examined SIB in patients being treated for other conditions. Only 2 studies specified that chronic pain patients were included [4,33]; however, it is possible that patients with chronic pain were included in the other studies that examined patients with any indication for antidepressant treatment. Although there is no evidence that antidepressant-associated risks of SIB differ as a function of the specific condition being treated, the research specifically addressing this issue is limited, and relationships between antidepressant treatment and SIB in chronic pain may be different from what has been described for psychiatric disorders.

Despite the limitations of the studies and inconsistencies among their results, the data that we have reviewed have clear clinical implications. SIB should be carefully evaluated in young adults 18 to 25 years of age with chronic pain, both when initiating antidepressant treatment and periodically during treatment, regardless of the specific antidepressant being considered. Special attention should be devoted to young adults with evidence of past or current SIB and those with past or present mood disorder, because the results of multiple studies suggest that co-morbid depression can be expected to increase the risk of SIB in chronic pain patients. Caution is also required because antidepressant overdose in suicide attempts can cause death as a result of respiratory, cardiac, renal, and convulsant effects. Potential lethality varies among different antidepressants, both within and between drug classes. TCAs have greater lethality than SSRIs, with SNRIs occupying an intermediate position closer to SSRIs than to TCAs [11,14,16,18,31,40]. In addition, polypharmacy is common in chronic pain treatment, and the increase in overdose risk when patients are taking opioids, benzodiazepines, and other sedative hypnotics should also be considered. Because there is no evidence at present that one class of antidepressant medication is associated with a lower risk of SIB than another, the selection of an antidepressant for its analgesic effects should be based on results of randomized trials conducted in subjects with that patient’s chronic
pain condition as well as the different antidepressants’ side effect profiles. Although available data from adults 25 years and older suggest that antidepressants probably do not increase the risk of SIB and appear to reduce it in those 65 years and older [33,36], most of these considerations are also relevant in the evaluation and treatment of older patients, because chronic pain and the depression that often accompanies it are risk factors for suicide. As well, many patients with chronic pain present with significant psychiatric and medical co-morbidities that complicate diagnosis and make it challenging to tease apart the effect of antidepressants on SIB from the various other factors that can contribute to SIB in these patients.

In deciding whether to initiate or continue antidepressant treatment in chronic pain patients, careful evaluation is necessary to determine whether treatment benefits outweigh risks. As concluded regarding the use of AEDs in neuropathic pain and fibromyalgia [23], the effectiveness, safety, and tolerability of other pharmacologic and nonpharmacologic treatments that have not been associated with increased SIB should be taken into account in this benefit–risk assessment. To maximize the value of such benefit–risk assessments, additional research is needed to determine whether there are differences among antidepressants in their risks of SIB; whether these risks vary depending on the specific condition being treated; and the extent to which these risks vary with patient characteristics such as age, sex, and race/ethnicity. In this research, it will be critically important to take into account multiple other factors that potentially contribute to SIB in patients with chronic pain as well, for example, mood, substance, and other psychiatric disorders, psychosocial stressors, and comitant medications.

Conflict of interest

A.P. has no potential financial conflicts of interest to report. V.C. has received research grant support from the US National Institutes of Health and the US Centers for Disease Control and Prevention, and his effort was supported in part by R49 CE002093. M.J.G. has received in the past 12 months honoraria from Bristol-Myers Squibb and Eli Lilly. R.H.D. has received in the past 12 months research grants from the US Food and Drug Administration and US National Institutes of Health, and compensation for activities involving clinical trial research methods from Astellas, AstraZeneca, Avanir, Biogen, Centrexion, Charlestown, Chronocell, Concert, Daiichi Sankyo, Eli Lilly, Johnson & Johnson, Lpath, Metys, Nektar, Neura, Olatec, PeriPhenA, Phosphagenics, Q-Med, QTX Pharma, Reldma, Salix, Sorrento, Spinifex, and Teva.

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[9] Schneeweiss S, Patrick AR, Solomon DH, Mehta J, Dormuth C, Miller M, Lee JC, Wang PS. Variation in the risk of suicide attempts and completed suicides by psychiatric indication and treatment of older patients, because chronic pain and the most of these considerations are also relevant in the evaluation and treatment of older patients, because chronic pain and the depression that often accompanies it are risk factors for suicide. As well, many patients with chronic pain present with significant psychiatric and medical co-morbidities that complicate diagnosis and make it challenging to tease apart the effect of antidepressants on SIB from the various other factors that can contribute to SIB in these patients.

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