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Topical review

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

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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 individuals 18 years and older. Associations between antidepressants and SIB in children and adolescents are beyond the scope of this article, as is antidepressant use for migraine prophylaxis [9]. We reviewed associations between SIB and antiepileptic drugs (AEDs) and their implications for the treatment of neuropathic pain and fibromyalgia in a previous article [23].

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

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Table 1
Study characteristics and key results.

Study	Indications for AD treatment	Sample	Research design	Outcomes	Key results
Carpenter et al. [4]	Any indication (including 1 fibromyalgia trial)	14,911 Adult patients (mean age = 41 y)	Meta-analysis of 57 paroxetine RCTs and 4 long-term extension studies	SIB	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)
Ferguson et al. [10]	Any indication	87,650 Patients (in 91% of the trials, mean age <60 y)	Meta-analysis of 702 RCTs of SSRIs	Completed suicide, suicide attempts	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
Gibbons et al. [12]	Depression	226,866 Veterans (mean age = 59 y)	Cohort study; before and after AD treatment, no AD treatment	Suicide attempts	Suicide attempt rates were lower with SSRI and TCA treatment than no AD. Suicide attempts 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
Gibbons et al. [13]	Depression	9,185 Patients (7,517 adult, 960 geriatric, 708 youth)	Meta-analysis of 20 fluoxetine and 21 venlafaxine RCTs	SIB	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; $P = .17$)
Gunnell et al. [15]	Any indication	52,503 Adult patients	Meta-analysis of 477 RCTs of SSRIs	SIB	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)
Mulder et al. [21]	Depression	72 Young adult patients (18–24 y); 123 adult patients (24–65 y)	Prospective cohort study	SIB	Number of suicide attempts decreased from 39 in the 6 months before AD treatment to 20 during treatment. Suicidal ideation was reduced from 47% at baseline to 14% or less after 3 weeks
Olfson et al. [22]	Depression	607 Adult patients (19–64 y); 271 child and adolescent patients (6–18 y)	Case-control study	Completed suicide, suicide attempts	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
Rubino et al. [28]	Depression or anxiety	219,088 Adult patients (18–89 y)	Cohort study	Completed suicide, suicide attempts	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)
Schneeweiss et al. [29]	Depression	287,543 Adult patients ($\geqslant$18 y)	Cohort study with propensity score adjustment	Completed suicide, hospitalization for self-harm	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
Simon et al. [30]	Any indication	82,285 Episodes of AD treatment in patients aged 5–105 y (mean age = 44 y)	Cohort study	Completed suicide, suicide attempts requiring hospitalization	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
Stone et al. [33]	Any indication (including trials of neuropathic pain, fibromyalgia, migraine)	99,231 Adult patients (mean age = 43 y)	Meta-analysis of 372 RCTs submitted to the FDA	SIB	For suicidal behavior (ie, completed, attempts, and preparatory acts), the ORs were 2.30 (95% CI = 1.04–5.09) for ages <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 $\geqslant$65 y. Analyzing age as a continuous variable, the OR for suicidal behavior declined at the rate of 4.6% per year of age ($P = .001$), which was steeper than for suicidal ideation

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.