COMMENTARY

ANTIDEPRESSANTS AND SUICIDAL BEHAVIOR: ARE WE HURTING OR HELPING?

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Summary

There is ongoing discussion of potential increases in suicidal risk among patients being treated with antidepressant drugs, particularly juveniles treated with serotonin-reuptake inhibitors (SRIs). Evidence of moderately greater risk of non-lethal suicidal behaviors among juveniles exposed to SRIs vs. placebo in controlled trials is suggestive, but a comprehensive meta-analysis of risks of suicides and attempts in adults and juveniles fails to show either increased or decreased risk with antidepressants of all types, nor significant differences between SRIs and tricyclics. We propose that prudent clinical practice calls for particularly close clinical monitoring of patients starting on any mood-elevating treatment in certain high-risk circumstances, including any patient with previous suicidal behavior and adults or children, especially new patients, who present with or develop agitated-irritable features or may have undiagnosed bipolar or psychotic disorders.

Key Words: Antidepressants – Suicidal risk

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There has been much renewed discussion of a previously vigorously debated question (Teicher et al. 1993, Healy et al. 1997) about suicidal risk arising with use of the most widely employed antidepressant drugs, the serotonin reuptake-inhibitors (SRIs). Renewed interest arises from critically reassessed findings of trials involving children and adolescents that suggest increases of broadly-defined "suicidality," and have led to new regulatory warnings and reminders that most SRIs are not explicitly approved for use in juvenile depression (Hammad 2004, US FDA 2004, Whittington et al. 2004). However, the findings involved are not easily interpreted, nor are the implications clear regarding safe use of mood-elevating agents in adults.

Estimated suicide rates for the US general population are approximately 4/100,000/year in juveniles (0.6–7.4 for ages 5–19 years), or about one suicide per 300,000 person-months at risk in this age-range, compared to a suicide rate of 11.0/100,000/year for all ages (US NCHS 2004). In a recently-compiled summary of 25 randomized, controlled trials involving over 4400 children or adolescents with various disorders exposed to SRIs for 1–4 months, there were no suicides (Hammad 2004, US FDA 2004), indicating a risk below 0.1%/year. These studies did provide data on broadly-defined "suicidality"—ranging from thoughts or planning to self-injuries of varied lethality and intent. Acts considered probable suicide-attempts numbered 30 or fewer, or about 3/100/year, independent of treatment.

Suicide attempt-rates in children and adolescents are not well established, but can be estimated at 10–20-times the suicide rate (Tondo et al. 2003), or 0.04–0.08/100/year, in the general population. Among juveniles with depressive or anxiety disorders in SRI trials, the suicide-attempt rate (about 3/100/year) was 50-times greater, despite efforts to exclude suicidal subjects from most trials. The pooled *relative* risk (RR) for attempts during treatment of juveniles randomized to SRI vs. placebo was 1.90 (95%CI: 1.00–3.63), despite a wide range across trials (RR=0.30–4.70), supporting recent regulatory cautions about the use of SRIs in children and adolescents (Hammad 2004, US FDA 2004). Of particular interest to us, in these trials, suicidality was much more frequent with newly emerging anger or agitation (RR=6.60, CI: 3.50–12.5; Hammad 2004). In our overview of studies of antidepressant treatment of adults or children, meta-analysis of risks of suicides and attempts found no significant risk-differences with/with-

out antidepressant exposure, nor between SRIs and TCAs (Baldessarini et al. 2005). There was also little association of antidepressant-use and county-level suicide rates across the US in a recent study (Gibbons et al. 2005).

Such evidence regarding possible risk of suicidal behaviors needs to be balanced against the clinical efficacy of antidepressants. Our meta-analysis of response-rates in trials of all antidepressants in juvenile depression found only modest average superiority over placebo (Tsapakis et al. 2005). Though SRIs yielded more robust-appearing drug/placebo differences than tricyclic antidepressants (TCAs), this impression mainly reflected larger samples (statistical power) rather than greater effect-sizes; indeed, estimated differences between SRIs and TCAs were nonsignificant. Overall, the preceding findings suggest that risk/benefit considerations for SRI use with any depressed patient, and juvenile depressed patients in particular, are far from straightforward at this time. A clinical implication is that considerable skill and judgment are required to successfully manage individual persons at risk for suicide.

An intriguing and important question is why evidence of an expected protective effect of antidepressant treatment against suicide or life-threatening attempts appears to be lacking (Baldessarini et al. 2005a). There are substantially lower risks of suicides or attempts during long-term treatment with lithium salts in manic-depressive disorders (Baldessarini et al. 2001, 2003; Goodwin et al. 2003; Tondo et al. 1998, 2001, 2003; Tondo and Baldessarini 2005), and long-term use of clozapine in chronic psychotic disorder patients has recent, precedent-setting, regulatory recognition of reduced risk of non-lethal suicidal acts (Meltzer et al. 2003, Hennen and Baldessarini 2005). These considerations encourage hope for a comparable protective effect for antidepressants, but as noted, data pertaining to such an effect are not supportive (Hammad 2004, Baldessarini et al. 2005a).

Hypothetical possibilities concerning the lack of evidence of protection from suicide by antidepressant treatment include the following. [1] The efficacy of antidepressants in controlled clinical trials has remained modest and inconsistent in adults as well as children (Baldessarini 2005, Tsapakis et al. 2005), suggesting that non-reduction of suicidal risk may simply reflect limited overall therapeutic effectiveness, particularly as contemporary treatment with antidepressants typically is much less closely monitored than with clozapine or lithium (Baldessarini 2005). [2] It may be difficult to document potential antisuicidal effects owing to technical limitations of available studies, particularly the relative paucity of well-controlled, *long-term* maintenance trials for antidepressants, the rarity of life-threatening suicidal acts, often informal and incidental assessment of surrogate measures of "suicidality," and mismatched treatment-exposure-times in controlled trials, which often are shorter with placebo and so may exaggerate observed antidepressant/placebo suicidal risk-differences to disfavor antidepressants (Viguera et al. 1998, Khan et al. 2000, Baldessarini 2005, Baldessarini et al. 2005a). [3] Most antidepressants appear to have particularly limited beneficial effects on clinical features that may be especially relevant to suicidal risk, including agitated dysphoria, impulsivity, and aggressive tendencies, and may even worsen such features in some patients (Baldessarini 2005, Pompili et al. 2005, Tondo and Baldessarini 2005). [4] Mixed effects, with both decreases and increases in suicidal risk, may tend to cancel each other out in estimates of average trends.

With regard to mixed effects of antidepressant treatment on suicidal risk, particular circumstances may require both careful clinical monitoring and timely modification of treatment regimens. This caveat may be especially important with bipolar disorder patients (Tondo and Baldessarini 2005), for whom antidepressants probably are over-prescribed (Ghaemi et al. 2004), and with depressed patients who experience new or worsening agitation, anger, and other adverse behavioral effects when exposed to any mood-elevating agent (Pompili et al. 2005). Of particular concern are mixed effects of antidepressants in juvenile depressed patients. Children and early adolescents have high risks of undiagnosed bipolar disorders, and can become newly agitated, manic, or psychotic, with increased suicidal behavior when treated with a mood-elevating drug—perhaps even more during treatment with SRIs than other antidepressants or stimulants (Faedda et al. 2004, Baldessarini et al. 2005b).

As additional research is awaited, we suggest that a high index of suspicion about newly emerging suicidal risk be maintained in particular clinical circumstances. These include the treatment of any previously unknown depressed patient, persons with previous suicidal behavior and associated risk factors for suicide (Jacobs 2003), those who present or become more agitated, irritable, or sleepless, and patients with known or potential bipolar or psychotic forms of depression (Pompili et al. 2005). It is important to emphasize that suicidality newly emerging during antidepressant treatment seems rarely to arise without warning, provided that patients are adequately monitored (Pompili et al. 2005). It would be unfortunate if the potential advantages of better-tolerated, modern antidepressants including the SRIs were avoided because of concerns about potential adverse effects on suicidal risks, and this further compromised the already severely deficient recognition and treatment of depressed patients (Sheehan 2004, Baldessarini 2005).

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