

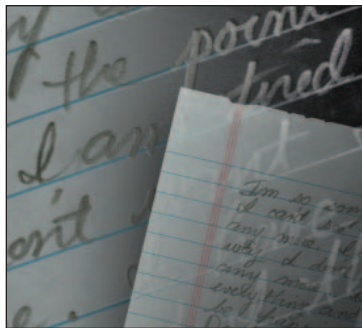
## The Antidepressant Quandary — Considering Suicide Risk When Treating Adolescent Depression

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In March 2004, the Food and Drug Administration (FDA) issued a public health advisory regarding worsening depression and suicidal thoughts and behavior in patients treated with the newer antidepressant drugs fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), escitalopram (Lexapro), bupropion (Wellbutrin), venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron). In February 2005, the agency extended the warning to include all antidepressant drugs. This warning was prompted by analyses of data from placebo-controlled trials of antidepressants suggesting that the drugs were associated with an increased risk of suicidal behavior in children and adolescents.

Subsequent research leaves considerable uncertainty regarding this relationship. In response to concerns about the validity of the data behind the advisory, the FDA reanalyzed all episodes of suicidal behavior in pediatric trials of antidepressants. Investigators found that the risk of suicidal ideation, suicidal behavior, or a suicide attempt was approximately twice as high among children and adolescents receiving one of the newer antidepressant drugs (4%) as among those receiving placebo (2%).<sup>1</sup> In contrast, large observational studies have documented that the risk of a suicide attempt actually decreases after patients begin taking medication<sup>2</sup> and that communities with higher rates of antidepressant use have, on average, lower rates of suicide.<sup>3</sup>

And the uncertainty is bound to continue. The FDA meta-analysis covered more than 20 placebo-controlled trials involving approximately 4000 patients, among whom there were 36 suicide attempts and no completed suicides. Given these rates, a randomized trial that is large enough to detect a doubling of the risk of a suicide



attempt in association with an individual drug would require approximately 6000 participants (50% more than have thus far been enrolled in all pediatric trials combined). A study that is large enough to detect a doubling of the risk of death from suicide would require hundreds of thousands of participants. With large observational studies, on the other hand, we trade increased statistical power for an increased likelihood of bias or confounding. At best, such studies can only offer reassurance that suicide attempts by patients who are taking antidepressants are not common and that the increasing use of such drugs by children and adolescents has not been accompanied by increasing suicide rates.

Furthermore, it is almost certain that no single answer will apply to all medications, all types of

suicidal behavior, or all patients. The FDA meta-analysis, for instance, suggests that there is variation among drugs in the level of risk, but the numbers were not large enough to permit an accurate evaluation of the differences. Newer antidepressants may be specifically associated with violent suicide attempts, rather than with suicide in general. The likelihood that agitation or suicidal ideation will develop with antidepressant use in any given patient may vary widely and may be influenced by differences in genes controlling serotonin transmission or cyclic AMP signaling.

In addition to the concern about the risk posed by antidepressants in children and adolescents, the benefit of such drugs in this population is less well established than it is in adults. Fluoxetine is the only drug whose antidepressant effect has been clearly established in a pediatric population and is the only drug approved in the United States for the treatment of depression in children and adolescents. Although many other antidepressants may also be effective in this population, most of them have shown inconsistent benefit in pediatric trials — a failing that probably reflects several distinguishing characteristics of depression in younger patients, including its imperfect conformity to diagnostic criteria developed for adults, the fact that its severity is more difficult to assess reliably, and its higher likelihood of improving spontaneously (i.e., a higher rate of response to placebo).

The FDA did not advise against

the use of antidepressants in children and adolescents; instead, the agency recommended more frequent follow-up visits for patients of all ages. But communicating information about risks to physicians and patients can have unintended effects. After the initial advisory was issued, prescriptions for antidepressants for children and adolescents decreased by nearly 25%,<sup>4</sup> whereas the rates of appropriate follow-up care showed no improvement.<sup>5</sup> Among adults who began taking antidepressant medication, only 20% received a minimal level of follow-up (three or more visits over a 3-month period) — one of the poorest performances in the entire U.S. health care “report card.”<sup>5</sup>

For the time being, physicians who are considering the treatment of depression in a child or adolescent must make recommendations to patients and families in an environment of substantial risk and uncertainty. Nevertheless, some specific recommendations are possible. First, the efficacy of medication for depression among children and adolescents is established only for patients with a current major depressive episode. Consequently, a diagnosis should be clearly established by means of a structured assessment or diagnostic checklist before an antidepressant drug is considered.

Second, since fluoxetine is the only antidepressant that has been proved to be effective and been approved in the United States for treatment of depression in children and adolescents, it should be the first-choice medication; any physician recommending another antidepressant should advise patients or their families that such treatment is off-label and has not been proved to be effective.

Third, suicide attempts (regard-

less of whether they are associated with starting antidepressant treatment) are unpredictable. In fact, case reports that raised concerns about suicide risk during antidepressant treatment emphasized the sudden onset of suicidal



ideation in patients with no history suggesting a suicide risk. Consequently, all patients and families should be warned that suicidal ideation may arise suddenly and that agitation and restlessness may be early signs of danger. That warning should place individual risk in the context of overall benefit: treatment has significant benefit on average but can have adverse effects for some patients.

Fourth, regular follow-up is essential, and it will not happen by accident. Erratic follow-up care can undermine the effective management of many chronic illnesses, but the fatigue and hopelessness that define depression create additional barriers to effective treatment. Given the high dropout rates seen in depression treatment, systematic identification of patients who are overdue for follow-up is essential. And given the nature of depression, active outreach will often be necessary. Although we lack clear evidence that more frequent follow-up visits will reduce the risk of suicide, randomized trials involving adults clearly demonstrate that systematic follow-up increases the likelihood of recovery from depression.

Suicide is the most feared outcome of psychiatric illness. Among 10,000 children and adolescents who begin taking antidepressants for depression, approximately 6 will die by suicide during the next 6 months, and another 30 will be hospitalized after a serious suicide attempt. For adults, the corresponding numbers are 4 suicide deaths and 10 hospitalizations for suicide attempts. Of those 10,000 children and adolescents, approximately 3000 will stop taking their medication within a few weeks, 4000 will never return for a follow-up visit, and 6000 will not recover from depression during the next 6 months. Although the rates of antidepressant use have increased dramatically among both adults and adolescents during the past 20 years, the disappointing quality and outcomes of depression treatment have changed little. Our treatment of depression is growing wider, but it is often only inches deep.

Dr. Simon reports receiving consulting fees and research grants from Wyeth and consulting fees from Bristol-Myers Squibb.

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