CATCH-22:

Does Prozac contribute to suicidality in pediatric patients?

By Sarah Harland-Logan

"Suicide is the third leading cause of death of 10- to 24-year-olds in the U.S."

Ever since Prozac first appeared on the market in 1987, physicians have had the option of treating depression (in addition to a range of other mental health conditions) with the class of antidepressants known as SSRIs, or selective serotonin reuptake inhibitors. These medications act on pre-synaptic receptors at the brain's serotonin-releasing axon terminals to block the reuptake of serotonin after it has been released into the synaptic cleft, in order to increase the amount of serotonin available to bind at post-synaptic receptors. (1)

While the use of SSRIs to treat adult patients with depression is both widely accepted and regarded as a significant advance in the treatment of this disorder, prescribing SSRIs to pediatric patients has become a controversial and much-publicized topic in recent years. In October 2004, the FDA issued "black box" warnings for Prozac (fluoxetine) and several other SSRIs, recommending that they be used only with great caution in the treatment of juveniles, due to concerns regarding the possibility of an increased risk of suicidality in pediatric patients. (2) In May 2007, moreover, the FDA extended these warnings to apply to young adults aged 18-24 years. (3) Despite its "black box" warning, however, Prozac is the only antidepressant approved by the FDA to treat pediatric major depression. (4)

Catch-22

Suicide is the third leading cause of death of 10- to 24-year-olds in the U.S. (5). Contrary to what one might expect given the "black box" warnings, however, a recent meta-analysis of six studies shows that, of the 574 young people in these studies who had committed suicide, only 9 youths (or 1.6%) had recently taken SSRIs. (3)

More broadly speaking, statistician Robert D. Gibbons and his team found

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a negative correlation between SSRI prescription rates (by county) and the prevalence of adolescent suicide. (6) In a subsequent study, Gibbons et al. specifically investigated the effects of the new "black box" warnings on SSRI prescription rates and the rate of suicide in children and adolescents. They found that SSRI prescriptions written for patients under age 20 declined by 22% between 2003 (when the FDA issued its first advisory) and 2005 (when it mandated the "black box" warnings); correspondingly, the U.S. youth suicide rate increased by 14% from 2003 to 2004. (7)

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Psychiatrists Zoltán Rihmer and Hagop Akiskal admirably explain the "catch-22" of teasing out the suggested correlation from the symptomatology of depression as follows: "psychiatrists must always be vigilant of the rare risk of iatrogenesis when prescribing potent agents like antidepressants for patients with depressive disorders where the risk of suicidality is inherent." (8)

Cause for Concern?

Questions concerning fluoxetine's potential for increasing suicidality in young patients began to surface in the scientific literature shortly after Prozac appeared on the market in 1987. (1) In 1991, Dr. Robert King et al. published a now widely cited article that presented six cases of suicidal ideation and/or behavior in patients 10 to 17 years of age who had been treated with fluoxetine in a 42-person study of the drug's effects on pediatric patients with obsessive-compulsive disorder (OCD). However, it is important to note that three of the patients in this small-scale study had previously experienced suicidal ideation. (9)

King et al. proposed three possible explanations for their findings: first, that there was in fact no causal relationship between the fluoxetine treatment and the emergence of suicidality in these patients; second, that these symptoms arose due to certain consequences of a fluoxetine-induced shift toward mania; and third, that the patients exhibited suicidal ideation and behavior due to the effect of fluoxetine on a component of the serotinergic system that impacts the regulation of aggression, whether externally or internally directed. (9) However, the authors of a similar 1992 study finding no such increase in suicidal ideation pointed out that the length of time between the commencement of fluoxetine treatment and the onset of symptoms (1-6 months), as well as the time between the cessation of treatment and the resolution of the symptoms (1 month), suggest that factors besides fluoxetine use played important roles in these findings. (10)

Nothing to See Here?

In recent years, Dr. Graham Emslie and colleagues have published several very often cited studies that do not substantiate the link between pediatric fluoxetine treatment and suicidality that was proposed by King. In 2002, Emslie's team published the results of a nine-week, placebo-controlled, randomized clinical trial in which 122 children and 97 adolescents with MDD were treated with a fixed dose of 20 mg of fluoxetine. This trial was conducted at several different sites and (as is generally the case in similar studies) excluded patients deemed to pose "serious suicidal risk." In order to identify adverse events related to suicidality that might emerge over the course of this trial, researchers made appropriate adverse event reports after general discussion with patients at the beginning of each patient visit; in addition, they were required to ask specifically about suicidal feelings and behaviors at the end of the fourth (baseline) and tenth visits. (11)

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The research team found that, in addition to being generally effective at treating the patients' depression (as measured by a number of depression rating scales, such as Childhood Depression Rating Scale-Revised (CDRS-R)), the fluoxetine in no way contributed to suicidal ideation or behavior among the study's patients. In fact, only one patient—who was receiving a placebo—was recorded as suffering an adverse event, self-mutilatory behavior, that could be interpreted as an expression of suicidality. (11)

However, the researchers who completed the seminal 2007 Treatment for Adolescents With Depression Study (known as TADS) came away with more sobering results. The large TADS study, documented over several stages, sought to evaluate the effectiveness of fluoxetine therapy, cognitive behavior therapy (CBT), and combination therapy in 327 patients between 12 and 17 years old who had received a diagnosis of MDD. TADS was conducted over 36 weeks, at 13 separate U.S. sites, some but not all of which were in university settings. The researchers commented on the fact that although the study was initially conducted according to the standard double-blind method with regards to the administration of fluoxetine alone and placebo alone, the cognitive behavior and combination therapies were not masked, meaning that this study deviates from one of the core components of accepted best study design. Indeed, the fluoxetine and placebo treatments

were also unblended after 12 weeks; the researchers accordingly chose not to include the placebo group in the final analyses of their results. (12)

The TADS reported a response rate at 36 weeks of 86% for combination therapy, 81% for fluoxetine alone, and also 81% for CBT. Unlike Emslie et al., the TADS team did encounter a number of treatment-emergent suicidal events, although no patients completed a suicide attempt during the trial. Treatment-emergent suicidal events occurred in 14.7% of the patients receiving fluoxetine only, as compared with 8.4% in the combination therapy group and 6.3% in the CBT group. In addition, during the first 12 weeks of the trial (before the fluoxetine-only and placebo-only groups were unblended), 9.2% (10 of 109) of the fluoxetine-only patients exhibited suicidal behavior, as compared to 4.7% of combination therapy patients, 4.5% of CBT patients, and a mere 2.7% of placebo patients. The researchers also pointed out that the increased risk of a suicidal event in the fluoxetine-only patients could not be attributed simply to improvement in some symptoms enabling patients to take decisive, destructive action; after all, the CBT and combination therapy patients also improved to at least the same extent, but did not exhibit a corresponding increase in suicidality. (In addition, CBT patients experienced the greatest improvement during weeks 12 to 14, with no increase in suicidality.) (12)

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In light of these findings, the TADS concluded that both CBT and fluoxetine are appropriate treatments for moderately to severely depressed teenagers, despite finding a statistically significant association (P=.04) between fluoxetine-only therapy and suicidality versus placebo. However, they recommend that adolescents being treated with fluoxetine also receive CBT as a safeguard against the potential increase in suicidality. (12)

A Dangerous Game

Although Emslie et al. and the TADS reached different conclusions about the existence of this correlation, even the TADS—which did find a statistically significant association between fluoxetine treatment and suicidality—nonetheless concluded that this risk is not worth the greater risk of allowing severely depressed teenagers to go untreated. (12) These concerns take on new urgency in the face of substantial evidence that adolescent depression is not simply outgrown, but rather predicts a variety of poor adult mental health outcomes, including a greatly increased risk of developing adult MDD and anxiety disorders. (13, 14)

This seemingly apparent conclusion that treating pediatric MDD patients with Prozac is indeed the wise course of action, however, is undermined by the near-universality of apparent over-involvement by Eli Lilly (the company that makes Prozac) in the clinical trial process. Of particular note is the disturbing fact that Dr. Emslie (who has contributed to an impressively high percentage of recent work on this topic) and one of his co-authors were paid consultants of this company at the time of publication of his 2002 paper; in addition, every one of the remaining six co-authors were employees of that company who potentially owned stock in it. (11) The TADS also discloses a disturbingly long list of potential financial conflicts of interest. Indeed, the vast majority of articles consulted during this research disclosed close connections between co-authors and pharmaceutical companies, especially Eli Lilly.

In addition, as several prominent members of the medical community discussed in a 2004 editorial, the current system allows for selective reporting of trial results because investigators are not obligated to register clinical trials or to make public the results of completed trials, and journals are not interested in publishing ambiguous results. (15) So it seems that until significant changes are made in the current procedures for separating scientific progress from corporate profit, no truly confident response can be made to the SSRI suicide question. H

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