FDA Panel Seeks to Balance Risks in Warnings for Antidepressants

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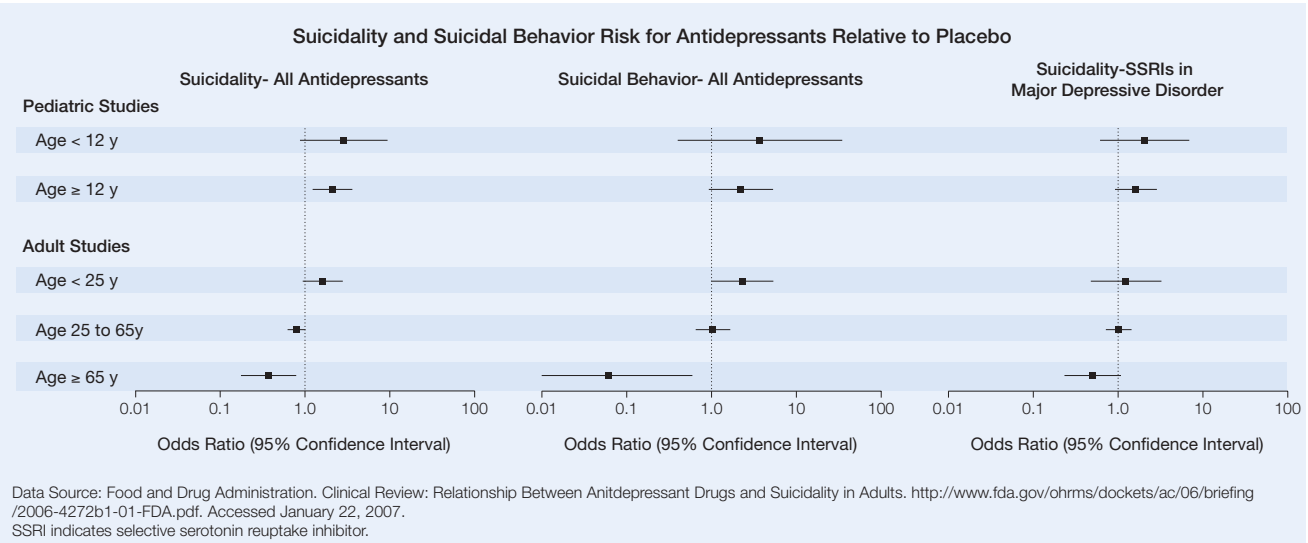
NEWER GENERATION ANTIDEPRESsants should carry a broader warning of an increased risk of suicidal thoughts and behaviors in not only children and adolescents, but also young adults, recommended a US Food and Drug Administration (FDA) advisory committee after considering new data from the agency. But in an unprecedented step, the panel also recommended that the warnings include information on the benefits of treating depression and the risk of suicide associated with untreated depression, based on emerging data that warnings about potential adverse effects of medications may lead to undertreatment and subsequent suicides.

The committee met December 13 and voted 6 to 2 in favor of extending the existing black box warnings, although members also agreed that the warning should address the benefits of treatment and the risks associated with declining treatment, said Daniel S. Pine, MD, acting chair of the committee and chief of child and adolescent research at the National Institute of Mental Health. The FDA has yet to decide whether to accept the recommendations, but typically the agency does follow its committees' advice.

AN EMERGING PICTURE

This nuanced decision comes 2 years after the agency asked pharmaceutical companies making certain antidepressants, mostly selective serotonin reuptake inhibitors (SSRIs), to add black box warnings to their products, noting that these drugs may pose an increased risk of suicidal behavior in children and adolescents. The warnings were based on data from an FDA meta-analysis of 24 short-term, placebo-controlled trials. Since then, the agency has conducted an expanded analysis, including trials in adults. A total of 372 placebo-controlled antidepressant trials involving a total of nearly 100 000 patients were analyzed by two separate teams of agency scientists using different statistical approaches (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf). The results of this pair of analyses were presented at the December committee meeting.

Both analyses, which examined data from trials of bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazadone, paroxetine, sertraline, and venlafaxine, concluded that there was an elevated risk of suicidal thoughts and behaviors among adults younger than 25 years taking these drugs, similar to that noted in children and adolescents. However, for adults between 25 and 64 years of age, the drugs appeared to have a neutral or



Data Source: Food and Drug Administration. Clinical Review: Relationship Between Anitdepressant Drugs and Suicidality in Adults. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf. Accessed January 22, 2007.
SSRI indicates selective serotonin reuptake inhibitor.

FDA analyses suggest that antidepressant use raises the risk of suicidal thoughts and behaviors in children, adolescents, and young adults. However, the drugs appear to have a neutral or protective effect against these adverse effects in older adults.

possibly protective effect against these problems, and for individuals aged 65 years or older, taking the drugs reduced the risk.

"The data were quite compelling in terms of the degree to which the relationship between treatment and suicidal behavior or ideation changed with age," said Pine. He cautioned, however, that the analysis does have certain limitations: the trials analyzed were not designed to examine these particular adverse effects, they leave questions about the precise age when the risk changes, and they do not explain the mechanism for such age-related risks. "Is it one or another specific aspect of development that accounts for [the relationship]?" he said.

Carolyn Robinowitz, MD, president-elect of the American Psychiatric Association (APA), also questioned the lumping together of suicidal thoughts and actions in the analyses. "The increase was in what they called suicidality, which was anything from adolescent suicidal angst—'what's the purpose of life,' 'why am I here'—all the way to attempts at self-harm, which ranged from very superficial to most severe." Also, she added, there may be explanations other than a true drug adverse effect for why this relationship is seen in young people treated for depression. For example, she speculated that many young people with bipolar disorder may initially be misdiagnosed with depression and treated with antidepressants, which could cause hypomania or mania and lead to suicidal thoughts or behavior. Such a misdiagnosis is much less likely for an older individual diagnosed with depression for the first time, she said.

Pine also stressed that there has been no evidence of an association between antidepressant use and completed suicide in trials of the drugs in children or adults, although such data would be difficult to obtain because completed suicide is a very rare event.

UNINTENDED CONSEQUENCES

Emerging data suggest that the black box warnings added to antidepressants in 2004 may have had the unintended consequence of raising completed suicide rates. The Centers for Disease Control and Prevention (CDC) presented data to the committee that showed a decrease in antidepressant treatment and an increase in suicide deaths since 2004, a reversal of a decade of declines in suicide deaths. The data on suicide deaths were derived from the CDC's Web-based Injury Statistics Query and Reporting System (WISQARS™) (http://www.cdc.gov/ncipc/wisqars/default.htm).

Coupled with the evidence from the FDA analysis, the CDC findings led the panel to seek a measured approach. "The committee was concerned about the trend and how to balance that on one hand, with the concern about most appropriately alerting the public and physicians about the [potential suicidality] side effect," Pine said. "There was a fair amount of discussion as to how it might be phrased so as not to discourage the appropriate use of antidepressants for people who genuinely need them."

"This new CDC information and the Advisory Committee's own findings on the efficacy of antidepressants in adults send a clear message: antidepressants save lives," Robinowitz said in an APA statement. The statement also expressed concerns about the potential negative impact of a new black box warning, but applauded the committee's recommendation to include information about both risks and benefits in the black box.

A study published in November also suggested that antidepressant treatment may protect against completed suicide in children and young adolescents (Gibbons RD et al. *Am J Psychiatry*. 2006;163:1898-1904). Gibbons and colleagues compared county-by-county suicide data for children aged 5 through 14 years across the United States from 1996 to 1998 with county antidepressant prescription rates. They found that higher rates of SSRI prescriptions were associated with lower rates of suicide in this age group. In areas with a low SSRI prescription rate, the overall suicide rate between 1996 and 1998 was 1.7 per 100 000 compared with 0.7 per 100 000 in areas with higher SSRI prescription rates. Based on models, they concluded that 253 more suicides would occur per year in the absence of SSRI prescriptions.

"Untreated depression causes more loss of life than any approved treatment," said Robinowitz.

EARLY CARE CRITICAL

While the FDA and its advisors wrestle with balancing the risks and benefits of antidepressant treatments on labels, physicians are left to determine how to manage these risks and benefits in practice.

Robinowitz advised physicians to give patients and their families as much information as possible about the risks and benefits of treatment, including the risks of no treatment. She also emphasized that it has long been known that during the early phases of treatment, individuals may begin to have more energy before the depression lifts, and that this may be a risky time for patients.

"The early stages of treatment are really critical in addressing potential adverse reactions, side effects, and self-harm, and there is a need to closely monitor people early on," Robinowitz said. Patients and their families should be advised to be proactive: "If you start to feel agitated, or highly energetic, or uncomfortable in any way, or if your depression worsens, you should call or come in here and treat it like an emergency," she noted.

Pine encouraged physicians to keep up to date on the emerging data on antidepressant medications and to collaborate with mental health specialists to help balance the risks and benefits for their patients.

"There are risks with not providing treatment when it's appropriate, but also with providing treatment in such a way that it is not given with the appropriate care," he said. "Probably the most important thing for physicians to know is that it's to their advantage to pay attention to the relevant issues that have come out now and to also pay attention to the future findings and research that's likely to emerge over the next few years." □