Data Mixed on SSRIs and Adult Risk of Suicide

BY DIANA MAHONEY
New England Bureau

Three new studies published in the British Medical Journal on the use of popular antidepressants and suicide risk in adults reach conflicting conclusions.

One study reviewed data from 702 randomized controlled clinical trials (87,650 patients) that compared selective serotonin reuptake inhibitors with placebos or other treatments in patients with various conditions, including depression, bulimia, panic disorder, and sexual dysfunction. The authors found that suicide attempts were twice as likely among patients taking the SSRIs than among those taking a placebo or receiving interventions other than tricyclics (BMJ 2005;330:396-9).

That finding suggests that patients who take antidepressants are more likely to talk about their suicidal thoughts or tell someone about their suicidal attempts—and in doing so, hopefully get help, David Fassler, M.D., a trustee of the American Psychiatric Association, told FAMILY PRACTICE NEWS.

When asked about his reaction to the BMJ studies, Rodrigo Muñoz, M.D., a psychiatrist who practices in San Diego, agreed that SSRIs could have the effect of increasing communications about suicide among patients. In addition, Dr. Muñoz also pointed to a recently published study of county-level suicide rates among adults (Arch. Gen. Psychiatr. 2005;62:165-72), in which SSRIs and other newer antidepressants were associated with lower suicide rates.

SSRIs have been under scrutiny over the last year amid concerns about an increased risk of suicidality among adolescents while on the drugs. Ultimately, those concerns prompted the Food and Drug Administration to order a black box warning for the medications, noting the potential risks in children and adolescents.

The findings published in BMJ did not show an increase in overall suicide attempts among SSRI users, compared with patients taking tricyclics. And an increased risk was not observed between SSRI use and placebo when only fatal suicides were considered.

"We documented a difference in absolute risk of 5.6 suicide attempts per 1,000 patient years of SSRI exposure, compared with placebo," wrote Dean Fergusson, Ph.D., of the Ottawa Health Research Institute and his colleagues. "Although small, the incremental risk remains an important population health issue because of the widespread use of SSRIs." This information should be relayed to physicians and patients, as long as the risk is kept in perspective relative to the benefits of the drugs, the authors stated.

Methodologic limitations among the published trials considered in this analysis may compromise the findings. For example, the risk of suicide attempts may be underestimated, the authors said. "We were unable to find documentation confirming or refuting suicide attempts in 51,205 of the 87,650 patients."

Much of the data currently available are from relatively short-term clinical trials, yet ... depression is a chronic illness.

DR. FASSLER

Additionally, many of the trials only reported adverse events that occurred in excess of a prespecified threshold, leaving open the possibility of rare but lethal complications going unreported or underreported, the authors noted. And many of the randomized control trials considered small patient populations for short time periods, and as such were not designed to identify completed or attempted suicides, thus making it impossible to infer long-term risks and treatment benefits.

In fact, although pooling the data from hundreds of trials increased the overall numbers, the absolute numbers of patients attempting and committing suicide remained very low, according to the authors of an accompanying editorial. This means that "reporting or not reporting a few cases could have completely changed the overall outcome," wrote Andrea Cipriani, M.D., of the University of Verona (Italy) and her colleagues in an accompanying editorial (BMJ 2005;330:373-4).

Dr. Fassler said one of the problems with interpreting these findings is that it is difficult to tease out the methodologic details. "The current findings do not demonstrate that antidepressants are associated with an increased risk of suicide. This result is consistent with previous studies and should be reassuring to physicians and patients," said Dr. Fassler, a clinical associate professor of psychiatry at the University of Vermont at Burlington.

The largest of the three new investigations was a nested case-control study based on the British general practice research database that assessed the risk of nonfatal self harm and suicide among 146,095 patients newly diagnosed with depression who received SSRIs or tricyclics (BMJ 2005;330:389-93).

"We found no evidence that the risk of suicide or nonfatal self harm in adults prescribed SSRIs was greater than in those prescribed tricyclic antidepressants," reported Carlos Martinez, M.D., of the Medicines and Healthcare Products Regulatory Agency in London and his colleagues in the review.

The results of the third study—a meta-analysis of published and unpublished randomized control trials of SSRIs, compared with placebo, in about 40,000 adults submitted by drug companies to the safety review arm of the Medicines and Healthcare Products Regulatory Agency—are similarly vague and inconclusive. The authors determined that because of the low incidence of suicide, "it is not possible to rule out either a threefold increase or a decrease in its occurrence among people treated with SSRIs." To detect an important effect on risk, an analysis would require large trials randomizing "around 2 million individuals," according to David Gunnell, M.D., of the University of Bristol (England) and his colleagues in the study (BMJ 2005; 330:385-8).

"We found weak evidence of an increased risk of non-fatal self harm, but our results are compatible with either no reduction or a risk that is 2.5 times higher than in placebo-treated patients," the authors wrote. The possible differences in risk in relation to self harm and suicidal thoughts is noteworthy, they stated. Though the differences could be attributable to chance given the relatively low number of events, they could also be a function of efficacy in treating depression. "The possible rise in self harm may result from a different mechanism, such as a disinhibiting effect of SSRIs in the early stages of treatment."

The authors' conclusions echo those of most professionals in response to growing concern about the possible connection between suicide risk and SSRI treatment. "In view of the widespread prescribing of SSRIs and the possibility that they may increase the risk of suicidal behavior in some individuals, research is urgently needed both to clarify appropriate indications for their use and to determine whether it is possible to identify people at risk of possible suicidal side effects," they wrote.

"There's no question that we need more studies on this issue. In particular, we need more long-term follow-up studies. Much of the data currently available are from relatively short-term clinical trials, yet for many people, depression is a chronic illness with multiple relapses. We need to know the risk and benefits of treatment over time," Dr. Fassler said. "From the child literature, we know that over 40% of young people diagnosed with depression will eventually attempt suicide, and over 3% will ultimately die as a result. But research has also demonstrated that we can reduce suicidal ideation and the risk of relapse with effective and appropriate treatment."

Several studies funded by the National Institute of Mental Health are underway that will provide insight into the many variables that contribute to suicidal thinking and behavior, "and we have made considerable progress in terms of access to data from clinical trials," said Dr. Fassler, referring to the growing momentum in support of a centralized public registry. The new studies "add to the larger and ongoing discussion" about the FDA's ability to evaluate drug dangerousness, Dr. Fassler said. "It's clear that this is a complex issue with no easy answers. The more information we have, the better." ■

Suicide Causality Excluded From Antidepressant Labeling

BY KATE JOHNSON
Montreal Bureau

Revised requirements for antidepressant labels that would omit references to a causal link between the drugs and suicide in children and adolescents have drawn mixed reactions.

"I think it's good that the FDA has shied away from making a blanket statement about causality," said Adelaide Robb, M.D., medical director of inpatient psychiatry at Children's National Medical Center in Washington.

But she says the black box warning is extreme.

"I wish the black box wasn't there," she told FAMILY PRACTICE NEWS. "I think it is overly cautious, and I think it will steer people away from [prescribing] treatment that can be very effective."

The originally proposed wording for the labeling said, "A causal role for antidepressants in inducing suicidality has been established in pediatric patients." However, before the new labeling was implemented, the Food and Drug Administration decided to soften the language.

Current wording reads, "Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders."

Manufacturers began implementing the new labeling in January, although packaging already in production or circulation was allowed to keep the old labeling.

The revised wording improves consistency and accuracy, according to FDA spokesperson Christine Parker. "[The decision] was based on feedback from several groups and individuals who expressed concern that [the causality sentence] was too broad a statement and might be misinterpreted, and thereby, misleading," she told this newspaper.

Richard Gorman, M.D., chair of the American Academy of Pediatrics' committee on drugs, said he thinks the current labeling accurately reflects the data.

And he says the decision to drop the reference to causality has little implication for clinical care.

"Whether you say it's causal or that there's an increased risk of suicide—that's legal terminology. I don't think it makes much difference to the clinician. The message is pretty identical—which is that there is an increased risk of suicide when you use these medications," he said in an interview.

Unlike Dr. Robb, Dr. Gorman does not believe that the black box warning will deter physicians from prescribing antidepressants when they are appropriate.

"I think they will be less likely to prescribe this medication for the borderline cases—but not for patients who meet the criteria for major depressive disorder. You would not give cancer chemotherapy to people who have colds. But you would have no hesitation giving it to people with cancer," Dr. Gorman pointed out. ■