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FDA Stance On Antidepressant Warnings Unchanged By NIMH Suicide Findings

A National Institute of Mental Health-funded study showing no increased risk of suicide with newer antidepressants does not change FDA's stance on the need for warnings about suicidality for the drug class.

"The new study bears only a tangential relationship at best to the previous information," Center for Drug Evaluation & Research Office of Medical Policy Director Robert Temple said.

"The previous analysis that led to the 'black box' [warning] was a comparison between drugs and placebo in people who are depressed and it compared the likelihood of suicidality in the drug-treated and placebo-treated patients," Temple noted in an interview with *"The Pink Sheet*".

Temple observed that "the new study doesn't have an untreated group. They have no information at all about what would have happened to those people had they not been treated. It simply sheds no light at all on the particular point raised in the labeling or the analysis of those trials."

The NIMH-funded study, published in the January 2006 issue of the American Psychiatric Association's *Journal of Psychiatry attracted wide media attention for its findings that patients starting on newer antidepressant agents such as selective serotonin reuptake inhibitors did not have an increased risk of suicide attempts or death.*

The study by Gregory Simon et al. (Seattle-based Group Health Cooperative Center for Health Studies) analyzed the health records of more than 65,000 patients who received antidepressant treatment between Jan. 1, 1992 and June 30, 2003.

The risk of serious suicide attempt was higher in the month after starting treatment than in the following five months, the study found. However, the rate of suicide attempts was even higher during the month prior to treatment. The rate dropped by about 60% from the month prior to therapy to the month after.

"Available data do not indicate a significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs."

The study al! so found that newer antidepressants had a much lower suicide profile compared to older agents.

"Only among those who used older antidepressant drugs (not included in the FDA warning) was the risk of suicide attempt in the first month of treatment as high as in the

month before starting medications," the authors note.

However, the authors added that "this pattern may reflect the longer time necessary to reach a therapeutic dose with older antidepressants."

The study result "challenges" the FDA warning "that suicidal behavior may emerge after treatment is begun with antidepressant medications," the American Psychiatric Association said in a Jan. 1 release.

"The finding also calls into question the FDA focus on 10 newer antidepressants," APA added.

*Antidepressants currently carrying a black box warning about suicidality include Lilly's **Prozac** (fluoxetine), GlaxoSmithKline's **Wellbutrin** (bupropio! n) and **Paxil** (paroxetine), Forest's **Celexa** (citalopram) and **Lexapro** (escitalopram), Pfizer's **Zoloft** (sertraline) and Wyeth's **Effexor** (venlafaxine).*

In comments before the Morgan Stanley Pharmaceutical CEOs Unplugged Conference in New York on Jan. 4, Lilly CEO Sidney Taurel observed that "concerns over safety are overwhelming any sense of balance with efficacy in the press and with legislators and in the public."

Pfizer said in a statement that "it is important to note that a large-scale, federally-funded NIMH study found no increased risk of suicide or suicide attempts after starting treatment with new antidepressant medications. Our hope is that these data will encourage people suffering from depression to seek and receive treatment."

FDA's Temple pointed out that the population included in the NIMH-funded study is different from that of the studies leading to the antidepr! essant warnings. "As a general matter, anyone who is actively suicidal will not be randomized into a placebo-controlled trial."

"There is no comparison at all in the placebo-controlled trials with how much suicidality you had before the study versus after the study. It is simply not addressed. So the finding stands," he added.

FDA Deputy Commissioner of Operations Janet Woodcock said in an interview with "The Pink Sheet" that observational studies such as Simon's provide valuable context for safety information; however, they may not definitively answer questions about efficacy and the risk of infrequent adverse events.

"It just means that if you are depressed and you want to know what the odds are if you go on a drug out in the real world for your depression, the odds are you are going to be better in a few months," she said. "That's really very comforting...and important for practice. It doesn't mean though that those products are 100! % safe."

Temple maintained that FDA shares the concerns of the authors that "warnings regarding suicide precipitated by antidepressants may do more to discourage effective

treatment than to improve the quality of follow-up care."

"We share that worry, that the language and labeling will keep people who really do need treatment from getting it," Temple said.

"There is nothing that says these drugs cause or promote suicide," Temple maintained. Labeling states the drugs may " promote suicidality, which translates into suicidal thinking and suicidal gestures," he said.

"What labeling does say is that you should observe people at the time they start on therapy," Temple said, noting that the study authors also believe monitoring is important.

Temple also noted that the warning about increased risk of suicidality only applies to adolescents. FDA has asked manufacturers to review data of antidepressant use in adults for suicid! ality events ([1]" The Pink Sheet" July 11, 2005, p. 5). FDA is "at least six months" off from releasing an analysis of the adult data.

The Simon et al. study found that the risk of suicide attempt was 314 per 100,000 in children and adolescents, compared to 78 per 100,000 for adults.

However, as with adults, "the risk of death by suicide was not significantly higher in the month after starting medication than in subsequent months. The risk of suicide attempt was highest in the month before starting antidepressant treatment and declined progressively after starting medication."

Adolescents only constituted a small percentage of the populations studied, about 5,000 patients. "Our data contribute nothing to the debate regarding the efficacy or clinical appropriateness of antidepressant treatment for adolescents," the authors acknowledge! d.

Temple said that he would ultimately like to see a withdrawal study conducted with adolescents in a randomized setting.

"I'd like to see a randomized withdrawal study [in adolescents] who are already on the drug," Temple said. "The reason I think that's promising is that in the adult setting, those trials are almost always successful in sharp contrast to the acute trials, which are successful only about half the time."

"It also tells you not just whether the drugs can treat the acute episode, but whether you can keep people from recurring or having another episode. It's not easy to figure out who's going to do them, but there are some straws in the wind."

Simon said that he has applied for funding to conduct an additional study that would look at a larger sample and include analysis of more adolescents who have undergone antidepressant treatment.

The Journal of Psychiatry article is the most recent article tha! t has questioned FDA

decisions regarding the safety of certain classes of drugs.

A Dec. 1 New England Journal of Medicine article authored by Philip Wang (Brigham & Women's Hospital) challenged an FDA black box warning on atypical antipsychotics. Wang's analysis found that older conventional drugs appear to have higher mortality rates in elderly patients ([2]" The Pink Sheet" Dec. 5, 2005, p. 12).

Wang also co-authored the Journal of Psychiatry study and is a member of FDA's Psychopharmacologic Drugs Advisory Committee.

In October, the psychopharmacologic committee rejected long-term studies for antidepressants pre-approval, saying the requirement would delay new therapies ([3]" The Pink Sheet" Oct. 31, 2005, p. 7).