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FDA Sat on Report Linking Suicide, Drugs

Officials ordered more studies after their own expert found children on antidepressants were twice as likely to show suicidal behavior.

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WASHINGTON — Ten months ago, when concerns arose about a possible link between children taking antidepressant drugs and suicide attempts, senior officials at the Food and Drug Administration ordered their leading expert to head up an examination of the evidence.

When the government scientist filed his report last winter, however, his bosses decided to keep it secret -- even though it found that children who took the drugs were twice as likely to be involved in serious suicide-related behavior as those who did not.

Instead of revealing the findings, senior FDA officials ordered more studies, which were not expected to be completed until summer. They also squelched plans to have the author, Dr. Andrew Mosholder, present his conclusions to an FDA advisory committee when it took up the issue in February.

And in March, when the agency issued a warning about the possibility of problems for young patients taking the drugs, FDA officials said no conclusive scientific evidence existed on the link between antidepressants and potentially suicidal behavior by children. Officials said they based their action on anecdotal complaints from physicians and families that had been presented to the advisory committee.

They gave no hint that their own chief expert on the subject had examined the results of more than two dozen clinical trials conducted by antidepressant manufacturers, and that he had found an unusually high correlation between their use and potentially suicidal behavior in young patients.

The report still has not been made public, but news of Mosholder's conclusions first surfaced in a CBS News report last week. His findings were detailed in an internal FDA document obtained by the Los Angeles Times and authenticated by government officials.

In defending their decision to hold back Mosholder's report, his superiors questioned the reliability of the data on which he based his conclusions. They suggested drug companies, which manufacture antidepressant drugs and conducted the clinical trials in order to market them, might have been too quick to count some behavior as potentially related to suicide -- that is, too quick to raise questions about their products.

Among the kinds of actions the officials said should not necessarily have been counted as potentially suicide-related were instances of children who deliberately cut themselves.

Some FDA officials defended the decision to sit on the report and seek more analysis of the data, but some psychiatrists and congressional leaders were angered that the agency had kept Mosholder silent.

"Evidence that they're suppressing a report like this is an outrage, given the public health and safety issues at stake," said Dr. Joseph Glenmullen, a Harvard psychiatrist who wrote a book on problems with the drugs known as serotonin reuptake inhibitors, which alter brain chemistry to manage depression. "They've been claiming that there's no evidence. Here's the evidence."

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Congress Asks for Data

Senate and House committees have ordered the FDA to hand over documents -- such as the ones obtained by The Times -- that might illuminate what the agency knew about the possible link between the drugs and suicidal behavior. They specifically asked for any of Mosholder's reports, e-mails, correspondence or notes on pediatric or adolescent antidepressant trials.

These members of Congress are concerned that the FDA may be keeping information from Americans that would help them better assess the possible risks of taking antidepressants or giving them to children.

"It would have been very wrong for the FDA to withhold any information it had about unintended consequences that might result from the use of antidepressants, especially for children and adolescents," Sen. Charles E. Grassley (R-Iowa), chairman of the Senate Finance Committee, said in a statement.

"The public deserves to know of every possible risk so that family members can closely monitor any changes in behavior," he said.

Suicide is the third leading cause of death in teenagers ages 15 to 19. From 1980 to 1997, the rate of suicide among this group increased by 11%. Suicide is rare but growing among younger children. The suicide rate for those 10 to 14 years old increased by 109% between 1980 and 1997, according to the Centers for Disease Control and Prevention.

Since peaking in the late 1990s, suicide rates appear to be declining among teenagers, but remain a serious problem. Experts say depression is the leading factor in suicide.

Depression affects 1 in every 33 children and 1 in every 8 adolescents, according to the National Mental Health Assn. Although only one antidepressant, Prozac, is explicitly approved by the FDA for children, doctors routinely prescribe others to their young patients, and the use of these drugs by children has been steadily rising.

The antidepressant drugs -- Prozac, Zoloft, Paxil, Luvox, Celexa, Lexapro, Effexor, Wellbutrin, Serzone and Remeron -- are taken by 30 million Americans, according to some estimates. The first seven are serotonin reuptake inhibitors, and their sales in 2003 exceeded those of any other drug class except the group of painkillers that includes codeine.

An estimated 7% of the Americans taking the medications are children. Drug use is tracked by the number of prescriptions written. A total of 2.7 million antidepressant prescriptions were dispensed for children younger than 12 and 8.1 million were written for adolescents in 2002, according to the FDA, although some individuals received more than one prescription a year.

In studying reports from 28 clinical trials, most of them unpublished and thus not open to public inspection, Mosholder concluded the data showed a "statistically significant" risk of serious suicidal events among children taking the drugs. And he stressed that what he acknowledged were limitations in the data he was analyzing would not change his conclusion.

"Finding a statistical association despite these limitations makes the finding difficult to dismiss," he wrote in one of the documents, which was authenticated by government officials familiar with the document. FDA officials would not comment directly on the documents.

Dr. Robert Temple, associate director for medical policy at the FDA's center for drug evaluation, said Mosholder "thought those data were persuasive just as they were." But his superiors believed that it was "premature" to come to the conclusion that the drugs were linked to suicide, he said.

Temple and other senior FDA officials think that some of the data from the drug companies were flawed because they were based on the firms' own decisions about what constituted serious suicide-related events.

For instance, there were several cases of teenagers who cut themselves but were not planning to kill themselves. Still, those cases were counted as serious suicide-related events by the drug companies;

senior FDA officials decided they should not have been counted. The FDA is having suicide experts at Columbia University reexamine the data.

"We would be doing something bad if we made them look like they are more dangerous than they are, just as we would be doing something bad to make them look much less dangerous than they are," Temple said. "It's important to do this right."

Although drug trials have yet to show efficacy for most of the drugs in children, many doctors and patients think that they help depressed kids, FDA officials said.

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Expert's Results Differ

Mosholder was assigned in June to head up the FDA's assessment of a possible association between Paxil and suicidal behavior in children, but his mandate was broadened to include other antidepressants. By January he had come up with conclusions that did not jibe with the FDA's official position, according to internal FDA e-mails and interviews with FDA officials other than Mosholder.

The FDA's official public position was that there was not adequate data to support a link between antidepressants and possible suicide.

At first, FDA officials had planned to have Mosholder tell the advisory panel about his conclusions. One of the internal documents was a trial question-and-answer session, rehearsing what Mosholder would tell the committee. In italic type, Mosholder was asked questions about his analyses and coached on how he should handle them.

Mosholder's answers, summarizing his findings, appeared in normal type.

Mosholder wrote that trials of eight antidepressant drugs, involving 4,100 pediatric patients, showed 108 suicide-related events -- 74 on drugs and 34 on placebo.

About a quarter of the events could be classified as serious; and most of the suicide-related events were among children suffering major depressive disorder, not from the other diseases treated with the medications, such as obsessive-compulsive disorder. In these seriously depressed patients, there was one serious suicide-related event per five patient years on the drug, compared with one per 10 patient years on the drug for placebos. Patient years are a statistical measure of the frequency of drug side effects.

Mosholder also wrote that the risk was most evident for paroxetine, or Paxil, and venlafaxin, or Effexor. His findings also suggested that patients should not quickly stop taking the drugs. About a quarter of the suicide-related events on paroxetine occurred within four days of discontinuing the drug, he wrote.

In italics, Mosholder was advised not to give any recommendations to the panel and to acknowledge the limitations of his analyses "relative to the definitive analyses being prepared."

Later, senior officials decided Mosholder should not appear before the advisory committee, and it was not told of his work

During the panel session, FDA officials explained that the Columbia University experts would analyze the data from the drug company trials, and their results would be published this summer.

One of the reasons that some senators and representatives decided to investigate the FDA's approach to regulating antidepressants was that the British government -- faced with the same information -- took a much more protective action, warning doctors not to prescribe any of the drugs to children except Prozac, or fluoxetine, according to congressional staffers.

Mosholder wrote that his conclusion "essentially mirrors the conclusions" of the Medicines and Healthcare products Regulatory Agency, the FDA's British counterpart.

Glenmullen said that given Mosholder's findings, the FDA should have given a stronger warning to Americans about the possible risks of using the drugs.

"For the FDA to issue an ambiguous warning when they had unambiguous data like this is an outrage," Glenmullen said.