

Antidepressants Get FDA's "Black Box" Warning

LINKED TO SUICIDAL THOUGHTS/BEHAVIORS IN CHILDREN

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On Oct. 15, the Food and Drug Administration (FDA) issued a public health advisory directing manufacturers of all antidepressant drugs to revise their product labeling to include a "black box" warning. The warning is intended to alert health care providers of an increased risk of suicidal thoughts and behavior in children being treated with the drugs. The black box is the government's most serious warning that can be placed on the labels of prescription medications. Products with the black box warning are not allowed to be included as part of "reminder ads," the purpose of which is to remind health care providers of the product's availability. Currently, 10 other drugs approved for use in children require the warning.

Because the warning will be seen primarily by doctors, the FDA has also informed drug manufacturers that a patient medication guide (*Medguide*) is being developed and will be given to all patients receiving antidepressant medications, in order to advise them of the risks and precautionary measures that can be taken. Pharmacists will distribute the guides to patients with each prescription or refill of an antidepressant medication. According to the guide, parents should closely monitor children taking antidepressants for any signs of clinical worsening, suicidal thoughts or behavior, or unusual changes in behavior.

The FDA's decision comes after months of escalating controversy regarding the safety of antidepressant use, particularly by adolescents and children. In the June 3, 2004 issue, we reported on a *British Medical Journal (BMJ)* study which found that in six published trials of newer antidepressants in children, researchers downplayed the negative side-effects of the drugs while exaggerating their benefits. For example, in a study of paroxetine (Paxil), 11.8% of children in the drug group experienced serious adverse events, while seven patients were admitted to a hospital during their treatment; only 2.3% of the children in the placebo group experienced negative side-effects. Despite these findings, the authors of the trial concluded that paroxetine "was generally well tolerated in this adolescent population, and most adverse effects were not serious."

Interestingly, the *BMJ* review noted that pharmaceutical companies paid for four of the trials and paid or provided services to the authors of at least three of the larger studies.

We also reported that as of March 2004, the FDA was already taking steps to warn doctors and patients about the potential link between antidepressants and suicidal thoughts/behavior in children - despite insisting at the time that no clear link existed. The FDA sent a letter to major antidepressant manufacturers, requesting that their labels be changed to include warnings about possible suicide, worsening depression, anxiety, and panic attacks. It also announced that it had launched its own investigation into alleged links between antidepressants and suicide.

The FDA's Oct. 15 announcement affects the entire general class of antidepressant medications, including Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine), Luvox (fluvoxamine), Celexa (citalopram), Lexapro (escitalopram), Wellbutrin (bupropion), Effexor (venlafaxine), Serzone (nefazodone), and Remeron (mirtazapine), among others. Currently, Prozac is the only medication approved by the FDA to treat depression in children.

The following "black box" statement will be added at the beginning of packaging inserts included with antidepressant medications:

Suicidality in Children and Adolescents

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Drug Name] is not approved for use in pediatric patients except for patients with [Any approved pediatric claims here]. (See warnings and Precautions: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Numerous other language changes have also been made to the current packaging inserts. For example, under the section labeled WARNINGS - Clinical Worsening and Suicide Risk, the following statement will replace the current language (excerpted as follows):

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases...Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases...Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior...as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.

"Today's actions represent FDA's conclusions about the increased risk of suicidal thoughts and the necessary actions for physicians prescribing these antidepressant drugs and for the children and adolescents taking them," said Dr. Lester M. Crawford, acting FDA commissioner. "Our conclusions are based on the latest and best science. They reflect what we heard from our advisory committee last month, as well as what many members of the public have told us."

Resources

1. FDA launches a multi-pronged strategy to strengthen safeguards for children treated with antidepressant medications. FDA News, Oct. 15, 2004:
www.fda.gov/bbs/topics/news/2004/NEW01124.html.
2. Labeling change request letter for antidepressant medications. Department of Health and Human Services, Oct. 26, 2004:
www.fda.gov/cder/drug/antidepressants/SSRIlabelchange.html.
3. Suicidality in children and adolescents being treated with antidepressant medications. FDA

Public Health Advisory, Oct. 15, 2004:

www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.html.

4. Antidepressants and children: a dangerous combination. *Dynamic Chiropractic*, June 3, 2004:
www.chiroweb.com/archives/22/12/05.html.
5. Antidepressants to get "black box" warning. CNN.com, Oct. 15, 2004:
www.cnn.com/2004/HEALTH/10/15/antidepressants.children.ap/index.html.

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