

# Antidepressant medication usage in the pediatric population

Clarence Chou, MD

There has been a significant amount of interest and concern over the use of antidepressant medications in the pediatric population. In October 2004, the FDA recommended that the manufacturers of all antidepressant medications include a “black box” warning of the potential for suicidal thoughts and actions when a child is taking these medications. This “black box,” which is prominently displayed on the drug package inserts, is used only to signify a significant risk associated with a particular medication. The FDA did acknowledge that the “black box” warning is not a contraindication to the use of these medications. There was also discussion as to whether to add to the medication labels information about the studies that often found no difference in effect of most of the antidepressant medications and a placebo, or sugar pill. This paper will discuss the recent history of antidepressant usage, the sequence of the process that led up to the warning, and speculation about the possible mechanisms for the action of the medications. There will be a brief discussion of the general process of the evaluation and treatment of a

child with depression, and a brief summary with discussion of future directions in treatment.

## Background

In 2002, 10 million prescriptions for antidepressant medications were written for the pediatric population in this country. This was between 7%-8% of the total number of antidepressant prescriptions. The vast majority of the prescriptions were for medications in the class of selective serotonin reuptake inhibitors, or SSRIs, which include Prozac, Zoloft, and Paxil. The great increase in the number of prescriptions written in the past few years was due to the perception that these medications were safer than the older classes of antidepressants, such as the tricyclics (e.g. amitryptiline), or the monoamine oxidase inhibitors-MAOIs (e.g. phenelzine).

For a number of years, there have been reports of suicidal thoughts and actions and some completed suicides with the use of these medications. This writer recalls a young woman who had to stop taking her SSRI medication because of increased agitation and suicidal thoughts well before there were published reports in the literature. The FDA held a public meeting in 1991 to address the relationship between Prozac and suicides. In 1996, an FDA official raised the concern about the risk of suicide in children taking Zoloft in a study of its possi-

ble use in obsessive compulsive disorder, as compared to placebo or adults taking the medication.

The worry over the increased incidence of suicidal thoughts and behavior in the pediatric population was publicized again last year by British regulators. In July of 2003, the FDA asked the pharmaceutical industry for more information about the possible suicidal risk in clinical trials of these medications. In October of 2003, the American Academy of Child and Adolescent Psychiatry held an open forum to hear presentations by clinicians and representatives of the manufacturers to address the concerns of academy members. They were told that the FDA commissioned a group of professors at Columbia University to study the original data from the clinical trials and compare the incidence and severity of episodes between patients on antidepressants and patients on placebo. The 10 medications under study included such brands as Prozac, Zoloft, Paxil, Luvox, Celexa, Remiron, Effexor, and Wellbutrin. The incidents ranged in severity from self-depreciation to striking oneself on the head to hanging or shooting oneself.

In February of 2004, an FDA researcher, Dr Andrew Mosholder, had data that did demonstrate a statistical link between the use of antidepressants and suicidal thoughts and behaviors (with a focus on

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Doctor Chou is a child and adolescent psychiatrist and medical director of the Milwaukee County Child-Adolescent Inpatient Service and Wraparound Milwaukee. He is also an assistant clinical professor for Medical College of Wisconsin.

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Paxil, Effexor, and Zoloft), but was not allowed to present his findings at that time. In March of 2004, the FDA asked the pharmaceutical manufacturers to change the labeling to include the need to observe adults and the pediatric population for suicidal tendencies and depressive symptoms. The pharmaceutical manufacturers complied with the request. In August of 2004, the review of the FDA data was completed by the Columbia University group, under the direction of Dr Tarek Hammad of the FDA. They concluded that there was a statistically significant increase in suicidal thought and behaviors for children taking these medications as a group, although it was less clear on a drug-by-drug basis. Both Drs Hammad and Mosholder noted an almost 2:1 ratio of suicidal thoughts vs. placebo. Even Prozac, which was the only medication approved by both the FDA and British authorities for use in pediatric depression, showed an increased incidence in these thoughts and actions, although it was not felt to be statistically significant. The original studies included over 4400 subjects, 78 of whom reported thoughts of self-harm or demonstrated self-injurious behavior. It should be noted that there were no completed suicides. The reviewers also concluded that there was some evidence that benefits from antidepressants were not statistically significant from the benefits of placebo in two thirds of the original trials. In addition, the data was not made available to physicians and patients. The FDA data can be found at the link: [www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1.htm](http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1.htm). After 2 days of hearings, the FDA advisory panel voted 15-8 on September 14, 2004, to recommend that manufacturers place a "black box" warning on all classes of antidepressants to ad-

dress the issue of suicidal risk while taking these medications. The FDA made the decision to follow the recommendation on October 15, 2004. This even includes antidepressants that were not in the recent groups that were studied (including those with a different mechanism of action than the SSRIS). The complete list is at the link: [www.fda.gov/cder/drug/antidepressants/default.htm](http://www.fda.gov/cder/drug/antidepressants/default.htm).

The conclusions of the panel have led to a lot of questioning of previous clinical practice. However, researchers have definitely noted that untreated depression carries a high risk of thoughts of self-harm and suicidal behavior. According to the Centers for Disease Control and Prevention, 14% of adolescent males and 25% of adolescent females have contemplated suicide. Although there are no national registries and many researchers feel that suicide is underreported (for a number of reasons), it has been estimated that 8%-10% of all adolescents have made at least one suicide attempt in their lives, as have 1% of all preadolescents.<sup>1</sup> The ratio of serious suicide attempts to completions is estimated to be 140:1 in males and 1000:1 in females. The diagnosis may co-exist with other psychiatric conditions such as anxiety, obsessive compulsive disorder, and substance abuse. Some clinicians and researchers have noted that the rate of suicide seems to have decreased somewhat during the same time that the number of prescriptions for antidepressant medications has risen. It is unclear as to whether the numbers are related, or whether factors such as suicide prevention programs, more rapid screening, and earlier and improved identification of depression in children have had an impact on the numbers.

The mechanism of actions as to why there is a connection between suicidal thinking/behavior and an-

ti-depressant usage is unclear. There is speculation that in some patients the medications may be more activating, or disinhibiting, or lead to more anxiety or agitation. It has been suggested that patients who exhibited depression with other symptoms that include restlessness, irritability, or anxiety may not do as well on these medications. A recent study by Jick et al<sup>2</sup> showed no difference in frequency of suicidal thought between the older and newer medications and that there was an increase in incidents shortly after the onset of treatment. All antidepressant medications have the potential to uncover a bipolar affective (manic-depressive) disorder, which may in itself lead to dangerous self-harm behavior. It also has been enshrined in psychiatric training that the risk for suicidal behavior increases shortly after treatment is initiated, for a number of possible reasons (predating the usage of antidepressant medications). There are some indications that there may be some truth to this assertion.

## Diagnosis

The diagnosis of depression needs to be made carefully. One needs to obtain a good medical and psychiatric history, including that of family members. A thorough review of neurovegetative symptoms, such as eating and sleeping patterns, ability to concentrate, energy levels, the presence of self-depreciation and/or anhedonia, current mood, thoughts of self-harm or harm to others, etc. helps to clarify the diagnosis. One should be aware of medical conditions or medications, including over-the-counter medications, which affect these symptoms. With children, much of this information may be provided by the parent or guardian, who can also add information about the child's developmental and education history, resiliency, and coping skills. With children, whose lan-

guage and self-awareness skills are not fully developed, the observation of others is a valuable source of information, especially since the presenting signs and symptoms of depression in children do not always resemble those noted for adults in the Diagnostic and Statistical Manual (DSM) IV.

### Management

After a diagnosis of depression is carefully made, treatment is initiated, which may include the use of an antidepressant. The medication should address the target symptoms of depression. The choice of medication may be influenced by the patient's past treatment history or a history of a family member who has or has not responded to antidepressant treatment. Informed consent is extremely important. Benefits, side effects and risks, and treatment alternatives are discussed with the parents or guardians and the child. The dosages of medications are carefully titrated and monitored. Both an adequate dosage and a sufficient length of time for a medication trial are extremely important, as a true antidepressant effect may take weeks to be seen. The FDA has suggested weekly monitoring for the first four weeks, with subsequent visits on a less frequent basis. There is a definite place for therapy to encourage expression of feelings, address distortions in a patient's thinking, and to develop coping mechanisms. Family therapy is useful to deal with interpersonal and dynamic issues. Therapists should be sensitive to developmental issues in children and adolescents and their families. A recent article reported by the Treatment for Adolescents with Depression Study (TADS) team,<sup>3</sup> led by Dr John March, noted that 43% of patients benefited from therapy (cognitive behavioral) alone, 60% responded to medication alone, but 70% of the subjects

studied responded to a combination of medication and therapy.

Parents and guardians are urged to carefully observe their child's symptoms for changes, including the possible onset of bipolar disorder or suicidal thought or actions, and children are encouraged to let their parents or others know if they are not feeling safe, whether medication is used or not. Abrupt discontinuation of a medication may also have negative physiological effects.

### The Future

At the time of this writing, it is uncertain as to what impact the recommendation for a "black box" warning will have on treatment. There was discussion at the annual meeting of the American Academy of Child and Adolescent Psychiatry (October 2004) that there already has been an impact on the prescribing patterns of physicians who are not child and adolescent psychiatrists (in fact, medication management companies have noticed a significant drop in the number of prescriptions written for antidepressant medications in the first few months of this year). More government- (not industry-) sponsored studies of the use of these medications in children are necessary. In the industry-sponsored studies, children who were suicidal were initially excluded from the study. This excluded population also needs to be studied. The newly formed advisory Pediatric Ethics Subcommittee will address the ongoing issue of using children for trial studies for all groups of medications. There is the need for a better understanding as to why certain depressed children react adversely to a particular medication. The development of a registry for studies of drugs to see if they have negative side effects or no clinical benefit for patients—rather than just the positive findings published in the past—is being encouraged by the major medical jour-

nals and the AMA. In addition, the FDA will be scrutinized more closely to see how it addresses the data from clinical trials, particularly in the areas of adverse side effects, safety, and the timeliness of disclosing data to clinicians and the public.

### Summary

Untreated depression in the pediatric population is a serious health risk. Although there is a risk of increased suicidal thoughts and behavior with the use of antidepressants, most clinicians feel that no treatment at all leads to a worse outcome for our patients. It remains a clinical conundrum that the use of antidepressant medication in a depressed child has significant risks as well as documented benefits. The physician needs to independently verify the diagnosis of depression in a child (which might be made by a therapist), use informed consent with the parent or guardian and the patient as well, and provide careful monitoring of the treatment course for a number of weeks and months. One should be made aware of side effects of the medication, including increased agitation or impulsivity, as well as suicidal tendencies. We tell our patients that all medications have side effects as well as benefits, that none is completely benign. However, despite the potential problems, the treatment of depression does include the careful usage of medication.

### References

1. Pfeffer, 2002.
2. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA*. 2004;292(3):338-343.
3. Treatment for Adolescents With Depression Study Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA*. 2004;292(7):807-820.