

# Drug Information Letter

Independent best evidence analyses and commentary

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## **PSYCHIATRIC ADVERSE EVENTS WITH DRUGS FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)**

*Editors Note: The Food and Drug Administration's (FDA) Pediatric Advisory Committee will convene on March 22, 2006 will hear and discuss neuropsychiatric adverse events possibly related to approved attention deficit hyperactivity disorder (ADHD) medications. The presentations will focus on neuropsychiatric adverse event reports and clinical trial data from approved ADHD medications.*

*The following is from the briefing information prepared by the FDA for discussion at advisory committee meetings. Briefing documents must be made available to the public at least one day prior to an advisory committee meeting. These documents may contain unpublished data and studies.*

*Below is a lightly edited version of the executive summary of the FDA's review of postmarketing reports of psychiatric adverse events associated with the drug treatment of ADHD.*

*The FDA's full report is available on the agency's Web site at:*

*[http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b\\_11\\_01\\_AdverseEvents.pdf](http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_11_01_AdverseEvents.pdf).*

A BPCA (Best Pharmaceuticals for Children Act) review of methylphenidate [Ritalin] products, prompted by Concerta [methylphenidate] pediatric exclusivity requirements, identified psychiatric adverse events as a possible concern. The review found some psychiatric adverse events mentioned in labeling, but a need for improved clarity was identified. The Pediatric Advisory Committee<sup>1</sup> agreed at the June 2005 meeting at which the methylphenidate reviews were discussed, that the issue of psychiatric adverse events with all drugs indicated to treat ADHD should be examined with the goal of better characterizing these events so that drug labeling could be updated and made consistent between products. Thus, DDRE [Division of Drug Risk Evaluation] embarked on reviews of postmarketing and clinical trial reports of psychiatric adverse events associated with drugs used to treat ADHD. This document presents the results of the review of postmarketing reports. A companion document<sup>2</sup>, from Dr. Andrew Mosholder, presents the results of the review of clinical trial reports.

Information pertaining to selected psychiatric adverse event reports received since January 1, 2000 was requested from the manufacturers of products approved or with pending applications for the treatment of ADHD. Sponsors were asked to provide information regarding four broad categories of psychiatric adverse events: 1) signs and/or symptoms of psychosis or mania; 2) suicidal ideation and behavior; 3) aggression and violent behavior; and, 4) miscellaneous serious adverse psychiatric events. In addition, searches of the FDA AERS [Adverse Event Reporting System] safety database were conducted covering the same time period, and the identified cases were assessed by a DDRE Review Team. Duplicates, and reports which were considered to be of poor quality or highly unlikely to be related to the drug of interest were excluded from this analysis.

Cases received from Sponsors [manufacturers], as well as those identified from the FDA AERS safety database, were systematically reviewed and analyzed to assess the probability of adverse drug reactions and to describe characteristics or risk factors observed in these reports. This review focuses on postmarketing safety data from the first three search categories. The miscellaneous category was considered to be beyond the scope of this current analysis due to the large volume of data for review.

The most important finding of this review is that signs and symptoms of psychosis or mania,

particularly hallucinations, can occur in some patients with no identifiable risk factors, at usual doses of any of the drugs currently used to treat ADHD. Current approved labeling for drug treatments of ADHD does not clearly address the risk of drug induced signs or symptoms of psychosis or mania (such as hallucinations) in patients without identifiable risk factors, and occurring at usual dosages. In addition, current labeling does not clearly state the importance of stopping drug therapy in any patient who develops hallucinations, or other signs or symptoms of psychosis or mania, during drug treatment of ADHD. We recommend that these issues be addressed.

A substantial proportion of psychosis-related cases were reported to occur in children age ten years or less, a population in which hallucinations are not common. The occurrence of such symptoms in young children may be particularly traumatic and undesirable, both to the child and the parents. The predominance in young children of hallucinations, both visual and tactile, involving insects, snakes and worms is striking, and deserves further evaluation.

Positive rechallenge (i.e., recurrence of symptoms when drug is re-introduced) is considered a hallmark for causality assessment of adverse events. Cases of psychosis related events which included a positive rechallenge were identified in this review for each of the drugs included in this analysis.

In many patients, the events resolved after stopping the drug. In the FDA AERS review, resolution of the events after stopping the drug was reported in 58% of amphetamine / dextroamphetamine cases, 60% of modafinil cases, 33% of atomoxetine cases, and 48% of methylphenidate cases. (Note: Outcome of the psychiatric adverse events was not reported in 21% of amphetamine / dextroamphetamine cases, 9% of modafinil cases, 41% of atomoxetine cases, and 30% of methylphenidate cases.)

For drugs currently approved for ADHD treatment, no risk factors were identified which could account for the majority of reports of psychosis-related events. For instance, drug abuse was reported in fewer than 3% of overall cases from the FDA AERS analysis of psychosis-related events. Also of note, in the overwhelming majority of cases (roughly 90% overall), the patient had no prior history of a similar condition.

Numerous postmarketing reports of aggression or violent behavior during drug therapy of ADHD have been received, most of which were classified as non-serious, although approximately 20% of cases overall were considered life-threatening or required hospital admission. In addition, a few cases resulted in incarceration of juveniles. The majority of the reports of aggression for drugs currently approved for the treatment of ADHD were in children and adolescents, with a striking male predominance. No specific risk factors for

aggression or violent behavior were identified in this analysis. For instance, drug abuse was reported in fewer than 5% of overall cases identified from the FDA AERS search. Also of note, a striking majority (80 to 90% overall) of patients identified in this review had no prior history of similar events. Several cases describing positive rechallenge were reported for each of the drugs included in this analysis. Consideration should be given to stopping the medication in patients who develop aggressive or violent behavior during drug therapy of ADHD.

Suicidality has been identified as a safety issue for STRATTERA (atomoxetine), and this information is clearly conveyed in current labeling. A causal association between other drug therapies of ADHD and suicidality cannot be ruled out on the basis of this review. Further evaluation of this issue is recommended. For instance, clinical case review of data obtained for this analysis may yield additional insights regarding possible co-occurrence of undesired psychiatric effects in some vulnerable patients that could contribute to suicidal ideation or behaviors.

#### References

<sup>1</sup> Pediatric Advisory Committee Meeting, June 29 and 30, 2005; <http://www.fda.gov/oc/advisory/accalendar/2005/fda12604dd06293005.html>.

<sup>2</sup> Mosholder. Psychiatric Adverse Events in Clinical Trials of Drugs for Attention Deficit Hyperactivity Disorder (ADHD). March 3, 2006. PID# D050243.

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