

# **MEDICATION WARNINGS: NEW CONCERNS FOR ADHD AND COMORBID MOTOR PROBLEMS**

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## **ABSTRACT**

*The FDA committees and the manufacturers of the most common ADHD drugs have recently modified the prescription information to include warnings on sudden death, serious cardiovascular events, and suicidal ideation. The purpose of this article was to document the association between traumatic brain injury, cerebral palsy, and ADHD and to clarify the new warnings for these medications. Suggestions are put forth for parents, teachers, and support personnel.*

In a previous issue of this journal a bolded warning for Strattera was discussed. Since that publication, additional warnings have been recommended for other commonly prescribed stimulant medications for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Parents and teachers of two groups of students with physical disabilities may find that these warnings are of special interest as ADHD commonly accompanies traumatic brain injury and cerebral palsy.

## **TRAUMATIC BRAIN INJURY**

Traumatic Brain Injury is caused by “severe trauma to the head that results in lasting physical and cognitive impairments” (Werts, Culatta, & Tompkins,

2007, p. 212). Motor difficulties such as poor balance and poor coordination are commonly seen in students with TBI (Smith, 2001).

Also, numerous citations have substantiated the associations between Attention Deficit Hyperactivity Disorder (ADHD) and Traumatic Brain Injury (TBI). ADHD is a common comorbid condition following TBI. Hill (1999) found that extreme distractibility is a common cognitive change for students with TBI. In 2000 Bowe noted that TBI which involves the prefrontal cortex often leads to problems associated with attention deficit hyperactivity disorder. An investigation in 2004 revealed that 19–44% of children with TBI develop ADHD (Wassenberg, Max, Lindgren, & Schatz, 2004). Other prevalence estimates of ADHD in children with TBI report a rate of 8% up to 53% (Max, Lansing, Koele, Castillo, Bokura, & Schachar, 2004). In addition, the onset of ADHD is significantly correlated with the severity of the head injury (Max et al., 2004). The above research clearly indicates that many students with TBI also experience the challenges of ADHD.

### **CEREBRAL PALSY**

Cerebral palsy is a non-progressive disorder affecting movement and posture. The condition can be caused by neurological damage to the motor control centers of the brain during the prenatal, perinatal, or postnatal period. Cerebral palsy affects the tone of muscles and compromises voluntary and involuntary muscle control (Kirk, Gallagher, Anastasiow, & Coleman, 2006). In addition, a number of researchers have documented a link between cerebral palsy and ADHD. The Kennedy Krieger Institute reported that ADHD often coexists with cerebral palsy (“A glimpse,” 1999). Hill (1999) found that attention deficit disorder is a compounding factor with students having cerebral palsy. The Cerebral Palsy Index (n.d.) noted 4%-12% of typical school aged children are diagnosed with ADHD, but it is more common among students with cerebral palsy. ADHD is a common dual diagnosis for students with cerebral palsy; in fact, up to 28% of students with cerebral palsy are also diagnosed with ADHD (Gross-Tsur, Shalev, Badihi, & Manor, 2002).

As previously noted, ADHD often appears in association with both Traumatic Brain Injury and Cerebral Palsy. Many of these students with comorbid conditions are treated with the common ADHD medications.

## CHRONOLOGY OF RECENT ADHD DRUG WARNINGS

In February, 2006, the Food and Drug Administration (FDA) Drug Safety and Risk Management Advisory Committee voted to require blackbox warnings (the most serious type) for popular drugs used for the treatment of ADHD (Aldhous, 2006). This decision was based on reports of sudden unexplained death and serious cardiovascular problems in persons taking the drugs. Specifically, during a five year period there were 25 reported cases of sudden unexplained death, 19 of which were in children, and 43 reported cases of individuals experiencing strokes, cardiac arrests, and heart palpitations. One panel member noted “for us to sit around and talk about it and for us to not make a very strong warning about the uncertainty of these drugs and their possible risk, would be unethical” (Rosack, 2006, p.1).

However, in March, 2006, the FDA Pediatric Advisory Committee addressed this same issue and voted against requiring blackbox warnings for these popular drugs used for the treatment of ADHD. This committee did recommend the addition of more specific information to the labels of these medications targeting physicians, parents, and patients.

Five months later, in August, 2006, Dexedrine received a blackbox warning which indicated that the medication may cause sudden death or serious cardiovascular problems. This blackbox warning is similar to the one currently used for Adderall. The FDA came to the conclusion that all amphetamines used to treat ADHD including Ritalin will carry a warning addressing the risk of serious cardiovascular events (including sudden death) and psychiatric adverse events. This warning will indicate that children and adults with cardiac problems should not be treated with amphetamine-based products.

This chronology and the dissimilar votes by various FDA committees is confusing at best. The investigators propose to summarize and clarify the most recent label warnings related to the use of ADHD medications (as revised in 2006) . In Table 1, information is presented for 6 specific medications that have been prescribed for ADHD.

## DISCUSSION

Physicians write ADHD prescriptions, Schedule II drugs, for 3 million children and adults per month, including those with comorbid conditions (Rosack, 2006). Because of this fact, the recent added warnings from the FDA are a matter of serious concern for children, parents, and related service providers. These warnings address a multitude of issues that appear to

TABLE I

Common ADHD Drugs	Sudden Death/ Serious Heart Problems	Suicide Concerns	Dependence/ Abuse	Liver Injury	Psychiatric Issues	Banned from Market
Adderall	x Blackbox		x Blackbox		x Warning	
Concerta	x Warning		x Blackbox		x Blackbox	
Dexedrine	x Blackbox		x Blackbox		x Warning	
Ritalin	x Warning		x Blackbox		x Blackbox	
Strattera	x Warning	x Blackbox		x Warning	x Warning	
Cylert						x

increase regularly. The investigators have structured this discussion around five indicators/descriptors for the medications. Cylert is not included in this discussion as it was banned from the market in October, 2005 because the risk of hepatitis outweighed its usefulness in treating ADHD.

Sudden death and cardiovascular adverse events were the central issues considered by the FDA committees in 2006 resulting in warnings for all five commonly used ADHD medications. Two medications (Adderall and Dexedrine) now carry a blackbox warning regarding sudden death and cardiovascular adverse events. The remaining three (Concerta, Ritalin, and Strattera) now carry a general warning related to this phenomenon. These warnings are especially important for individuals with structural heart defects or serious cardiac conditions such as cardiomyopathy or rhythm abnormalities.

In only one of the five medications, Strattera, was suicide a matter of concern. A blackbox warning was added to the prescription information for Strattera indicating that especially in the early phases of treatment, suicidal thinking and behavior may be present.

As a result, parents, caregivers, and other professional service and health-care providers should monitor the child's behavior closely.

In four of the five common medications for ADHD (Adderall, Concerta, Dexedrine, and Ritalin), a blackbox warning cautions patients or their parents of the potential for abuse/dependence. A major concern is the potential for addiction or dependence on these amphetamines, especially after long term use. Two other issues are also addressed: the use of the medications for nontherapeutic purposes and obtaining the drugs for distribution to others.

Liver injury, as documented in a previous article, is a potential concern for persons taking Strattera. In the event of jaundice, dark urine, or unexplained flu-like symptoms, testing for liver enzymes should be conducted immediately. In a small number of patients, severe drug-related liver injury may result in the need for a liver transplant.

In all five of the common ADHD medications, a warning for potential psychiatric disturbance is present. A blackbox warning is present in two of the medications (Concerta and Ritalin). The other three medications (Adderall, Dexedrine, and Strattera) carry a general warning of potential psychiatric disturbances. In particular, administration of these medications may exacerbate pre-existing mental illness, especially with a history of suicide, bipolar disorder, and depression. In a small percentage of children without a history of mental illness, the medications may lead to disordered thought processes. Other reported problems include aggression, hostility, agitation, and irritability.

Since ADHD is a well-documented condition with significant implications, the intention of this article is certainly not to encourage parents to discontinue all ADHD medications. In light of the new warnings, however, parents and physicians must evaluate the problems inherent with ADHD and then weigh the benefits of medications against the risks of these drugs. This decision is not unlike other critical decisions faced by parents of children with any medical conditions, including TBI and cerebral palsy. These decisions must be made by examining the risks and benefits in consultation with the primary physician and other health service providers

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