Clonidine Approved for Use with Stimulants

The FDA has approved use of extended-release clonidine (Kapvay) as an add-on to stimulants and as monotherapy for ADHD in children aged 6–17 years. This is the first ADHD drug approved for concomitant use with a stimulant. The approval is based on 2 trials, one of monotherapy and the other add-on therapy, which showed significantly greater improvements with clonidine than with placebo or with psychostimulants alone. Common adverse effects included fatigue, somnolence, and abdominal pain. Clonidine is an alpha2-adrenergic receptor agonist, and patients taking other antihypertensives should not take Kapvay. Tricyclic antidepressant use may reduce the efficacy of clonidine.


Depression, Suicidal Behavior Risk in ADHD

Children who received a diagnosis of ADHD before the age of 7 years had elevated risk of depression, recurrent depression, and suicidal behavior in later childhood and adolescence, according to a longitudinal study.

Methods: Assessments were carried out in 125 children, aged 4–6 years, with ADHD and in 123 age-, gender-, and ethnicity-matched control children recruited from the same neighborhoods and schools. Study participants were evaluated nearly every year through year 14, when they were in their late teens. The Diagnostic Interview Schedule for Children was administered to the mother or primary caregiver at each visit and to the children beginning in year 6, when they were aged 9–11 years. Parents and teachers completed the Impairment Rating Scale. Depression was identified if the child met full criteria for major depression or dysthymia and had functional impairment in 1 setting from combined child and parent evaluations.

Results: After controlling for gender and other covariates, children with ADHD between the ages of 4 and 6 years were more than 4 times as likely as their peers to experience depression over the 14 years of follow-up (hazard ratio,* 4.32; p<.001). Of the 59 children with ADHD in whom depression developed, 25 (42.4%) had recurrent episodes. By the end of follow-up, 17 of the study participants reported having had a specific suicidal plan—12% of those with early
ADHD, compared with 1.6% of the comparison group (hazard ratio, 5.79; p=0.03). Those with ADHD were also more likely to make at least 1 suicide attempt—18.4% vs 5.7% of controls (hazard ratio, 3.6; p=0.005).

A total of 83% of study participants who experienced depression were in the ADHD group, but they accounted for only 60% of children with ADHD. To improve the specificity of ADHD in predicting depression, the investigators examined the contributions of several covariates. Children with the combined or predominantly inattentive subtype of ADHD were at further increased risk for depression, but those with the predominantly hyperactive-impulsive subtype were at no greater risk than controls. Girls with ADHD were at greater risk for depression than boys, and maternal depression and the number of parent-reported child depressive symptoms at ages 4–6 years were also associated with increased risk.

Discussion: Previous studies of ADHD as a risk factor for depression have not shown a consistent link. The strong relationship found in the present study may be the result of near-annual follow-up throughout childhood and adolescence, or of the participants’ young age at diagnosis, which may suggest a more severe form of ADHD. The findings of this study should be helpful in identifying at-risk children for early prevention programs.


ADHD, Conduct Disorder, and Substance Abuse

Results of a longitudinal study suggest that conduct, but not attentional, problems in adolescence are directly related to adult substance abuse disorders.

Background: Some data indicates adolescents with ADHD may have heightened risk of adult substance abuse disorders. However, attempts to link the diagnoses have not consistently found an independent association. Because conduct disorder is a common comorbidity in young patients with ADHD and it has been suggested to have a strong relationship with substance abuse, the associations of all 3 disorders were evaluated in a longitudinal study.

Methods: Study subjects were a community sample of 485 adolescents from 2 counties in upstate New York who were assessed for ADHD and other psychiatric disorders using structured interviews at ages 14 and 16 years. Substance abuse screenings were subsequently administered to participants on 3 separate occasions between the ages of 27 and 37 years. Odds ratios* (ORs) for adult substance abuse were calculated based on adolescent diagnoses.

Results: Adolescent evaluations identified 19% of the population as having ADHD (7%), conduct disorder (8%), or both (4%). Substance-abuse screens were positive for 11% of adults. Adults who had received a diagnosis of ADHD or conduct disorder as an adolescent were more likely than those without to have a substance abuse disorder (ORs, 1.9 and 3.5, respectively). Conduct disorder was significantly more prevalent among adolescents with ADHD than among those without (38% vs 9%; OR, 6.4). After controlling for the comorbid condition, the association between ADHD and substance abuse was no longer significant (adjusted OR, 1.4), while the association with conduct disorder remained so (adjusted OR, 3.2; p<0.001). Logistic regression analysis found conduct disorder to be a large and statistically significant (p=0.005) mediator of the association between ADHD and later substance abuse. Likewise, adolescent ADHD has a mediator effect on conduct disorder and hence increases risk for later substance abuse.

Discussion: Although a link between ADHD and later substance abuse has been frequently reported, the present results suggest the association is indirect and mediated by the presence of
comorbid conduct disorder. Although the study had several limitations, including a predominantly Caucasian sample and the use of self-report measures of substance use, it is noteworthy that it included longer follow-up (to a later developmental stage) than previous research.

Brook D, Brook J, Zhang C, Koppel J: Association between attention-deficit/hyperactivity disorder in adolescence and substance use disorders in adulthood. *Archives of Pediatric and Adolescent Medicine* 2010;164 (October):930–934. From New York University School of Medicine, N.Y. Funded by the National Cancer Institute; and the National Institute on Drug Abuse. The authors disclosed no competing interests.

*See Reference Guide.*

**Residual Symptoms in Pediatric Depression**

Even after clinical remission, residual depressive symptoms are common in children and adolescents, according to a post-hoc analysis of trial data.

**Methods:** Patients, aged 7–18 years, with major depressive disorder (n=168) who had been treated with 10–40 mg/day fluoxetine (*Prozac*) in a controlled trial were included in the analysis. Primary results of the placebo-controlled comparison have been previously published. The present study evaluated baseline characteristics, timing of symptom improvement, and presence of residual symptoms after 12 weeks of acute treatment. Patients were assessed using the Children’s Depression Rating Scale-Revised (CDRS-R) and the Clinical Global Impression scales. Remission was defined as a CDRS-R score of ≤28.

**Results:** Nearly half of the patients (48%) were aged ≤11 years, and 42% were female. Of the 168 patients enrolled, 138 completed 12 weeks of treatment. On presentation, the most commonly reported symptoms were depressed mood (99%); irritability (97%); difficulty having fun (96%); decreased self-esteem (96%); and impaired school performance (92%). Reported depression and somatic symptoms were significantly more common in females (p=0.04), and adolescents reported significantly more sleep problems and fatigue (p=0.03) than younger children. Few other baseline differences existed. The mean CDRS-R score at baseline was 58 points.

After 12 weeks of fluoxetine treatment, all depressive symptoms were improved. The greatest improvements occurred in the initial 4 weeks. Improvement continued, but to a lesser degree, during weeks 4–8, and in the final 4 weeks further gains were limited. By week 4, the percentages of patients experiencing depressive symptoms dropped to ≤50%.

Of the 168 patients, 105 met remission criteria. However, at 12 weeks nearly half endorsed at least 1 residual symptom, most commonly poor school performance (20%), insomnia (11%), and irritability (11%). In addition, anhedonia and fatigue continued to affect about 20% of adolescents and <8% of children.

**Discussion:** Baseline irritability was nearly as common as depressed mood in this study sample, but unlike depressed mood, which improved rapidly, it tended to continue with treatment. Because the sleep problems and fatigue that often occur early in treatment may be associated with increased irritability, addressing these could potentially improve irritability as well. It should be noted that these results may not generalize to all antidepressants or to other treatment modalities. Because residual symptoms may predict relapse, further study evaluating other treatments appears to be warranted.

1 Tao R, Emslie G, Mayes T, Nakonezny P, et al: Symptom improvement and residual symptoms during acute antidepressant treatment in pediatric major depressive disorder. *Journal of Child and Adolescent Psychopharmacology* 2010;20 (October):423–430. From the University of Texas Southwestern Medical Center at Dallas; and the Children’s Medical Center of Dallas. Funded by the NIMH. Medication was supplied by Eli Lilly. One study author disclosed commercial relationships with multiple pharmaceutical-industry sources. All other authors reported no competing interests.

**Delayed School Entry and ADHD Diagnosis**

Children with a birthday just before the cutoff date for starting kindergarten are more likely to receive a diagnosis of ADHD than their older classmates, according to an analysis of longitudinal data. The results suggest that teachers may misinterpret these children’s relative immaturity as “symptoms.”

**Methods:** Data were evaluated from the Early Childhood Longitudinal Study, a national cohort study of students who began kindergarten in the fall of 1998. A total of 11,784 children from states with a mandated kindergarten cutoff age were evaluated in kindergarten and again in grades 1, 3, 5, and 8. Parents were asked at each evaluation if their child had ever received a diagnosis of ADHD by a mental health professional, and positive responses were followed up with additional questions on medication usage. Both parents and teachers completed ratings of emotional, social, and cognitive development.

**Results:** Of the total sample, 6.4% of children received a diagnosis of ADHD by the 8th grade and 4.5% were using stimulants. In the 15 states with a September 1 cutoff date, the rates of ADHD diagnosis were lowest in children born in the fall and winter, increased steadily beginning in February, and reached a peak among children born in August. The rate of ADHD in August-born children (the youngest at kindergarten entry) was more than twice that of children born in September who were required to wait an additional year before starting school (10% vs 4.5%). Findings in states with different cutoff dates showed a similar pattern, as did rates of medication use.

ADHD diagnoses, medication use, and maturity ratings were compared between children born during the 6 months before the cutoff date and those born in the subsequent 6 months. The younger group had higher prevalence of ADHD and stimulant use (7.5% and 5.4%, respectively) than older children (5.1% and 3.5%). Children with a birthday before the cutoff also received lower parent and teacher ratings of social and cognitive development.

**Discussion:** The analysis suggests that delaying school entry for a year can reduce a child’s likelihood of ADHD by 5.4 percentage points and the likelihood of receiving ADHD medications by 4.4 percentage points. The implication is that many children diagnosed with ADHD may have no underlying biological marker of the disorder, but may be misdiagnosed on the basis of behavioral immaturity relative to their classmates. Assuming that the incidence of ADHD in the older children within a classroom is identified correctly, as many as 20% of children diagnosed with ADHD may be misdiagnosed on the basis of transient deficiencies in maturity—an estimated 900,000 children. Legitimate cases of ADHD in older children may be underdiagnosed because they lack the hyperactivity and inattentiveness that is typical of their younger classmates.

Elder T: The importance of relative standards in ADHD diagnoses: evidence based on exact birth dates. *Journal of Health Economics* 2010;29 (September):641–656. From Michigan State University, East Lansing. Funded by the National Institute of Child Health and Human Development. The author did not include a disclosure of potential conflicts of interest.

**Pediatric Delirium**

Children may be particularly vulnerable to delirium, but there is limited information available on assessment and treatment. Antipsychotics are rarely used for treatment, but a small body of research supports their efficacy and short-term safety.

DSM-IV criteria for delirium include: acute onset of and an often fluctuating course of disturbances in arousal and cognition associated with an underlying medical condition. Delirium can
be characterized by hyperactive or hypoactive disturbances in arousal, or it can be mixed. The Delirium Rating Scale is the most comprehensive measure, but it has not been validated in pediatric samples.

Although they are not generally causative, environmental stressors can exacerbate delirium. Delirium can, however, be caused by certain medications, such as benzodiazepines, opioids, steroids, and sedatives. To resolve delirium, conventional or atypical antipsychotics can be used to reduce agitation while stopping potentially offending agents. However, antipsychotic dosage recommendations for the treatment of delirium in children have not been formally devised. The study authors included their own recommendations (see table), but they caution that all uses are off-label.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age</th>
<th>Dosage Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>3–12 years</td>
<td>0.05–0.15 mg/kg/day in 2 or 3 divided doses</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>6 months–12 years</td>
<td>2.5–6 mg/kg/day administered at 4–6 hour intervals; maximum dosages: 50 mg/day in children aged &lt;5 years, and 200 mg/day in older children</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>6–17 years</td>
<td>2–15 mg/day either as a single dose or administered b.i.d.</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>13–17 years</td>
<td>2.5–10 mg/day either as a single dose or administered b.i.d.; maximum 20 mg/day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>10–17 years</td>
<td>12.5–400 mg, usually dosed b.i.d; maximum 750 mg/day</td>
</tr>
<tr>
<td>Risperidone</td>
<td>5–16 years</td>
<td>0.5–2.5 mg/day administered in 2–4 doses; maximum dosages &lt;44 lbs, 1 mg/day; 44–99 lbs, 2.5 mg/day; &gt;99 lbs, 3 mg/day</td>
</tr>
</tbody>
</table>

Haloperidol may be more effective for hyperactive delirium, while atypical antipsychotics may be more useful in mixed or hypoactive delirium. Adverse effect profiles, particularly in terms of cardiac safety, should also be considered in the choice of antipsychotic.


Drug Trade Names: aripiprazole—Abilify; chlorpromazine—Thorazine; haloperidol—Haldol; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal

Reference Guide

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

**Odds Ratio:** A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.
In Memory of Our Founding Editor

Our founding editor, Michael J. Powers, passed away on October 21, 2010, following a courageous battle with leukemia. Michael started the Drug Alert publications in 1974, with the mission of providing readers with the most up-to-date, clinically relevant information in an easy-to-read format. His keen sense of integrity, his work ethic, and his expectation of excellence were, and will always be, an inspiration to all of us at M.J. Powers & Co. Michael was a wonderful mentor and taught us well; we will forge ahead with his mission always in mind.

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