

Antinarcology Drug May Improve ADHD

Modafinil could prove an alternative to stimulants for addressing symptoms, phase III studies show.

BY MARY ELLEN SCHNEIDER
Senior Writer

ATLANTA — Results from new research point to a possible alternative to stimulants for the treatment of attention-deficit hyperactivity disorder in children and adolescents.

Two phase III studies presented at the annual meeting of the American Psychiatric Association show that a once-daily pediatric formulation of modafinil is well tolerated and improves attention-deficit hyperactivity disorder (ADHD) symptoms in children and adolescents.

Modafinil is currently marketed by Cephalon under the brand name Provigil in 100-mg and 200-mg strengths. Provigil is indicated for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea, hypopnea syndrome, and shift work sleep disorder.

The company, which funded the phase II trials, is seeking approval from the Food and Drug Administration to market modafinil in 85-mg, 170-mg, 255-mg, 340-mg, and 425-mg strengths. If approved, the drug would be indicated for treatment of ADHD in children and adolescents aged 6-17 years.

The company is planning to launch the drug under the brand name Attenace by early 2006.

In one study, 189 patients with ADHD aged 6-17 years were randomized to a 7-week double-blind, fixed-dose treatment with either modafinil or placebo. This protocol was followed by a 2-week withdrawal period in which half of the modafinil-treated patients were placed on placebo without tapering, and half were continued on the drug, said Joseph Biederman, M.D., the lead investigator in the study and professor of psychiatry at Harvard University in Boston.

Modafinil was administered once daily, starting at 85 mg/day, and was rapidly titrated over 7-9 days to dosages of either 340 mg/day for patients who weighed less than 30 kg or 425 mg/day for patients who weighed 30 kg or more.

The results of the study were assessed using the school and home ADHD Rating Scale-IV total score change from baseline to last treatment visit.

After 1 week, the 125 modafinil-treated patients had significantly greater improvements in school scores, compared with the 64 placebo patients, and those results were maintained through week 7.

On the school scale, patients on modafinil experienced a 17.2-point drop in symptoms, compared with an 8.2-point drop for patients on placebo. Modafinil also significantly improved total scores from parents, compared with placebo.

The side effects included insomnia and appetite decrease. Overall, the side effects were generally mild and occurred at initiation of the treatment. There were two se-

rious adverse events not associated with the trial, said Dr. Biederman, who is an advisory board member for Cephalon and receives research/grant support from the company.

The researchers also assessed ADHD symptoms and physical/emotional response after rapid discontinuation. During the 2-week withdrawal phase there were no reported symptom rebounds, no adverse events related to withdrawal, and no physical or emotional responses.

Modafinil appears to work like a gentler stimulant, Dr. Biederman said in an interview.

The findings present possible new treatment options, he said. Although stimulants are effective, they are not universally effective. About 30%-40% of patients are nonresponsive to stimulants, he said, and some patients also have tolerability problems.

Stimulants also have the potential for acute deterioration and symptom rebound if treatment is interrupted or discontinued without tapering, Dr. Biederman said.

In the second study, researchers considered the effect of a flexible dose of modafinil in children and adolescents.

The study included 198 patients aged 6-17 years who were started on a dose of 85 mg/day of modafinil, which was titrated over 22 days based on clinical effectiveness. The maximum dose was 425 mg/day with once-daily dosing, said James Swanson, Ph.D., of the University of California at Irvine Child Development Center, who was the lead investigator.

The results were assessed using the school and home ADHD Rating Scale-IV, the Clinical Global Impression of Improvement (CGI-I), and Test Variables of Attention (TOVA).

The home score showed a mean drop of 17.6 points in symptoms for the 131 patients receiving modafinil at a mean stable dose of 361 mg/day, compared with a 7.5-point drop in symptoms for the 67 patients on placebo. The improvement in the total school score was also significantly greater for modafinil patients, Dr. Swanson reported.

Modafinil was shown to significantly improve inattention and hyperactivity/impulsivity, and there was an improvement in overall clinical condition and in the TOVA measurements of ADHD.

The researchers focused not only on decreasing symptoms of ADHD, but on increasing positive interaction and social skills, and they saw an increase in positive behaviors, he said.

The side effects included insomnia, headache, and appetite problems, which are similar to the side effects for stimulants, said Dr. Swanson, who is an advisory board member with Cephalon, receives research/grant support from the company, and is a member of the company's speakers' bureau. ■

Conduct, Bipolar Disorder Often Comorbid With ADHD

BY HEIDI SPLETE
Senior Writer

HOUSTON — "When I am asked whether I think [attention-deficit hyperactivity disorder] is overdiagnosed, I say that kids are underfoot now more than they used to be," Sandra Gilfillan, D.O., said at the annual meeting of the American Society for Adolescent Psychiatry.

"Did we miss ADHD before? No, the hyperactive kids wore themselves out," said Dr. Gilfillan, a child and adolescent psychiatrist at the University of Texas Southwestern Medical Center at Dallas, which cosponsored the meeting.

Comorbidities are common with ADHD: As many as 80% of children and adolescents with ADHD meet criteria for a related category disorder, particularly conduct disorder, oppositional defiant disorder, and bipolar disorder. When evaluating a child or adolescent for ADHD, it is important to consider other conditions as well.

When Dr. Gilfillan assesses children and adolescents for ADHD, with or without comorbidities, she starts by asking parents about the child's behavior as an infant.

Hyperactive children were often very active in utero and active as infants; they didn't sleep well and were distracted when eating, she said. In addition, children with ADHD often skipped the crawling stage or spent very little time crawling. Dr. Gilfillan also asks whether the child or adolescent is invited to birthday parties.

"It's a very big developmental thing on the social side," and parents who recognize a "hyper," aggressive child may not want the child in their house, she noted. She also asks about emergency department visits and car accidents.

"I like to look at report cards, to see what teachers wrote about behavior," she said. Another question is who babysits. "If the grandmother won't babysit the child, then that's a problem."

People do not truly outgrow ADHD; the symptoms simply evolve. Motor hyperactivity in childhood evolves into internal feelings of restlessness in adolescence and adulthood. They often have problems in classes where they have to sit or take notes, she said.

Children with ADHD who do not have comorbid conditions generally exhibit less severe symptoms. Their carelessness and inattention may lead to destructiveness and misbehavior, but it appears to be unintentional. Children with ADHD who also have conduct disorder, oppositional defiant disorder, and bipolar disorder are more likely to have social problems, to require hospitalization, and to develop other problems such as depression and anxiety. Here are more specific observations on the comorbidities:

► **Conduct disorder.** "I call these the thugs and 'thugettes,'" Dr. Gilfillan said. These children or teens have no respect for societal norms—they genuinely do not care about the rights of others. The majority of child-onset cases of conduct disorder are in males, but by adolescence the numbers are approximately equal. Children with conduct disorder don't always make it to the psychiatrist because they go into the legal system first.

► **Oppositional defiant disorder.** By contrast, children with oppositional defiant disorders tend to be argumentative, but usually only within their immediate network of family and friends. Some kids negotiate that way; some derive satisfaction from engaging their parents in an argument.

► **Bipolar disorder.** More than 50% of adolescents with bipolar disorder have at least one coexisting psychiatric disorder.

"In many areas, to get a child some time in a psychiatric hospital, you must have a diagnosis of bipolar disorder," Dr. Gilfillan noted. As a result, many clinicians lead with the bipolar diagnosis because they know the child needs to spend some time in an inpatient facility, she said. Features of bipolar disorder in children and adults are similar to characteristics of ADHD. The prolonged outbursts, which

she described as "affective storms," are bipolar rather than hyperactive.

Early symptoms of childhood-onset bipolar disorder include oversensitivity to sensory stimulation and night terrors as an infant, and high levels of anxiety and difficulty controlling anger as a school-aged child. Reports from family members might suggest that the child has a difficult temperament.

Treatment options for children and adolescents with ADHD and other conditions include Strattera (atomoxetine), Adderall (amphetamine mixed salts), and Concerta (methylphenidate), as well as Ritalin (methylphenidate HCl) and Dexedrine (dextroamphetamine sulfate).

Underdosing is one of the most common reasons for discontinuing medication, Dr. Gilfillan said. Parents often are not used to titration for their children's medications, since it is not used for ear infections or urinary tract infections. Families become impatient and say that the medication is not working; they may want to switch drugs instead of increasing the dose. "Medication can do some things, but other things must be done at the same time," she said. Nonmedication therapies for ADHD and comorbid problems include hobbies, sports that channel excess energy, and strategies for better academic performance, said Dr. Gilfillan, a consultant and member of the speakers' bureau for Pfizer, Ortho-McNeil, and Abbott, and a member of the speakers' bureau for AstraZeneca. ■

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