STRATTERA: A NEW APPROACH TO ADHD AND COMORBID MOTOR PROBLEMS

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ABSTRACT

The purpose of this article is to review the literature related to the development of Strattera, a nonstimulant drug for treating individuals with attention deficit hyperactivity disorder (ADHD). Due to the fact that a number of individuals with motor and other disabilities also have attention problems, the writers devote special attention to this population.

Strattera is the first medication approved for ADHD that uses a nonstimulative approach to manage the disorder. While initial trials appear quite promising, caution is used in predicting the outcome of this treatment. Side effects and other related issues are also discussed.

Attention deficit hyperactivity disorder (ADHD) is one of the most frequently studied and diagnosed pediatric disorders ("FDA Approves," 2002). ADHD has received considerable professional and popular attention, but remains controversial in the educational and medical arena (Barkley, 2001). ADHD is generally defined as "a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development" (American Psychiatric Association, 1994, p. 78). Evidence of the condition must be observed or reported in more than one setting. The most frequently cited prevalence figure for ADHD in school-aged children ranges from 3%–5%, with a disproportionate number of males (Weyandt, 2001).
Comorbidity refers to the coexistence of two or more diagnosable conditions or diseases (Pugh et al., 2000). Contrary to popular belief, Kadesjo and Gillberg (2001) found that "ADHD as a 'pure' disorder is rare . . . Children with ADHD plus various kinds of comorbidity by far outnumber those with ADHD only" (pp. 490–491). In fact, one of the most common comorbid motor conditions associated with ADHD is developmental coordination disorder (DCD) also referred to as "clumsy child syndrome" (Kadesjo & Gillberg, 2001). In a Canadian study researchers found that more than two-thirds of children with ADHD also manifested DCD (Kaplan, Wilson, Dewey, & Crawford, 1998). Weyandt (2001) further noted conditions comorbid with ADHD included: delayed motor coordination (up to 52%), sluggish gross motor movements, and overflow motion.

Difficulties with attention, distractibility, and impulsivity in children with cerebral palsy have been well documented. In 1952 Miller and Rosenfeld reported distractibility in 40% of children with athetosis and 44% of children with spasticity. Cruickshank, Hallahan, and Bice (1976) noted that many children with cerebral palsy are highly distractible with limited attention spans; these associated disorders are most evident when dealing with multiple stimuli. In a list of neurological signs of children with cerebral palsy, Hill (1999) included inattention, distractibility, and hyperactivity which she notes is referred to as attention deficit disorder. In a recent publication ("A glimpse," 1999), the Kennedy Krieger Institute reported that ADHD often coexists with cerebral palsy. Gross-Tsur, Shalev, Badihi, and Manor (2002) found "that some 28% of children with cerebral palsy attending special schools also had ADHD . . . the percentage we found indicates that comorbidity between the two may be relatively common" (p. 865).

The history of ADHD is interesting indeed. The symptoms were first described by Dr. George Still (1902) in a paper delivered to the Royal College of Physicians. In 1942 children with brain damage who were hyperkinetic were commonly referred to as having Strauss Syndrome (Dunn, 1963). The term minimal brain dysfunction (MBD) began to replace Strauss Syndrome in the 1950s and was brought into clinical use in 1962 by Clements and Peters. This term is still referenced in the IDEA.

In 1968 (American Psychiatric Association) the Diagnostic and Statistical Manual (DSM-II) first codified ADHD, at that time referred to as hyperkinetic reaction of childhood. The DSM III (American Psychiatric Association, 1980) expanded the definition to include both attention deficit with hyperactivity and attention deficit without hyperactivity. In 1987 (American Psychiatric Association, DSM III-R) the terminology was refined to include levels of severity. The most recent refinement (American
Psychiatric Association, DSM IV, 1994) delineated three new subtypes of ADHD.

The first pharmacological treatment occurred as a result of a serendipitous event in the 1930s when physician Charles Bradley performed work-ups on children with behavior disorders including attention problems. As part of these work-ups he routinely performed spinal taps on all of his young patients. To relieve the severe headaches associated with the spinal taps, he administered Benzedrine. The effects on the headaches were negligible, but to his astonishment the teachers reported major improvements in academics and behavior with the children also noting greater ease of learning. The Benzedrine was administered individually in a daily morning dose of 10–30 mg with effects lasting 6–12 hours. The students nicknamed the medication “math pills,” presumably because mathematics was one of the more difficult subjects for them (Bradley, 1937; Gross, 1995).

Concerned about the use of Benzedrine in children, other researchers began to look for a less-threatening alternative medication. In 1950 Hartmann and Panizon discovered and patented Ritalin (methylphenidate) which provided the alternative medication that physicians were seeking (“History of Ritalin,” n.d.). Additional stimulant medications that have since been developed include SR Ritalin (SR methylphenidate), Dexedrine (dextroamphetamine), Cylert ( pemoline), and Adderall (dextroamphetamine sulfate) (Weyandt, 2001). Another approach to treating ADHD, especially in adults, is the use of selective tricyclic antidepressants in lieu of stimulant medications (Kratochvil et al., 2002).

Stimulant medications have not been without their critics. Michelson et al. (2003) reported that a number of physicians are hesitant to prescribe stimulant medications for fear of misuse, especially in at-risk populations, such as adolescents, college students, or individuals with physical disabilities. In fact, a recent study indicated that 60% of people with mobility impairments misused alcohol and other drugs (Watson, Franklin, Ingram, & Eileenberg,1998).

The U.S. Drug Enforcement Administration has designated stimulant medications as Schedule II drugs (significant abuse potential and/or addiction liability). The National Institutes of Drug Abuse (NIDA) (1999) reports that stimulant drugs, when abused, are often crushed and used intranasally. These concerns highlight the need for a non-stimulant, pharmacological treatment for ADHD.

The purpose of this article is to review the literature related to the use of Strattera (atomoxetine, recently changed from tomatoxetine to avoid confusion with tamoxifen), a drug approved by the FDA, to treat children and adults with ADHD including those with comorbid motor problems. The drug
was licensed, judged safe and effective, for the treatment of ADHD in November, 2002 ("FDA Approves," 2002). Strattera, developed by Eli Lilly and Company, is the first noncontrolled (without abuse potential or addiction liability) medication approved for the treatment of ADHD.

PHARMACOLOGY

Strattera, unlike the other widely used stimulant medications for the treatment of ADHD, is a nonstimulant drug classified as a “norepinephrine specific reuptake inhibitor” (Spencer et al., 2001, p. 252). It is believed to work by “blocking or slowing reabsorption of norepinephrine, a brain chemical considered important in regulating attention, impulsivity, and activity levels” ("FDA Approves," 2002, para. 8). More simply, Strattera keeps a greater amount of the vital chemical, norepinephrine, working in the brain.

The dosage is determined by age and weight. Recommended amounts for children varied from 1.4 mg/kg to 1.9 mg/kg (Spencer et al., 2001). For adults, the recommended dose is typically 100 mg (Aschenbrenner, 2003).

SIDE EFFECTS

Side effects are seen in a relatively large percentage of persons taking Strattera, but are not reported to be serious and did not prevent individuals from continuing the medication (Michelson et al., 2003). The most common adverse effects in children include gastrointestinal disturbance, rhinitis, headaches, anorexia, dizziness, nervousness, somnolence, increased blood pressure, and possible slower growth ("Atomoxetine" 2002, Michelson et al., 2002; Spencer et al., 2001; Wernicke et al., 2003). For adults, the most common adverse events were dry mouth, insomnia, decreased appetite, increased blood pressure, and negative sexual side effects (Michelson et al., 2003; Wernicke et al., 2003). There are no reported serious safety concerns associated with Strattera, and the adverse side effects tend to be transient in nature (Michelson et al., 2002).

RESEARCH FINDINGS

- Spencer et al. (2001) examined the dose ranges of Strattera for children ages 7–14. In an 11 week study, the core symptoms of ADHD were significantly reduced. The results indicated Strattera offers a distinct advan-
tage over tricyclic antidepressants, often used with individuals with ADHD, due to the fact that Strattera has little or no adverse effect on cardiovascular functioning. The investigators suggested that Strattera be seen as a “first-line nonstimulant treatment for ADHD” (p. 261).

- Spencer et al. (2002) employed a double-blind, 12-week, stratified random study to investigate the efficacy of Strattera in 291 children utilizing the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS), the Clinical Global Impressions-ADHD-Severity (CGI), and the Conners’ Parent Rating Scale-Revised. The authors concluded that Strattera was effective for the treatment of children with ADHD and was well tolerated by the participants.

- Michelson et al. (2002) investigated the efficacy of once-daily vs. twice-daily use of Strattera in a six week randomized controlled study of 170 children in nine outpatient centers across the United States. The ADHD Rating Scale-IV, and CGI severity score revealed that Strattera was superior to placebo and a once-daily dose had a similar effect to previous studies of twice-daily administrations.

- Kratochvil et al. (2002) compared the use of Strattera to Ritalin in a 10 week randomized, open-label study involving 228 children. The research found no statistically significant difference between the two drugs as both drugs yielded similar reductions in ADHD symptoms. However, a major benefit of Strattera, is that as a nonstimulant medication, it is unlikely to have significant abuse liability.

- Kratochvil, Vaughan, Harrington, and Burke (2003) utilized two open-label and seven randomized, double-blind, placebo-controlled trials to determine the effectiveness of Strattera for children and adults. A positive result was documented on both the ADHD-IV Rating Scale and the Conners Adult ADHD Rating Scale. The researchers concluded that Strattera is generally well tolerated and the only medication approved for the specific treatment of adult ADHD.

- Wernicke et al. (2003) studied the cardiovascular effects of Strattera in children, adolescents, and adults. Five randomized, double-blind trials were used over a 10 week period and indicated that Strattera was associated with a slight, but constant, increase in heart rate and blood pressure. This resulted in increases in systolic blood pressure in adults and diastolic blood pressure in children. However, the researchers reported “Discontinuations due to cardiovascular-related events were very uncommon in the adult group, and did not occur in the child/adolescent group” (p. 729).
• Michelson et al. (2003) conducted two identical studies with 536 adults using randomized, double-blind, placebo-controlled designs over a 10 week period. Strattera was effective in controlling ADHD symptoms in adults. Because adults can be at an increased risk for misuse of controlled substances, the lack of abuse potential in Strattera may be an advantage for them.

**DISCUSSION**

As can be seen from the above research findings, Strattera shows significant promise in the treatment of ADHD symptoms. One can only speculate that this same potential would apply to children who have ADHD with comorbid motor problems. A nonstimulant medication for the treatment of ADHD symptoms, such as Strattera, has obvious and important advantages when compared to commonly prescribed stimulant medications: no withdrawal or symptom rebound if the medication is discontinued, cardiovascular functioning only minimally affected, and fewer sleep disturbances and allergic reactions. The major advantages, however, may well be that nonstimulant medication has much less potential for substance abuse, especially among at-risk populations such as middle and high school students with ADHD.

In comparison, among the side effects of the most commonly prescribed stimulant medications are dyskinetic movements of the tongue, lips, face, and extremities which may exacerbate the existing motor issues in children with motoric disabilities (Medical Economics Company, Inc., 1998). A post on a cerebral palsy message board addressed this same issue. The mother of a 17 year old male with both spastic diplegia and ADHD noted that her son was unable to tolerate Ritalin as it worsened the muscle spasms in his feet and legs (Spradlin, 2003).

However, before changing medications, one must consider other factors. Strattera was only recently approved by the FDA (November, 2002), so multi-year, longitudinal studies are unavailable. The studies reviewed by the authors ranged from 6–12 weeks in length, leaving the implications of long-term use unknown. Additionally, the professional literature differs in regard to the appropriate beginning dosage for various populations. Finally, no clinical research studies have addressed the impact of Strattera on children with motor problems, such as cerebral palsy or DCD.

The researchers feel two majors concerns need to be addressed. First, preliminary findings indicate that Strattera may raise the diastolic blood pressure in children. This finding must be carefully considered before the use of Strattera with children who have congenital heart defects and other coro-
nary conditions. The opinion of a pediatric cardiologist may be essential. Second, initial findings also indicate that growth may be affected by Strattera. Children whose growth may already be compromised, such as those with spina bifida and osteogenesis imperfecta, should seek the advice of their medical specialist before beginning a regimen of Strattera.

Strattera is still in its infancy, but seems to offer an exciting alternative to typical stimulant medications prescribed for ADHD. Because of this newness, a paucity exists in the professional literature and significant research questions remain. Long-term comparisons between Strattera and stimulant medications should be undertaken. Perhaps the most important question is the impact of long-term use of Strattera on students with ADHD and comorbid motor problems. This question can only be answered by longitudinal studies.

REFERENCES


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