THE NEWEST ADHD AGENT: ITS PLACE IN THE THERAPEUTIC ARMAMENTARIUM

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ABSTRACT

Although the stimulants and tricyclic antidepressants are effective agents for treating attention-deficit/hyperactivity disorder, atomoxetine, as a specific noradrenergic compound, has several attractive features. Unlike the stimulants, atomoxetine does not have abuse liability; unlike the tricyclic antidepressants, atomoxetine does not affect cardiac conduction and is not associated with histaminergic or anticholinergic effects. Therapeutic effects are sustained into the evening with once-daily dosing, which may be of benefit to older children and adults. (Adv Stud Med. 2003;3(5C):S458-S462)

A large body of data supports the usefulness of the newly approved noradrenergic compound atomoxetine in the treatment of attention-deficit hyperactivity disorder (ADHD). Four thousand children have been exposed overall; 1070 children have been enrolled in multiple large, well-controlled, multisite studies. In these studies, the average effect size was approximately 0.7. This effect size is comparable to that reported in a meta-analysis of stimulant drugs. Although it has not yet been tested in an adequately powered head-to-head study, ADHD rating scale improvements in patients taking atomoxetine were similar to those in patients taking stimulants in an open-label study (Figure 1).

Because atomoxetine is a newly approved agent, clinicians are likely to question whether it has broad or narrow efficacy against ADHD. Across all completed placebo-controlled trials, atomoxetine worked well for all ADHD symptoms (assessed by rating scales) in both the inattentive and hyperactive/impulsive domains (Figure 2), and for combined inattentive and hyperactive/impulsive subtypes.

ADVANTAGES

Beyond negatively affecting academic performance, ADHD frequently affects maturity, social interactions, substance use, and the incidence of motor vehicle accidents. The clinical appreciation of these issues has resulted in a move to treat ADHD beyond school hours into evenings, nights, and mornings—not only to reduce symptoms, but also to prevent some of the associated behavioral risks. Unpublished data shows efficacy of once-daily atomoxetine into the evening hours as demonstrated by 3 different rating scales, with evidence of continuing control of ADHD symptoms into the next morning.

Reductions in core ADHD symptoms are associated with improvement in broader measures of functioning and quality of life, such as social relationships and emotional maturity, self-esteem, and academic success. These issues may respond optimally to a long-acting agent. A dose-finding trial of atomoxetine found that in psychosocial, self-esteem, and parent emotional/time measures, sub-

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jects taking drug therapy experienced dose-related improvements in each category. It is postulated that the 24-hour duration of the medication effects contributed to the improvements in the child's success, as well as the parents' emotional well-being and the reduced parental time needed to attend to issues associated with the child's disorder.

Atomoxetine is the first drug to be approved by the US Food and Drug Administration for the treatment of adults with ADHD. Supporting this decision were findings from 2 large, well-controlled studies including 536 adults across 31 centers establishing efficacy, tolerability, and safety within this population. An indication for adult use may encourage clinicians to consider this largely undertreated population.

Whereas the therapeutic use of stimulants has clearly demonstrated a reduction in substance abuse in ADHD patients, the potential of abuse remains a concern. For example, the general public may be reluctant to accept the use of stimulants in children due to misperceptions about their effects and the potential for abuse. Moreover, clinicians who are unfamiliar with stimulants may be reluctant to write monthly prescriptions for a controlled substance, opting not to treat instead.

The fact that atomoxetine is not abusable removes these potential barriers to treatment. Studies suggest that atomoxetine:

- Does not bind to receptors associated with abuse potential
- Does not increase dopamine in striatum or nucleus accumbens
- Is not reinforcing in self-administration studies
- Is not associated with abuse liability in humans at usual doses

Atomoxetine may prove advantageous in patients who have not responded to stimulants or who have experienced unacceptable adverse effects. Response in children and adolescents in large, well-controlled, multisite studies showed a significant reduction in overall ADHD symptoms (-15.6 atomoxetine vs -5.5 placebo; P ≤ .05) in the 60.4% subjects previously exposed to stimulants. Comparable efficacy was demonstrated in the inattention and hyperactivity subtypes.
Side Effects

The tricyclic antidepressants, also used to treat ADHD, are associated with several nuisance side effects, including anticholinergic, antihistaminergic, and alpha-adrenergic effects. Resulting symptoms include dry mouth, constipation, sedation, weight gain, blood pressure changes, and tremor. Tricyclics are also associated with quinidine-like effects related to potentially serious cardiac conduction and repolarization delays. Because atomoxetine is selective, it is not associated with these other effects.

Patients taking atomoxetine had the same rate of insomnia compared with those taking placebo and a lower rate compared with those taking methylphenidate (MPH; 7.0% vs 27.0%; n = 129 and n = 37, respectively; P < .05). The incidence of decreased appetite was also less in the atomoxetine group (21.7%) compared with the MPH study arm (32.4%), though this did not reach the level of statistical significance.

There are some ways in which atomoxetine does not differ from stimulant therapy. In particular, small blood pressure and pulse increases reported with stimulant use are similar to those associated with atomoxetine. Such effects are usually not clinically significant in children. It is estimated that 20% of adults (average age, 40 years) with or without ADHD have underlying asymptomatic low-grade hypertension, which clinicians should consider when treating adults with any ADHD therapy. Whereas decreased appetite appeared to occur less frequently with atomoxetine compared with stimulant therapy, no adequately powered head-to-head study of the 2 agents has been undertaken to conclusively demonstrate these findings.

Efficacy for Comorbid Conditions

Comorbidity is the rule rather than the exception for patients with ADHD and may directly impair and inhibit response to therapy. Only 31% of subjects in the Multimodal Treatment Study (n = 579) presented with ADHD alone. The remaining subjects experienced one or more coexisting conditions, including oppositional defiant disorder (ODD; 40%), anxiety (34%), conduct disorder (14%), tics (11%), and mood disorders (4%).

Depression

Atomoxetine's putative efficacy in treating depression is suggested by several factors. As a noradrenergic drug, atomoxetine's mechanism is similar to existing antidepressants, suggesting a probable effect in this domain, although this issue still awaits controlled clinical investigation. Children and adolescents who participated in a drug study who demonstrated some signs of depression, but were not fully clinically depressed, were seen to have a dose-dependent decrease in such symptoms.

Oppositional Defiant Disorder

Of children and adolescents with ADHD, 40% to 60% have ODD, which frequently motivates parents to bring children in for treatment. Although drug therapy may be effective for the ADHD, the disorder frequently remains unchanged and parents contend that children continue in behaviors such as refusal to do homework or to heed directives. In children with ODD (either with or without the full diagnosis of ODD) atomoxetine has been found to be efficacious, even at low doses, in reducing symptoms within both domains. Figure 3 shows the decrease of ODD symp-
symptoms in children with ADHD with and without a full diagnosis of ODD. 13

Tics/Tourette’s Syndrome

Noradrenergic tricyclic antidepressants have been found to be effective in ADHD in children and adolescents with tics. 14 Whereas ADHD typically onsets in the preschool period, tics typically originate somewhat later, between the ages of 5 and 8 years. Some motor tics progress with cephalocaudal course, and occasionally further manifest with vocal tics. Although stimulants were once contraindicated for tics, they are no longer thought to be causative but may trigger tics or exacerbate existing tics. At the same time, neither do stimulants resolve tics; an alternate therapeutic option for these patients may warrant clinical consideration. Studies of the noradrenergic antidepressant desipramine have demonstrated a mild improvement in ADHD symptoms in ADHD patients with tics (Figure 4). 14 Although these results hold some promise for other noradrenergic agents, such as atomoxetine, direct studies are needed in this area.

CONCLUSION

A number of open and controlled clinical trials have been conducted regarding atomoxetine’s efficacy, safety, and tolerability. This large database reports a broad, robust effect on ADHD symptoms. It is effective in both the inattention and hyperactivity/impulsivity subtypes. Moreover, its 24-hour duration of action provides a useful option for individuals affected late at night and early in the morning. Atomoxetine is not abusable and may be effective despite the presence of comorbidities. It is the first drug indicated for use in adult ADHD, which will likely prompt a more universal recognition of this undertreated population.

REFERENCES


ADHD = attention-deficit/hyperactivity disorder.

Adapted with permission from Spencer et al. 14

Figure 4. Tic Disorder and ADHD: ADHD Symptom Response to Desipramine

ADHD Symptom Checklist Scores

Week

Atomoxetine

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