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# Out of the pipeline > Atomoxetine

## A different approach to ADHD

A nonaddictive, once-daily agent has shown efficacy in pediatric and adult ADHD. Here are insights on using the drug to its most beneficial effect.

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**M**ethylphenidate and other amphetamine-based agents are mainstays in treating attention-deficit/hyperactivity disorder (ADHD). Although these stimulants are considered safe, their potentially addictive properties have concerned clinicians, adult patients, and parents of children and adolescents with ADHD.

Atomoxetine—a nonaddictive, nonstimulant medication—has demonstrated efficacy in placebo-controlled trials.

### HOW IT WORKS

Atomoxetine enhances synaptic concentrations of norepinephrine via the presynaptic transporter. The agent has a strong affinity with norepinephrine transporters, modest affinity with serotonin transporters, and no affinity with dopamine transporters.<sup>1</sup>

When applied directly to the prefrontal cortex, however, atomoxetine has been shown to increase both extracellular norepinephrine and dopamine. Sustained levels of norepinephrine and dopamine in the prefrontal cortex may explain why atomoxetine works well beyond its 5.3-hour biologic half-life.<sup>1</sup>

In contrast, methylphenidate has shown high affinity with dopamine transporters. It produces intense, brief prefrontal increases in norepinephrine and dopamine and sustained dopamine increases in the nucleus accumbens

#### Table

### Atomoxetine: fast facts

**Drug brand name:** Strattera

**Class:** Selective norepinephrine reuptake inhibitor

**FDA-approved indications:** Treatment of ADHD in children, adolescents, and adults

**Manufacturer:** Eli Lilly and Co.

**Dosing forms:** 5 mg, 10 mg, 18 mg, 25 mg, 40 mg, and 60 mg capsules

**Recommended dosage:** Determined primarily by body weight; optimal at 1 to 1.2 mg/kg/d

and striatum.<sup>2</sup> This might explain methylphenidate's rewarding properties and its association with stereotypic motor activity and tics. By comparison, atomoxetine has a lower abuse potential and does not affect basal ganglia motor output.<sup>3</sup>

Atomoxetine's pharmacokinetics have been evaluated in more than 400 children and adolescents. Its half-life, clearance (0.35 L/hr/kg), and volume of distribution are similar across age groups, and the dose-plasma concentration relationship is linear, suggesting that dosing can be reliably adjusted according to weight. Atomoxetine is rapidly absorbed, food does not appreciably affect absorption, and peak plasma concentrations are achieved within 1 to 2 hours. The drug is distributed mostly in total body water and is highly protein bound.

Atomoxetine is metabolized primarily through the cytochrome P (CYP)-450 2D6 pathway. The major metabolite is 4-hydroxyatomoxetine, which is equipotent to atomoxetine as a norepinephrine transporter inhibitor.

#### WHAT RESEARCHERS SAY

In an 8-week study, 297 patients ages 8 to 18 received a divided fixed dosage of atomoxetine (0.5, 1.2 or 1.8 mg/kg/d) or placebo. The 1.2 and 1.8 mg/kg/d dosages were more effective than placebo and were equally effective against hyperactivity/impulsivity and inattention symptoms. The 0.5 mg/kg/d dosage was not much more effective than placebo.<sup>4</sup>

In a 6-week, placebo-controlled study, 85 subjects ages 6 to 16 who received a single dose of atomoxetine each morning (mean dosage 1.3 mg/kg/d) achieved favorable outcomes based on investigator, parent, and teacher ratings and on an ADHD Rating Scale (ADHD-RS) primary out-

Box

#### Atomoxetine dosing recommendations

**Adults and adolescents >70 kg body weight**—Start at 40 mg/d and increase after 3 days to a target dosage of 80 mg/d, either as a single dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. If the patient does not respond, wait 2 to 4 more weeks and increase the dosage to 100 mg/d.

**Children and adolescents <70 kg body weight**—Start at 0.5 mg/kg/d. After 3 days, increase to a target dosage of 1.2 mg/kg/d, either as a single dose in the morning or as evenly divided doses in the morning and late afternoon/early evening.

**Caveats**—Because atomoxetine is metabolized primarily by CYP 2D6 isoenzymes, patients with hepatic disease, low metabolizers of CYP 2D6, and those taking strong CYP 2D6 inhibitors require lower dosages. Adjust dosages cautiously.

Extensive CYP 2D6 metabolizers may require higher dosages, although atomoxetine has demonstrated no additional benefit at >1.2 mg/kg/d. No systematic safety data exist for single doses >120 mg or total daily doses >150 mg.

Source: Prescribing information, Eli Lilly and Co., 2002.

come measure. The treatment effect size (0.71) was similar to that found in the twice-daily dosing studies, suggesting that single-daily dosing is effective.<sup>5</sup>

Two controlled, comparison studies involving 291 subjects ages 7 to 13 with ADHD found that atomoxetine (mean final dosage 1.6 mg/kg/d) compares favorably to methylphenidate with similar effect sizes across ADHD symptom domains (unpublished data). Limited published data indicate that randomized, open-label atomoxetine and methylphenidate are similarly effective across ADHD symptom domains in children.<sup>6</sup>

Atomoxetine also was shown to improve ADHD symptoms in two placebo-controlled trials involving a total of 536 adults (mean daily divided dose 95 mg).<sup>7</sup> Inattention, hyperactivity, and impulsivity—as measured with the Conners Adult ADHD Rating Scale—were reduced among both treatment groups.

continued

## DOSING AND ADMINISTRATION

No age- or gender-related differences in response to atomoxetine have been reported, although dosing varies with age and weight (*Box*).

The agent should be used cautiously in patients with cardiovascular or cerebrovascular disease, as side effects include slight elevation of pulse and blood pressure. Atomoxetine also may exacerbate urinary retention or hesitation in some adults. The drug may impair sexual function; at least 7% of men in placebo-controlled trials experienced erectile disturbance, and 3% experienced impotence.<sup>7</sup>

In children and adolescents, gastrointestinal discomfort, asthenia, fatigue, mild appetite decreases, and slight weight loss were reported adverse effects.<sup>5</sup> Nausea and vomiting were the most troublesome acute side effects in children, with most episodes lasting 1 to 2 days.<sup>5</sup>

## CLINICAL IMPLICATIONS

Atomoxetine may help patients with ADHD who respond inadequately or do not respond to stimulants. Its lack of abuse potential suggests it may be useful in adults with comorbid substance use disorders. Atomoxetine also does not appear to exacerbate insomnia—a potential benefit for ADHD patients with poor sleep quality.

Given its pharmacologic profile, the agent will reduce the impact of comorbidities (such as

## Related resources

- ▶ Spencer T, Biederman J, Wilens T, et al. Effectiveness and tolerability of tomoxetine in adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 1998;155:693-5.

## DRUG BRAND NAMES

Methylphenidate • Concerta, Ritalin

## DISCLOSURE

The author receives research/grant support from and is a consultant to and speaker for Eli Lilly and Co. He also receives research/grant support from Shire Pharmaceuticals and Johnson & Johnson, and is a consultant to Abbott Laboratories, Merck and Co., Pfizer Inc., and Organon.

anxiety and depression) common to adults with ADHD. Research is needed to determine its role in treating more complicated pathologies, such as ADHD with comorbid bipolar disorder.

Whereas some stimulants require multiple daily dosing, atomoxetine is administered once daily. This could save clinicians time by reducing the need for refills, out-of-visit prescribing, and monthly patient visits (our pediatric practice writes 20 to 40 stimulant refills per day) and enhance convenience for patients.

## References

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Atomoxetine offers a treatment option for patients of all ages with ADHD, including those who wish to avoid multiple daily dosing. Research will determine the agent's role in treating more complicated ADHD pathologies.

BottomLine