

Drug Therapy

Atomoxetine

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Atomoxetine is a non-stimulant drug licensed by the Food and Drug Administration in November 2002 for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents(1). Hitherto, ADHD was treated with stimulant drugs, *e.g.*, methylphenidate. Several other non-stimulants are also shown to be efficacious in ADHD(2-5), but their dose-response and safety profile is not well established in children.

Mode of Action

Atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter in the central nervous system. It increases both norepinephrine and dopamine levels, especially in the prefrontal cortex.

Pharmacokinetics

Atomoxetine is well absorbed after oral administration. It is metabolized through the cytochrome P450 2D6 (CYP 2D6) pathway and has a plasma half-life of approximately 4 hours in CYP 2D6 extensive metabolisers and 19 hours in CYP 2D6 poor metabolisers. The slow metabolisers have 10-fold higher area under curves (AUCs) and 5-fold higher plasma concentrations. The active metabolite, 4-

hydroxyatomoxetine, is glucuronidated and excreted in the urine.

Clinical trials

Atomoxetine has demonstrated a statistically significant reduction in core ADHD symptoms and improvement in social and family functioning compared with the placebo group(6,7) in randomized, placebo-controlled trials in children and adolescents 8 to 18 years of age. Another study has demonstrated the positive impact of atomoxetine on health related quality of life (HRQL) in children with ADHD(8). Atomoxetine was compared with methylphenidate in a randomized, open-label trial(9) in children with ADHD during a 10-week study period. Significant improvements were noticed in inattentive and hyperactive/impulsive symptom domains with both medications to a comparable extent.

Atomoxetine has a slower onset to action than do stimulants; thus, effects may not be seen until the end of the first week of treatment. However, it seems to have a longer duration of action after once-a-day dose with suggestions of symptom relief during the evening and early-morning hours. The treatment effect for core ADHD symptoms is similar when once-daily dosing is compared with twice-daily dosing; parent ratings document a sustained effect late in the day(10).

Treatment with atomoxetine is preferred over stimulants in patients with psychiatric comorbidities, contraindications to stimulants, or relatively heavy use of behavioral health care(11). Further, it is the drug of choice in adolescent ADHD associated with substance abuse disorder because it has a lower risk of abuse potential(12). In children and

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adolescents with ADHD and co-morbid tic disorders, atomoxetine does not exacerbate the tic symptoms. Rather, there was some evidence of reduction in tic severity(13). It is also effective for the treatment of ADHD in patients with comorbid oppositional defiant behavior (ODD) though it did not significantly reduce the severity of ODD symptoms(14). The drug has not been evaluated in children less than 6 years of age.

Side effects

Adverse effects of atomoxetine are similar to that of methylphenidate (appetite suppression, initial weight loss), with the exception that atomoxetine does not cause or worsen insomnia though, in the early phase of treatment, it can cause drowsiness(9). Atomoxetine treatment was associated with small but statistically significant increase in mean systolic pressure in adults and diastolic pressure in children and adolescents(15). Blood pressure and pulse tended to increase early in therapy, then stabilized, and returned toward baseline after drug discontinuation. There was no significant difference as revealed by electrocardiogram between atomoxetine and placebo groups in change in QT interval for all study populations. Discontinuation because of cardiovascular-related events did not occur in the child/adolescent group. It does not appear to be habit forming and is not a controlled substance and therefore it does not require observance of the stringent prescribing rules necessary for Schedule X drugs, such as methylphenidate and dextroamphetamine.

Other documented side effects mentioned are dizziness, light-headedness, and fainting when you get up too quickly from a lying position(16). To avoid this problem, children are advised to get out of bed slowly, resting their feet on the floor for a few minutes before standing up. Atomoxetin has caused severe

liver damage in some patients(16). Heartburn, upset stomach, vomiting, loss of appetite, constipation, dry mouth, excessive tiredness, difficulty falling asleep or staying asleep, headache, mood swings, irritability, weight loss, decreased sex drive or ability, difficulty urinating, painful menstrual periods, crying, fever, chills, muscle pain, sweating and hot flushes have also been reported(16). It is not known if atomoxetine is secreted in human milk. Caution should be exercised while administering the drug to lactating mothers.

Contraindications

Atomoxetine should be avoided in children with narrow angle glaucoma due to increased risk of mydriasis. Caution is needed in patients with hypertension, tachycardia, cardiovascular or cerebrovascular disease. The drug needs to be used carefully in any condition that may predispose to hypotension. Dose should be reduced by 25% and 50%, respectively, for moderate and severe hepatic dysfunction. Dose changes are not necessary in patients with endstage renal disease.

Atomoxetine should not be co-administered with a MAO inhibitor or within 2 weeks of discontinuing one(17). Clinically significant drug interactions also exist with antiarrhythmics, selective serotonin reuptake inhibitors, beta-blockers and sympathomimetics. Dosage adjustment of atomoxetine may be necessary when co-administered with CYP2D6 inhibitors, *e.g.*, paroxetine, fluoxetine and quinidine.

Dose

Dosing of atomoxetine, unfortunately, is not straightforward because of the potential for excessive dosing in patients who are slow metabolizers.

Children and adolescents may be started at 0.5 mg/kg/day and dose may be increased after

TABLE—*Comparison of Methylphenidate and Atomoxetine in Treatment of ADHD*

Methylphenidate	Atomoxetine
1. Schedule X drug	Non-scheduled drug
2. Stimulant drug	Non-stimulant drug
3. Sleep disturbances	Does not cause or worsen insomnia but in the early phase can cause drowsiness
4. Onset of action - within 20 to 60 minutes of dose	Slower onset to action - thus, effects may not be seen until the end of the first week of treatment
5. Duration of action - 3 to 6 hours with immediate release tabs and 5-10 hrs with the long and very long acting tabs which are not available in India	Longer duration of action after a once-a-day dose with suggestions of symptom relief during the evening and early-morning hours
6. Substance abuse disorder - contraindicated	Drug of choice
7. Patients with psychiatric comorbidities, contraindications to stimulants and those requiring frequent use of behavioral care services	Preferred drug
8. Brand name - Addwise (Sun Pharma)	Tomoxetine (Torrent)
9. Presentation - Tab 10 mg	Tab 10, 18, 25 and 40mg
10. Price - 10 tabs - Rs 88. 40p	18 mg - 10 tabs - Rs 65 25 mg - 10 tabs - Rs 89.79p

a minimum of 3 days to a target dose of 1.2 mg/kg/day, given once daily or in 2 divided doses in the morning and late afternoon(16). No additional benefit is seen in doses more than 1.2 mg/kg/day(7). Do not exceed 1.4 mg/kg/day or 100 mg/day(16).

Overdose

The most common symptom of acute and chronic overdose is somnolence. Agitation, hyperactivity, abnormal behavior and gastrointestinal symptoms may also occur. Sympathetic nervous system stimulation may occasionally manifest as mydriasis causing blurring of vision, tachycardia and dryness of

mouth. No specific information is available on the treatment of overdose. These children and adolescents should be monitored carefully and given supportive care. Gastric emptying and repeated doses of activated charcoal may prevent systemic absorption. Since atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

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Key Message

- Atomoxetine is a promising, non-stimulant, non-schedule drug now available for treatment of children with attention deficit hyperactivity disorder

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