ATOMOXETINE

THERAPEUTICS

Brands • Strattera
see index for additional brand names

Generic? Yes

Class • Neuroscience-based Nomenclature: norepinephrine reuptake inhibitor (N-RI)
• Selective norepinephrine reuptake inhibitor (NRI)

Commonly Prescribed for (bold for FDA approved)
• Attention deficit hyperactivity disorder (ADHD) in adults and children over 6
• Treatment-resistant depression

How the Drug Works
• Boosts neurotransmitter norepinephrine/noradrenaline and may also increase dopamine in profrontal cortex
• Blocks norepinephrine reuptake pumps, also known as norepinephrine transporters
• Presumably this increases noradrenergic neurotransmission
• Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, atomoxetine can also increase dopamine neurotransmission in this part of the brain

How Long Until It Works ✽ Onset of therapeutic actions in ADHD can be seen as early as the first day of dosing
• Therapeutic actions may continue to improve for 8–12 weeks
• If it is not working within 6–8 weeks, it may not work at all

If It Works
• The goal of treatment of ADHD is reduction of symptoms of inattentiveness, motor hyperactivity, and/or impulsiveness that disrupt social, school, and/or occupational functioning
• Continue treatment until all symptoms are under control or improvement is stable and then continue treatment indefinitely as long as improvement persists
• Reevaluate the need for treatment periodically

• Treatment for ADHD begun in childhood may need to be continued into adolescence and adulthood if continued benefit is documented

If It Doesn’t Work
• Consider adjusting dose or switching to another agent
• Consider behavioral therapy
• Consider the presence of noncompliance and counsel patient and parents
• Consider evaluation for another diagnosis or for a comorbid condition (e.g., bipolar disorder, substance abuse, medical illness, etc.)
• Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require atomoxetine discontinuation and a switch to a mood stabilizer

Best Augmenting Combos for Partial Response or Treatment Resistance
✽ Best to attempt other monotherapies prior to augmenting
• SSRIs, SNRIs, or mirtazapine for treatment-resistant depression (use combinations of antidepressants with atomoxetine with caution as this may theoretically activate bipolar disorder and suicidal ideation)
• Mood stabilizers or atypical antipsychotics for comorbid bipolar disorder
• For the expert, can combine with modafinil, methylphenidate, or amphetamine for ADHD

Tests
• None recommended for healthy patients
• May be prudent to monitor blood pressure and pulse when initiating treatment and until dosage increments have stabilized

SIDE EFFECTS

How Drug Causes Side Effects
• Norepinephrine increases in parts of the brain and body and at receptors other than those that cause therapeutic actions (e.g., unwanted actions of norepinephrine on acetylcholine release causing decreased appetite, increased heart rate and blood pressure, dry mouth, urinary retention, etc.)
• Most side effects are immediate but often go away with time
• Lack of enhancing dopamine activity in limbic areas theoretically explains atomoxetine's lack of abuse potential

Notable Side Effects

* Sedation, fatigue (particularly in children)
* Decreased appetite
* Rare priapism
• Increased heart rate (6–9 beats/min)
• Increased blood pressure (2–4 mm Hg)
• Insomnia, dizziness, anxiety, agitation, aggression, irritability
• Dry mouth, constipation, nausea, vomiting, abdominal pain, dyspepsia
• Urinary hesitancy, urinary retention (older men)
• Dysmenorrhea, sweating
• Sexual dysfunction (men: decreased libido, erectile disturbance, impotence, ejaculatory dysfunction, abnormal orgasm; women: decreased libido, abnormal orgasm)

Life-Threatening or Dangerous Side Effects

• Increased heart rate and hypertension
• Orthostatic hypotension
• Severe liver damage (rare)
• Hypomania and, theoretically, rare induction of mania
• Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain

• Reported but not expected
• Patients may experience weight loss

Sedation

• Occurs in significant minority, particularly in children

What to Do About Side Effects

•Wait
•Wait
•Wait
•Lower the dose

• If giving once daily, can change to split dose twice daily
• If atomoxetine is sedating, take at night to reduce daytime drowsiness
• In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

• For urinary hesitancy, give an alpha 1 blocker such as tamsulosin
• Often best to try another monotherapy prior to resorting to augmentation strategies to treat side effects
• Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
• Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
• Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of atomoxetine

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Usual Dosage Range

• 0.5–1.2 mg/kg/day in children up to 70 kg; 40–100 mg/day in adults

Dosage Forms

• Capsule 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg

How to Dose

• For children 70 kg or less: initial dose 0.5 mg/kg per day; after 7 days can increase to 1.2 mg/kg per day either once in the morning or divided; maximum dose 1.4 mg/kg per day or 100 mg/day, whichever is less
• For adults and children over 70 kg: initial dose 40 mg/day; after 7 days can increase to 80 mg/day once in the morning or divided; after 2–4 weeks can increase to 100 mg/day if necessary; maximum daily dose 100 mg

DOSING AND USE
Dosing Tips

- Can be given once a day in the morning
- Efficacy with once daily dosing despite a half-life of 5 hours suggests therapeutic effects persist beyond direct pharmacologic effects, unlike stimulants whose effects are generally closely correlated with plasma drug levels
- Once daily dosing may increase gastrointestinal side effects
- Lower starting dose allows detection of those patients who may be especially sensitive to side effects such as tachycardia and increased blood pressure
- Patients especially sensitive to the side effects of atomoxetine may include those individuals deficient in the enzyme that metabolizes atomoxetine, CYP450 2D6 (i.e., 7% of Caucasians and 2% of African Americans)
- In such individuals, drug should be titrated slowly to tolerability and effectiveness
- Other individuals may require up to 1.8 mg/kg total daily dose

Overdose

- No fatalities have been reported as monotherapy; sedation, agitation, hyperactivity, abnormal behavior, gastrointestinal symptoms

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper not necessary

Pharmacokinetics

- Metabolized by CYP450 2D6
- Half-life approximately 5 hours
- Food does not affect absorption

Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Plasma concentrations of atomoxetine may be increased by drugs that inhibit CYP450 2D6 (e.g., paroxetine, fluoxetine), so atomoxetine dose may need to be reduced if coadministered
- Coadministration of atomoxetine and oral or IV albuterol may lead to increases in heart rate and blood pressure
- Coadministration with methylphenidate does not increase cardiovascular side effects beyond those seen with methylphenidate alone
- Use with caution with MAOIs, including 14 days after MAOIs are stopped (for the expert)

Other Warnings/Precautions

- Growth (height and weight) should be monitored during treatment with atomoxetine; for patients who are not growing or gaining weight satisfactorily, interruption of treatment should be considered
- Use with caution in patients with hypertension, tachycardia, cardiovascular disease, or cerebrovascular disease
- Use with caution in patients with bipolar disorder
- Use with caution in patients with urinary retention, benign prostatic hypertrophy
- Rare reports of hepatotoxicity; although causality has not been established, atomoxetine should be discontinued in patients who develop jaundice or other evidence of significant liver dysfunction
- Use with caution with antihypertensive drugs
- Increased risk of sudden death has been reported in children with structural cardiac abnormalities or other serious heart conditions
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment and make sure to document this in the patient’s chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI (except as noted under drug interactions)
ATOMOXETINE (continued)

- If patient has pheochromocytoma or history of pheochromocytoma
- If patient has a severe cardiovascular disorder that might deteriorate with clinically important increases in heart rate and blood pressure
- If patient has angle-closure glaucoma
- If there is a proven allergy to atomoxetine

**SPECIAL POPULATIONS**

**Renal Impairment**
- Dose adjustment not generally necessary

**Hepatic Impairment**
- For patients with moderate liver impairment, dose should be reduced to 50% of normal dose
- For patients with severe liver impairment, dose should be reduced to 25% of normal dose

**Cardiac Impairment**
- Use with caution because atomoxetine can increase heart rate and blood pressure
- Do not use in patients with structural cardiac abnormalities

**Elderly**
- Some patients may tolerate lower doses better
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

**Children and Adolescents**
- Approved to treat ADHD in children over age 6
- Recommended target dose is 1.2 mg/kg per day
- Do not use in children with structural cardiac abnormalities or other serious cardiac problems
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment and make sure to document this in the patient’s chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment

- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Some animal studies have shown adverse effects
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- For women of childbearing potential, atomoxetine should generally be discontinued before anticipated pregnancies

**Breast Feeding**
- Unknown if atomoxetine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommend either to discontinue drug or bottle feed

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**
- No known abuse potential

**Potential Disadvantages**
- May not act as rapidly as stimulants when initiating treatment in some patients

**Primary Target Symptoms**
- Concentration, attention span
- Motor hyperactivity
- Depressed mood
ATOMOXETINE

**Pearls**

* Unlike other agents approved for ADHD, atomoxetine does not have abuse potential and is not a scheduled substance
* Despite its name as a selective norepinephrine reuptake inhibitor, atomoxetine enhances both dopamine and norepinephrine in frontal cortex, presumably accounting for its therapeutic actions on attention and concentration
  - Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, atomoxetine can increase dopamine as well as norepinephrine in this part of the brain, presumably causing therapeutic actions in ADHD
  - Since dopamine is inactivated by dopamine reuptake in nucleus accumbens, which largely lacks norepinephrine transporters, atomoxetine does not increase dopamine in this part of the brain, presumably explaining why atomoxetine lacks abuse potential
  - Atomoxetine’s known mechanism of action as a selective norepinephrine reuptake inhibitor suggests its efficacy as an antidepressant
  - Pro-noradrenergic actions may be theoretically useful for the treatment of chronic pain
  - Atomoxetine’s mechanism of action and its potential antidepressant actions suggest it has the potential to destabilize latent or undiagnosed bipolar disorder, similar to the known actions of proven antidepressants
  - Thus, administer with caution to ADHD patients who may also have bipolar disorder
  - Unlike stimulants, atomoxetine may not exacerbate tics in Tourette’s syndrome patients with comorbid ADHD
  - Urinary retention in men over 50 with borderline urine flow has been observed with other agents with potent norepinephrine reuptake blocking properties (e.g., reboxetine, milnacipran), so administer atomoxetine with caution to these patients
  - Atomoxetine was originally called tomoxetine but the name was changed to avoid potential confusion with tamoxifen, which might lead to errors in drug dispensing

**Suggested Reading**


