REBOXETINE

Therapeutics

Brands
• Norebox
• Edronax

see index for additional brand names

Generic? No

Class
• Neuroscience-based Nomenclature: norepinephrine reuptake inhibitor (N-RI)
• Selective norepinephrine reuptake inhibitor (SRI); antidepressant

Commonly Prescribed for (bold for FDA approved)
• Major depressive disorder
• Dysthymia
• Panic disorder
• Attention deficit hyperactivity disorder (ADHD)

How the Drug Works
• Boosts neurotransmitter norepinephrine/noradrenaline and may also increase dopamine in prefrontal cortex
• Blocks norepinephrine reuptake pump (norepinephrine transporter)
• Presumably, this increases noradrenergic neurotransmission
• Since dopamine is inactivated by norepinephrine reuptake in frontal cortex which largely lacks dopamine transporters, reboxetine can increase dopamine neurotransmission in this part of the brain

How Long Until It Works
• Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
• If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
• May continue to work for many years to prevent relapse of symptoms

If It Works
• The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
• Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
• Continue treatment until all symptoms are gone (remission)

If It Doesn’t Work
• Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
• Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
• Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
• Consider psychotherapy
• Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
• Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

Best Augmenting Combos for Partial Response or Treatment Resistance
• Trazodone, especially for insomnia
• SSRIs, SNRIs, mirtazapine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
• Modafinil, especially for fatigue, sleepiness, and lack of concentration
• Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression or treatment-resistant depression
• Benzodiazepines for anxiety
• Hypnotics for insomnia
• Classically, lithium, buspirone, or thyroid hormone

Tests
• None for healthy individuals

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
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 reboxetine

(e.g., unwanted actions of norepinephrine on acetylcholine release causing constipation and dry mouth, etc.)

Most side effects are immediate but often go away with time

**Notable Side Effects**
- Insomnia, dizziness, anxiety, agitation
- Dry mouth, constipation
- Urinary hesitancy, urinary retention
- Sexual dysfunction (impotence)
- Dose-dependent hypotension

**Life-Threatening or Dangerous Side Effects**
- Rare seizures
- 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

**Sedation**
- Reported but not expected

**What to Do About Side Effects**
- Wait
- Wait
- Wait
- Lower the dose
- 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 antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for drug-induced insomnia
- Benzodiazepines for drug-induced anxiety and activation
- Mirtazapine for drug-induced insomnia or anxiety

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**DOsing AND USE**

**Usual Dosage Range**
- 8 mg/day in 2 doses (10 mg usual maximum daily dose)

**Dosage Forms**
- Tablet 2 mg, 4 mg scored

**How to Dose**
- Initial 2 mg/day twice a day for 1 week, 4 mg/day twice a day for second week

**Dosing Tips**
- When switching from another antidepressant or adding to another antidepressant, dosing may need to be lower and titration slower to prevent activating side effects (e.g., 2 mg in the daytime for 2–3 days, then 2 mg bid for 1–2 weeks)
- Give second daily dose in late afternoon rather than at bedtime to avoid undesired activation or insomnia in the evening
- May not need full dose of 8 mg/day when given in conjunction with another antidepressant
- Some patients may need 10 mg/day or more if well tolerated without orthostatic hypotension and if additional efficacy is seen at high doses in difficult cases
- Early dosing in patients with panic and anxiety may need to be lower and titration slower, perhaps with the use of concomitant short-term benzodiazepines to increase tolerability
**Overdose**
- Postural hypotension, anxiety, hypertension

**Long-Term Use**
- Safe

**Habit Forming**
- No

**How to Stop**
- Taper not necessary

**Pharmacokinetics**
- Metabolized by CYP450 3A4
- Inhibits CYP450 2D6 and 3A4 at high doses
- Elimination half-life approximately 13 hours

**Drug Interactions**
- Tramadol increases the risk of seizures in patients taking an antidepressant
- May need to reduce reboxetine dose or avoid concomitant use with inhibitors of CYP450 3A4, such as azole and antifungals, macrolide antibiotics, fluvoxamine, nefazodone, fluoxetine, sertraline, etc.
- Via CYP450 2D6 inhibition, reboxetine could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine and TCAs
- Via CYP450 2D6 inhibition, reboxetine could theoretically increase concentrations of thiordizine and cause dangerous cardiac arrhythmias
- Via CYP450 3A4 inhibition, reboxetine may increase the levels of alprazolam, buspirone, and triazolam
- Via CYP450 3A4 inhibition, reboxetine could theoretically increase concentrations of certain cholesterol lowering HMG CoA reductase inhibitors, especially simvastatin, atorvastatin, and lovastatin, but not pravastatin or fluvasatin, which would increase the risk of rhabdomyolysis; thus, coadministration of reboxetine with certain HMG CoA reductase inhibitors should proceed with caution
- Via CYP450 3A4 inhibition, reboxetine could theoretically increase the concentrations of pimoaze, and cause QTc prolongation and dangerous cardiac arrhythmias

**Other Warnings/Precautions**
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Use with caution in patients with urinary retention, benign prostatic hyperplasia, glaucoma, epilepsy
- Use with caution with drugs that lower blood pressure
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants 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 has angle-closure glaucoma
- If patient is taking an MAOI (except as noted under drug interactions)
- If patient is taking pimozide or thiordizine
- If there is a proven allergy to reboxetine

**SPECIAL POPULATIONS**

**Renal Impairment**
- Plasma concentrations are increased
- May need to lower dose

**Hepatic Impairment**
- Plasma concentrations are increased
- May need to lower dose

**Cardiac Impairment**
- Use with caution
Elderly

- Lower dose is recommended (4–6 mg/day)
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants 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
- No guidelines for children; safety and efficacy have not been established

Pregnancy

- No controlled studies in humans
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstituted late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

Potential Advantages

- Tired, unmotivated patients
- Patients with cognitive disturbances
- Patients with psychomotor retardation

Potential Disadvantages

- Patients unable to comply with twice daily dosing
- Patients unable to tolerate activation

Primary Target Symptoms

- Depressed mood
- Energy, motivation, and interest
- Suicidal ideation
- Cognitive disturbance
- Psychomotor retardation

Pearls

- May be effective if SSRIs have failed or for SSRIs "poop-out"
- May be more likely than SSRIs to improve social and work functioning
- Reboxetine is a mixture of an active and an inactive enantiomer, and the active enantiomer may be developed in future clinical testing
- Side effects may appear "anticholinergic," but reboxetine does not directly block muscarinic receptors
- Constipation, dry mouth, and urinary retention are noradrenergic, due in part to peripheral alpha 1 receptor stimulation causing decreased acetylcholine release
- Thus, antidotes for these side effects can be alpha 1 antagonists such as tamsulosin, especially for urinary retention in men over 50 with borderline urine flow
- Novel use of reboxetine may be for attention deficit disorder, analogous to the actions of another norepinephrine selective reuptake inhibitor, atomoxetine, but few controlled studies
- Another novel use may be for neuropathic pain, alone or in combination with other antidepressants, but few controlled studies
- Some studies suggest efficacy in panic disorder
Suggested Reading


