Vortioxetine

Brands • Trintellix (formerly Brintellix)
see index for additional brand names

Generic? NO

Class
• Neuroscience-based Nomenclature:
  serotonin multimodal (S-MM)
• Multimodal antidepressant

Commonly Prescribed for
(bold for FDA approved)
• Major depressive disorder
• Generalized anxiety disorder (GAD)
• Cognitive symptoms associated with depression
• Geriatric depression

How the Drug Works
• Increases release of several different neurotransmitters (serotonin, norepinephrine, dopamine, glutamate, acetylcholine, and histamine) and reduces the release of GABA through 3 different modes of action
• Mode 1: blocks serotonin reuptake pump (serotonin transporter)
• Mode 2: binds to G protein-linked receptors (full agonist at serotonin 1A receptors, partial agonist at serotonin 1B receptors, antagonist at serotonin 1D and serotonin 7 receptors)
• Mode 3: binds to ion channel-linked receptors (antagonist at serotonin 3 receptors)
• Full agonist actions at presynaptic somatodendritic serotonin 1A autoreceptors may theoretically enhance serotonergic activity and contribute to antidepressant actions
• Full agonist actions at postsynaptic serotonin 1A receptors may theoretically diminish sexual dysfunction caused by serotonin reuptake inhibition
• Antagonist actions at serotonin 3 receptors may theoretically enhance noradrenergic, acetylcholinergic, and glutamatergic activity and contribute to antidepressant and pro-cognitive actions
• Antagonist actions at serotonin 3 receptors may theoretically reduce nausea and vomiting caused by serotonin reuptake inhibition
• Antagonist actions at serotonin 7 receptors may theoretically contribute to antidepressant and pro-cognitive actions as well as reduce insomnia caused by serotonin reuptake inhibition
• Partial agonist actions at serotonin 1B receptors may enhance not only serotonin release, but also acetylcholine and histamine release
• Antagonist actions at serotonin 1D receptors may enhance serotonin release and may also theoretically enhance the release of pro-cognitive neurotransmitters and thereby enhance pro-cognitive actions

How Long Until It Works
• Onset of therapeutic actions is usually not immediate, but often delayed 2–4 weeks
• However, vortioxetine has a specific claim of onset of action at week 2
• If it is not working within 6 or 8 weeks, 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) or significantly reduced
• Once symptoms gone, continue treating for 1 year for the first episode of depression
• For second and subsequent episodes of depression, treatment may need to be indefinite
• Use in anxiety disorders may also need to be indefinite

If It Doesn’t Work
• Many patients only have a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
SIDE EFFECTS

How Drug Causes Side Effects
• Theoretically due to increases in serotonin concentrations at serotonin receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin at central serotonin 1A receptors causing nausea, unwanted actions of serotonin in the CNS causing sexual dysfunction, etc.)
• Most side effects are immediate but often go away with time, in contrast to most therapeutic effects, which are delayed and are enhanced over time

Notable Side Effects
• Nausea, vomiting, constipation
• Sexual dysfunction

Life-Threatening or Dangerous Side Effects
• Rare seizures
• Rare induction of mania and activation of suicidal ideation

Weight Gain
• Reported but not expected

Sedation
• Reported but not expected

What to Do About Side Effects
• Wait
• Wait
• Wait
• In a few weeks, switch to another agent or add other drugs

Best Augmenting Agents for Side Effects
• Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
• Trazodone or a hypnotic for insomnia

Best Augmenting Combos for Partial Response or Treatment Resistance
• Augmentation experience is limited compared to other antidepressants
• Trazodone, especially for insomnia
• Bupropion, mirtazapine, reboxetine, or atomoxetine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
• Use with caution with antidepressants that are CYP450 2D6 inhibitors (e.g., bupropion, duloxetine, fluoxetine, paroxetine), as these agents will increase vortioxetine levels and may require a dose reduction of vortioxetine
• Modafinil, especially for fatigue, sleepiness, and lack of concentration
• Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, treatment-resistant depression, or treatment-resistant anxiety disorders
• Benzodiazepines
• If all else fails for anxiety disorders, consider gabapentin, pregabalin, or tiagabine
• Hypnotics for insomnia
• Classically, lithium, buspirone, or thyroid hormone

Tests
• None for healthy individuals
consider the possibility of activating a bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic.

**Overdose**
- No fatalities have been reported; nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, flushing.

**Long-Term Use**
- Long-term treatment of major depressive disorder is generally necessary.

**Habit Forming**
- No.

**How to Stop**
- Taper not necessary with recommended doses.

**Pharmacokinetics**
- Metabolized by CYP450 2D6, 3A4/5, 2C19, 2C9, 2A6, 2C8, and 2B6.
- Mean terminal half-life approximately 66 hours.

**Drug Interactions**
- Tramadol increases the risk of seizures in patients taking an antidepressant.
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14–21 days after MAOIs are stopped.
- Do not start an MAOI for at least 5 half-lives (about 14 days for vortioxetine with a half-life of 66 hours) after discontinuing vortioxetine.
- Strong CYP450 2D6 inhibitors can increase plasma levels of vortioxetine, possibly requiring its dose to be decreased.
- Broad CYP450 2D6 inducers can decrease plasma levels of vortioxetine, possibly requiring its dose to be increased.
- Could theoretically cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or possibly other triptans, requiring careful monitoring of patient.
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs).

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**DOSING AND USE**

**Usual Dosage Range**
- 5–20 mg/day.

**Dosage Forms**
- Tablet 5 mg, 10 mg, 15 mg, 20 mg.

**How to Dose**
- Initial 10 mg once daily; can decrease to 5 mg once daily or increase to 20 mg once daily depending on patient response; maximum recommended dose generally 20 mg once daily.

**Dosing Tips**
- Can be taken with or without food.
- Tablet should not be divided, crushed, or dissolved.
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activating a bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic.
Other Warnings/Precautions

- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Possible risk of hyponatremia related to SIADH (syndrome of inappropriate antidiuretic hormone secretion) with serotonergic drugs
- Not approved in children, so when treating children off label, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of non-treatment 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 is taking an MAOI
- If there is a proven allergy to vortioxetine

Elderly

- No dose adjustment necessary
- Some patients may tolerate lower doses better
- Risk of SIADH with SSRIs is higher in the elderly
- Reduction in risk of suicidality with antidepressants compared to placebo in adults age 65 and older

Children and Adolescents

- Safety and efficacy have not been established
- 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 strongly consider informing parents or guardian 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
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
- Must weigh the risk of treatment (first trimester fetal development, third trimester

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary

Hepatic Impairment

- No dose adjustment necessary for mild to moderate impairment
- Has not been studied in patients with severe hepatic impairment

Cardiac Impairment

- Not systematically evaluated in patients with cardiac impairment
- Treating depression with SSRIs in patients with acute angina or following myocardial infarction may reduce cardiac events and improve survival as well as mood; not known for vortioxetine
THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• Patients with sexual dysfunction
• Patients with cognitive symptoms of depression
• Patients with residual cognitive symptoms after treatment with another antidepressant
• Elderly patients
• Patients who have not responded to other antidepressants
• Patients who do not want weight gain

Potential Disadvantages
• Cost

Primary Target Symptoms
• Depressed mood
• Cognitive symptoms
• Anxiety

Pearls
• In May 2016 the US FDA approved a brand name change from Brintellix to Trintellix in order to decrease prescribing and dispensing errors due to name confusion with the anti-platelet medication Brilinta (ticagrelor)
• May have less sexual dysfunction than SSRIs
• Multiple studies show pro-cognitive effects greater than a comparator antidepressant in patients with major depressive episodes
• Patients who do not respond to antidepressants with other mechanisms of action may respond to vortioxetine
• Shown effective specifically in elderly patients with depression, with a positive trial in geriatric depression with improvement of cognition as well as mood
• Has a unique claim of preventing recurrences in major depression
• No weight gain in clinical trials
• Long half-life means vortioxetine can generally be abruptly discontinued, although some caution may be necessary when stopping higher doses (i.e., 15 or 20 mg/day)
• Despite serotonin 3 antagonist actions, nausea is common, presumably due to full agonist actions at serotonin 1A receptors
• Dose response for efficacy in depression: higher doses are more effective
• Vortioxetine has a unique multimodal mechanism of action
• Nonresponse to vortioxetine in elderly may require consideration of mild cognitive impairment or Alzheimer disease

Breast Feeding
• Unknown if vortioxetine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
• If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
• 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 re instituted 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

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
• Exposure to serotonin reuptake inhibitors early in pregnancy may be associated with increased risk of septal heart defects (absolute risk is small)
• Use of serotonin reuptake inhibitors beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
• Exposure to serotonin reuptake inhibitors late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
• Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying
VORTIOXETINE (continued)

Suggested Reading


