Serotonin Modulator Antidepressants

Summary

- Serotonin modulator antidepressants act by altering the activity of various post-synaptic serotonin (5-HT) receptors, in addition to inhibiting the reuptake of serotonin via the same mechanism as selective serotonin reuptake inhibitors (SSRIs).
- The serotonin modulator antidepressants are alternative choices to selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) in adults for the treatment of major depressive disorder. These agents have similar response rates to SSRIs and SNRIs.[65502][65503][65505][65516]
- Vilazodone should be taken with food and the dosage must be titrated on initiation in accordance with the manufacturer's recommendation. Vortioxetine does not need to be titrated; however, a dosage adjustment may be needed in some patients to optimize response and tolerability.[56041][43177]
- Dosage adjustments are not required for these agents in patients with renal or hepatic impairment; however, the safety of vilazodone in patients with severe hepatic impairment has not been formally evaluated.[56041][43177]
- Unlike many SSRIs and SNRIs, vortioxetine does not require tapering upon discontinuation; however, mild discontinuation symptoms may still develop in which case a taper may be warranted. It is recommended that vilazodone be tapered gradually.[56041][43177]
- Serotonin modulator antidepressants have not been shown to have a significant effect on body weight.[56041][43177]
- Unlike SSRIs and SNRIs, there is a lack of evidence with vilazodone and vortioxetine to determine their role, if any, in treating anxiety disorders.
- Drug interactions may occur with serotonin modulator antidepressants due to metabolism by CYP isoenzymes. Vortioxetine is primarily metabolized by CYP2D6 and vilazodone is primarily metabolized by CYP3A4. Dosage adjustments are recommended when either drug is taken with strong inhibitors of its respective metabolizing enzyme.[56041][43177]
- The safety of serotonin modulators in patients who are pregnant or breastfeeding has not been established.[56041][43177]

Pharmacology

Serotonin modulators change the activity of various 5-HT receptor subtypes in the brain. Vortioxetine is an agonist of the 5-HT1A receptor, a partial agonist of 5-HT1B, and an antagonist of 5-HT3, 5-HT1D, and 5-HT7. Vilazodone is a partial 5-HT1A agonist. Similar to SSRIs, vortioxetine and vilazodone are also inhibitors of the pre-synaptic serotonin transporter, increasing the synaptic concentration of serotonin. The contribution of the modulating mechanisms of vortioxetine and vilazodone to their antidepressant effects have not been established.[56041][43177]

Therapeutic Use

Therapeutic Use Table

Export to CSV (Excel)

Indications	Vilazodone hydrochloride	Vortioxetine
Renal Impairment Dosing Adjustment		
Hepatic Impairment Dosing Adjustment		Yes
depression	Yes	Yes

Yes – Labeled

Yes † – Off-label, Recommended

NR – Off-label, Not Recommended

Major depressive disorder

- Serotonin modulator antidepressants are alternative agents to SSRIs and SNRIs for the treatment of major depressive disorder in adults. One meta-analysis has determined that vortioxetine may have a more tolerable adverse reaction profile.[65502]
- Vortioxetine is recommended as a first-line option in adults for depression by the Canadian Network for Mood and Anxiety Treatments (CANMAT) evidence-based guidelines and listed as one of the drugs effective in preventing recurrence of depression by the World Federation of Societies of Biological Psychiatry (WFSBP) evidence-based guideline.[65503][65505]
- Vilazodone is recommended as a second-line agent versus a first-line agent in adults by the CANMAT guideline due to a lack of comparative research, the need for dosing titration, and the need to be administered with food.[65503]
- The safety and efficacy of serotonin modulator antidepressants in pediatric patients have not been established and these drugs are not approved for use in children; there are insufficient data for use of these agents in pediatric patients. Guidelines for pediatric patients generally recommend the use of SSRIs as first-line medication options when nonpharmacologic treatment is insufficient or illness severity is high.[43177][49959][56041][62891]
- Results of some clinical trials have shown efficacy in using vortioxetine to treat major depressive disorder in adult patients with high levels of anxiety symptoms; however, direct comparisons with

other antidepressants used for this purpose are not available. Serotonin modulators are not approved for the treatment of anxiety disorders.[65501]

Comparative Efficacy

- There are few publications directly comparing the efficacy of serotonin modulators with other classes of antidepressants. Meta-analyses indicate that the efficacy of serotonin modulators is similar to that of commonly prescribed SSRIs or SNRIs.[65502][65516]
- One indirect comparison determined that vortioxetine may be more tolerable than vilazodone and certain other antidepressants such as sertraline or venlafaxine.[65502]

Serotonin Modulators Comparative Efficacy Trials

Citation/Study Name	Design/Regimen	Results	Conclusion
Mathews M, et al. Int Clin Psychopharmacol. 2015;30(2):67-74. [65517]	A randomized, double-blind, placebo- and active-controlled, parallel-group, fixed-dose study spanning 10 weeks. Patients were randomly assigned to placebo, vilazodone 20 mg/day, vilazodone 40 mg/day, or citalopram 40 mg/day. Active doses were titrated appropriately. The primary outcome was a Montgomery-Asberg Depression Rating Scale (MADRS) measurement at baseline and weeks 1, 2, 4, 6, 8, and 10. Safety was measured via recording of adverse events, physical examination, various clinical laboratory and vital sign measures, and the Changes in Sexual Functioning Questionnaire (CSFQ).	**Mean MADRS change from baseline to week 10 (Standard Error):** vilazodone 20 mg/day, -17.3 (0.6) vilazodone 40 mg/day, -17.6 (0.7) citalopram 40 mg/day, -17.5 (0.6) placebo, -14.8 (0.6)	Treatment with vilazodone 20 mg/day, vilazodone 40 mg/day, and citalopram 40 mg/day showed similar and significant improvements in depression symptoms compared to placebo. All active treatment groups were generally well tolerated, with most adverse events being mild or moderate in severity.
Alvarez et al. Int J Neuropsychopharmacol. 2012;15(5):589-600. [65518]	A randomized, double-blind, placebo- and active-controlled, fixed-dose study spanning 6 weeks. Patients were randomly assigned to placebo, vortioxetine 5 mg/day, vortioxetine 10 mg/day, or venlafaxine XR 225 mg/day. Venlafaxine doses were titrated appropriately. The primary outcome was a MADRS measurement at baseline and week 6. Possible treatment-emergent adverse events (TEAEs) were recorded at each visit.	**Mean MADRS change from baseline to week 6 (Standard Error):** vortioxetine 5 mg/day, -20.4 (1) vortioxetine 10 mg/day, -20.2 (1) venlafaxine XR 225 mg/day, -20.9 (1) placebo, -14.5 (1)	Treatment with vortioxetine 5 mg/day, vortioxetine 10 mg/day, and venlafaxine XR 225 mg/day showed similar and significant improvements in depression symptoms compared to placebo. Withdrawal due to adverse events was significantly higher in the venlafaxine group than the placebo group. This was not the case for either dose of vortioxetine.

Mahableshwarkar AR, et al. Psychopharmacology (Berl). 2015;232(12):2061-70. [65519]	A randomized, double-blind, placebo- and active-controlled, parallel-group study spanning 8 weeks. Patients were randomly assigned to placebo, vortioxetine 15 mg/day, vortioxetine 20 mg/day, or duloxetine 60 mg/day. The primary outcome was a MADRS measurement at baseline and weeks 1, 2, 4, 6, and 8. Adverse events were recorded at every study visit.	**Difference in mean MADRS change from baseline to week 8 compared to placebo (Standard Error):** vortioxetine 15 mg/day, -1.48 (1.214) vortioxetine 20 mg/day, -2.75 (1.206) duloxetine 60 mg/day, -4.07 (1.214)	Treatment with vortioxetine 20 mg/day and duloxetine 60 mg/day showed significant improvements in depression symptoms compared to placebo. Rates of reported adverse events between active treatment groups were roughly similar.

Adverse Reactions / Side Effects

Top 20 Adverse Reactions / Side Effects Table

Export to CSV (Excel)

Adverse Reaction / Side Effect	Vilazodone hydrochloride	Vortioxetine
abnormal dreams	2 - 3%	<3%
diarrhea	28%	7 - 10%
dizziness	9%	6 - 9%
dyspepsia	3%	Reported
ejaculation dysfunction	2%	16 - 29%
flatulence	3%	1 - 3%
libido decrease	3 - 5%	Reported
nausea	23%	21 - 32%
orgasm dysfunction	2 - 4%	16 - 34%
vomiting	5%	3 - 6%
xerostomia	8%	6 - 8%
arthralgia	3%	
constipation		3 - 6%
drowsiness	3%	
fatigue	4%	
headache	14 - 15%	
insomnia	6%	
paresthesias	3%	
pruritus		1 - 3%
restlessness	2 - 3%	

Gastrointestinal adverse reactions

Gastrointestinal (GI) side effects are the most common adverse reactions in patients receiving serotonin modulator antidepressant treatment. Nausea is the most common adverse reaction with any serotonin modulator. In patients receiving vortioxetine, nausea was generally reported as mild or moderate in severity and lasted for a median of two weeks. The severity and extent of nausea was not reported for vilazodone. Other less frequently reported GI effects of vortioxetine and vilazodone included diarrhea, dry mouth, constipation, and vomiting.[56041][43177]

Central nervous system adverse reactions

The most common centrally-mediated adverse reaction of serotonin modulator antidepressants is dizziness. In general, centrally-mediated side effects were reported more commonly with vilazodone than vortioxetine during clinical trials. A wide range of centrally-mediated adverse reactions were reported in patients taking vilazodone, including insomnia, restlessness, somnolence, and paresthesia. Patients who are taking vilazodone should be cautioned about driving or performing other hazardous tasks until they know how vilazodone affects them. One clinical trial found that a 10 mg/day dose of vortioxetine did not impair driving or other psychomotor functions.[56041][43177]

Bleeding

Impaired platelet aggregation may occur during treatment with serotonin modulator antidepressants due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication. Mild (e.g., epistaxis) to severe (e.g., gastrointestinal bleeding) adverse effects have been documented during the use of serotonergic antidepressants, especially in combination with other drugs that have antiplatelet (e.g., aspirin) or anticoagulant effects.[56041][43177]

Hyponatremia

Serotonergic antidepressants may cause hyponatremia as a result of the syndrome of inappropriate antidiuretic hormone secretion. One case of hyponatremia was reported in a pre-marketing clinical study of vortioxetine. No cases of hyponatremia resulting from vilazodone treatment were reported in premarketing clinical studies. Elderly patients, those taking diuretics, or those who are otherwise volume depleted may be at greater risk. Serotonin modulator antidepressants should be discontinued in patients with symptomatic hyponatremia.[56041][43177]

Sexual dysfunction

Like other serotonergic antidepressants, the serotonin modulators may cause sexual dysfunction. Sexual dysfunction occurs in both men and women. In men, ejaculatory delay or dysfunction is most common, but decreased libido and erectile dysfunction are also reported. In women, decreased libido is most common, and orgasm dysfunction is also reported. Although the reported incidence of sexual dysfunction ranges from less than 1% up to 5% with vortioxetine and less than 1% up to 2% with vilazodone, the actual occurrence is likely higher due to patient underreporting. In one publication, use of the Arizona Sexual Experience Scale (ASEX) in patients receiving vortioxetine yielded rates of sexual dysfunction as high as 34% in females and 29% in males compared to 20% and 14% in females and males taking placebo, respectively. A study conducted using the Changes in Sexual Functioning

Questionnaire (CSFQ) in patients receiving vilazodone yielded rates of sexual dysfunction as high as 22.2% in females and 11.6% in males compared to 16.7% and 17.% in females and males taking placebo, respectively.[56041][43177][65506]

Drug Interactions

MAO inhibitors

Serotonin modulators are contraindicated in patients receiving MAO inhibitors (MAOIs) or who have discontinued an MAOI within 2 weeks due to the risk of serotonin syndrome. Medications with MAOI activity, such as linezolid or intravenous methylene blue, are also contraindicated for use with serotonin modulators because of an increased risk of serotonin syndrome.[56041][43177]

SSRIs, SNRIs, and other serotonergic drugs

Any use of a serotonin modulator antidepressant with other serotonergic agents increases the likelihood of serotonergic adverse effects such as serotonin syndrome and should be monitored closely. Drugs that have serotonergic properties include opiates, triptans, most antidepressants, amphetamines, St. John's wort, tramadol, lithium, buspirone, and others.[56041][43177]

Antithrombotic drugs

Anticoagulants, antiplatelet drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and aspirin should be administered with caution to any patient taking a serotonin modulator antidepressant, especially in the elderly. Platelet aggregation may be impaired by serotonin modulators due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication. Patients should be instructed to monitor for signs and symptoms of bleeding while taking a serotonin modulator with an antiplatelet, anticoagulant, or NSAID medication and to promptly report any bleeding events to the practitioner. [56041][43177]

CYP isoenzyme interactions

- Vortioxetine is primarily metabolized by CYP2D6. The dose of vortioxetine should be reduced by half when a strong CYP2D6 inhibitor is coadministered. The effect of other CYP450 enzyme inhibition on vortioxetine is minimal. Dose adjustment may be considered when vortioxetine is coadministered with strong CYP3A4 inducers, though the adjustment should not exceed 3 times the original dose. Vortioxetine is unlikely to significantly inhibit or induce CYP450 isoenzymes. [56041]

- Vilazodone is primarily metabolized by CYP3A4. The dose of vilazodone should not exceed 20 mg daily when a strong CYP3A4 inhibitor is coadministered. The effect of other CYP450 enzyme inhibition on vilazodone metabolism is minimal. Vilazodone exposure has not been evaluated when the drug is coadministered with CYP3A4 inducers. In vitro, vilazodone has been shown to moderately inhibit CYP2C8, CYP2C19, and CYP2D6; however, the effects of vilazodone on these isoenzymes in humans is not well established.[43177]

Safety Issues

Safety Issues Table

Export to CSV (Excel)

Safety Issue	Vilazodone hydrochloride	Vortioxetine
REMS		
MedGuide	Yes	Yes
children	BBW	BBW
MAOI therapy	X	X
suicidal ideation	BBW	BBW

X – Contraindicated

X-BBW – Contraindicated and Black Box Warning

BBW – Black Box Warning, Not Contraindicated

Yes – REMS or MedGuide is available

Increased risk of suicide

The approved labeling for all antidepressants carries a boxed warning of an increased risk of suicidal thoughts and behavior in children and young adults, particularly during the first few months of therapy. Experts state that the apparent increase in suicidality reflected by a greater number of spontaneously reported events is mitigated by the lack of any completed suicides, the decline in overall suicidality on rating scales, and the greater number of patients who benefit from antidepressants than who experience these serious adverse effects. Careful assessment and monitoring of suicidality are warranted in all patients initiating treatment with a serotonin modulator antidepressant.[43177][49959][56041]

Bipolar disorder

The use of antidepressants has been associated with the precipitation of mania or hypomania in susceptible individuals. If a patient develops manic symptoms, the antidepressant should be withheld, and appropriate therapy initiated to treat the manic symptoms. Depression may also be the presenting symptom of a mixed/manic episode of bipolar disorder. Patients should be adequately screened for bipolar disorder prior to initiating an antidepressant. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.[43177][56041]

Geriatrics

Changes in efficacy and safety of serotonin modulator antidepressants have not been observed in geriatric patients versus use in younger adults; therefore, dosage adjustments based on age are not recommended. However, geriatric patients may be at an increased risk for hyponatremia, an adverse effect associated with the use of serotonergic antidepressants. The federal Omnibus Budget Reconciliation Act (OBRA) regulates the use of antidepressants in residents of long-term care facilities; therapy should be in accordance with clinical practice guidelines and pertinent literature. Monitor for antidepressant side effects; some of these effects can increase the risk of falls. Per OBRA, review for

continued need of the drug at least quarterly and document the rationale for continuation. When the drug is being used to manage behavior, stabilize mood, or treat a psychiatric disorder, the facility should attempt to taper the medication as outlined in the OBRA guidelines, unless a taper is clinically contraindicated.[43177][56041][60742]

Pregnancy

Treatment with serotonin modulator antidepressants during pregnancy should be approached with caution. The American Psychiatric Association guidelines state that treatment of depression during early pregnancy requires careful individualized risk-benefit assessment, in collaboration with the patient and potentially a neonatal specialist. Use of serotonergic antidepressants, including serotonin modulators, during the third trimester may lead to neonatal complications including prolonged hospitalization, respiratory support, and tube feeding. There are limited data regarding the use of serotonin modulator antidepressants in pregnant patients. The benefits of treatment should clearly outweigh risks to justify treatment during pregnancy.[43177][56041][49961][62732]

Breast-feeding

There are no data regarding the presence of serotonin modulator antidepressants in human breast milk. The benefits of drug treatment to the mother need to be weighed against the potential risk for infant drug exposure. There are reports of agitation, irritability, poor feeding, and poor weight gain following exposure to other serotonergic antidepressants through breast milk. Any infant exposed to serotonergic antidepressants through breast-feeding should be monitored for these adverse effects.[43177][56041][46229][61269][62732]

Abrupt discontinuation

The extent of adverse effects resulting from abrupt discontinuation of serotonin modulator antidepressants is not well established; however, serotonergic agents are generally known to cause symptoms upon discontinuation. It is recommended that the dosage of vilazodone be gradually decreased to minimize the risk for developing discontinuation symptoms. Vortioxetine can be discontinued abruptly, however mild symptoms such as headache and muscle tension may occur.[43177][56041]