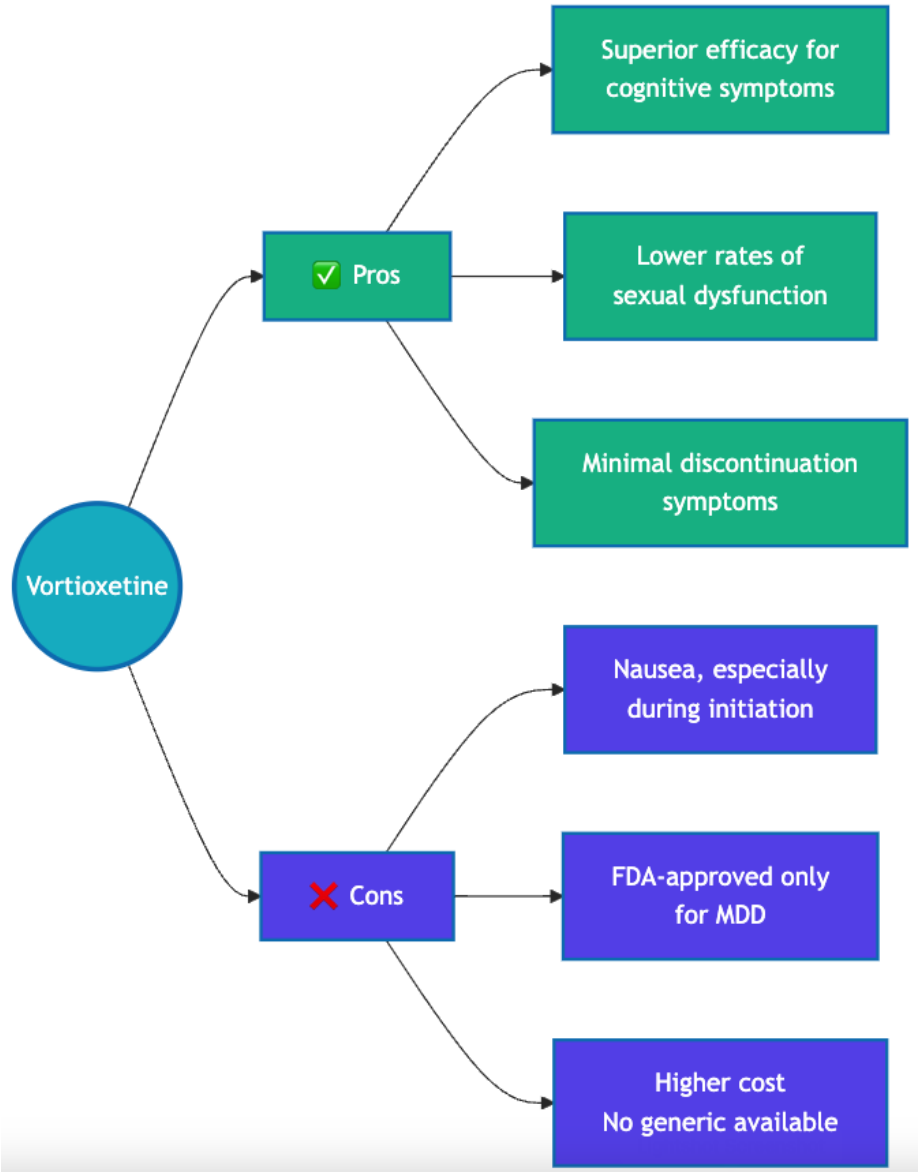
In a nutshell

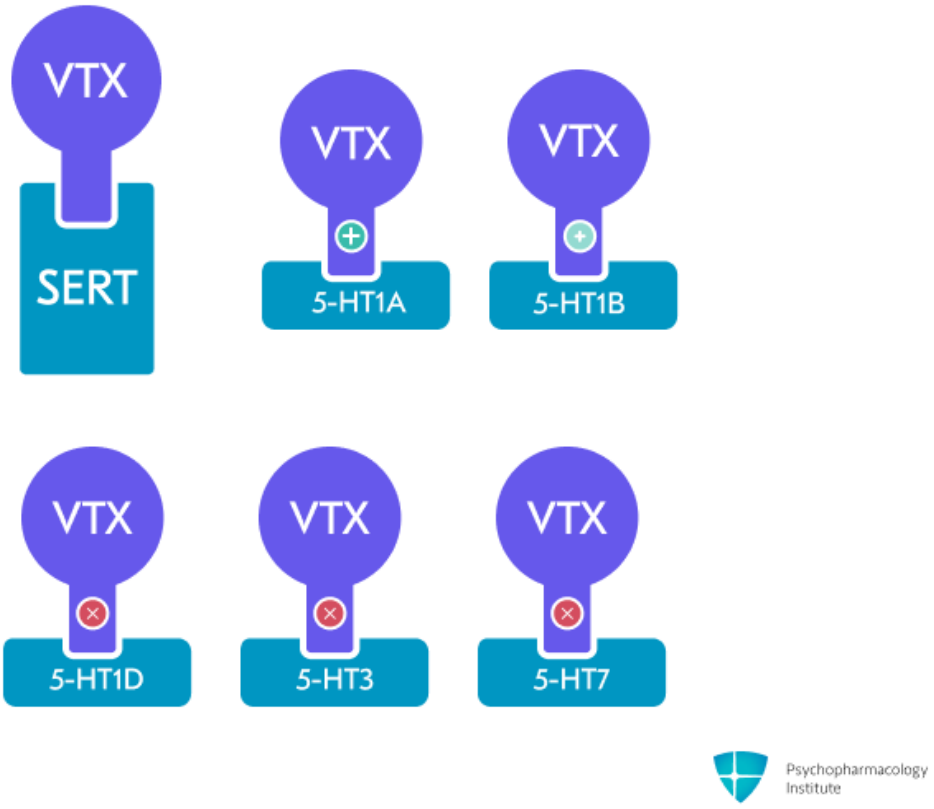
Vortioxetine combines serotonin reuptake inhibition with direct modulation of multiple serotonin receptors, potentially offering advantages for patients with cognitive symptoms of depression. Its main clinical advantage appears to be a favorable tolerability profile, particularly regarding sexual dysfunction and discontinuation symptoms.



    - Choosing vortioxetine over other antidepressants:

        - Preferred for patients with prominent cognitive symptoms of depression
        - Lower risk of sexual dysfunction compared to SSRIs
        - Minimal discontinuation symptoms due to long half-life
        - Low risk of drug interactions (except with CYP2D6 inhibitors/inducers)
- Consider alternatives when:
    - Patients sensitive to GI side effects (high rates of nausea)
    - Treating anxiety disorders (insufficient evidence for GAD)
    - Cost is a concern (newer branded medication)
    - Concurrent use of strong CYP2D6 inhibitors/inducers

Pharmacodynamics and mechanism of action

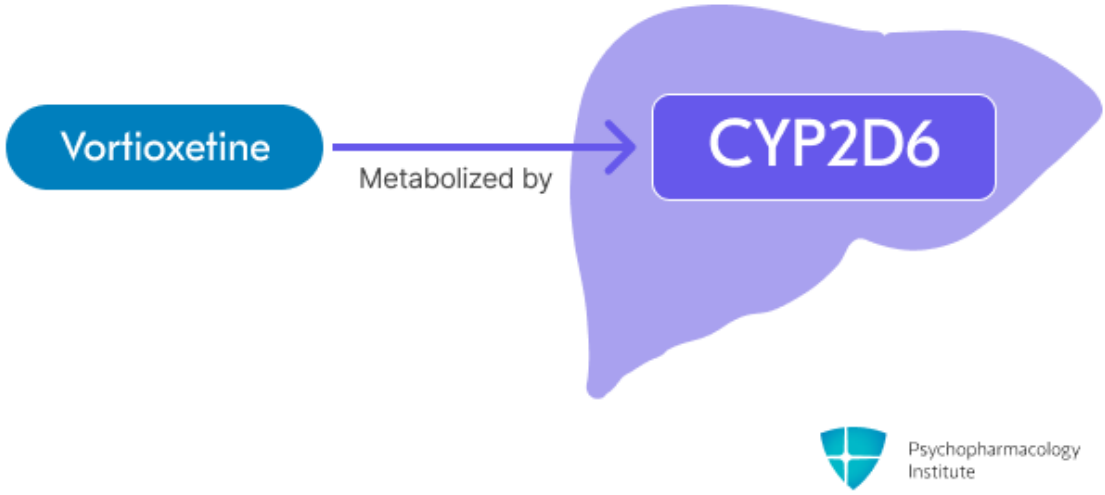


- Multimodal mechanism combining serotonin reuptake inhibition with direct modulation of serotonin receptors [1]

- Primary mechanism: Potent serotonin reuptake inhibition through SERT blockade [2]
- Direct receptor activity [2,3]
    - Agonist: 5-HT1A receptor
    - Partial agonist: 5-HT1B receptor
    - Antagonist: 5-HT1D, 5-HT3, 5-HT7 receptors
- Preclinical findings and potential implications
    - While vortioxetine's receptor binding profile distinguishes it from traditional SSRIs, the clinical significance of these pharmacological differences continues to be investigated [2].
    - 5-HT1A agonism
        - May accelerate antidepressant response through somatodendritic receptor desensitization [2,4]
    - 5-HT3 antagonism
        - May enhance anxiolytic and antidepressant effects [2]
    - 5-HT7 antagonism
        - Potentially enhances antidepressant effects when combined with SERT inhibition [2]
        - May be linked to pro-cognitive effects [5]
    - Combined 5-HT1B partial agonism and SERT inhibition
        - Increased serotonin levels in the prefrontal cortex and enhanced serotonergic neuron firing have been described in animal models [6].

Pharmacokinetics

Metabolism



- Primarily metabolized through oxidation via CYP2D6 [3]
- Minor pathways involve other CYP450 isoenzymes (CYP3A4/5, CYP2C19, CYP2C9, etc).
- CYP2D6 metabolism
    - CYP2D6 metabolizer status affects plasma concentrations
    - Poor metabolizers exhibit approximately double the plasma concentrations compared to extensive metabolizers.
    - Maximum recommended dose for CYP2D6 poor metabolizers is 10 mg/day [3]
- Vortioxetine levels increased by
    - Strong CYP2D6 inhibitors (bupropion, fluoxetine, paroxetine, quinidine
        - Reduce vortioxetine dose by 50%
        - Return to original dose when inhibitor is discontinued
- Vortioxetine levels reduced by
    - Strong CYP inducers (rifampin, carbamazepine, phenytoin)
        - Consider increasing vortioxetine dose
        - Maximum dose should not exceed 3 times the original dose

        - Return to original dose within 14 days of discontinuing the inducer [7]
- Serotonergic agents
    - Monitor for serotonin syndrome with other serotonergic medications (SSRIs, SNRIs, triptans, tricyclic antidepressants).
    - Also applies to tramadol, tryptophan, and St. John's Wort
- Contraindicated with MAOIs [3]
    - Due to vortioxetine's long half-life, a 21-day washout period is required after discontinuation before starting an MAOI.
    - A 14-day washout period is required after discontinuing an MAOI before initiating vortioxetine.

Half-life

- Vortioxetine half-life is approximately 66 hours.

False-positive drug tests

- Vortioxetine can trigger false-positive methadone results in urine immunoassays [3]
    - Confirmatory testing via chromatographic methods is recommended for positive screens.

Dosage forms

Dosage forms

- Immediate-release:
    - Film-coated tablets
        - 5 mg, 10 mg, 20 mg
        - Trintellix
- Formulation considerations
    - Tablets can be taken with or without food, at either morning or bedtime.

Indications

FDA-Approved Indications

Major depressive disorder

- First-line antidepressant treatment option for MDD based on efficacy and favorable tolerability profile [8,9]
- Shows advantages over other antidepressants when considering both efficacy and acceptability in network meta-analyses [10]
- Cognitive effects:
    - The labeling includes data showing improvements in cognitive processing speed (as measured by the Digit Symbol Substitution Test)
    - Despite seeking separate regulatory approval, vortioxetine was not approved for cognitive symptoms of depression as a standalone indication.
    - May be particularly beneficial for patients with cognitive symptoms (problems with concentration, memory, and executive functioning), and age-related cognitive decline [11,12]
    - Recent systematic review reports superior efficacy compared to SSRIs [13]
        - Half to two-thirds of the observed effect of vortioxetine on cognitive improvement is a direct effect on cognition itself, rather than being a consequence of improvements in depressive symptoms.
- Dosing:
    - Starting dose: 10 mg once daily
        - Sensitive patients: Start at 5 mg once daily for patients who experience nausea or who do not tolerate higher doses
    - Target dose: 20 mg/day
    - Maximum dose:
        - General population: 20 mg/day
        - CYP2D6 poor metabolizers: 10 mg/day [3]
    - May be taken day or night, independent of food intake

Off-label Uses

Generalized anxiety disorder

- The evidence does not support vortioxetine for use in GAD [14,15]

Obsessive compulsive disorder

- There are no double-blind studies investigating vortioxetine's efficacy in OCD [16]

- However, case report indicates vortioxetine's potential role for depressed patients with obsessive symptoms [17], or in OCD patients unsuitable for TCAs or unresponsive to SSRIs [18,19].

Side effects

Most common side effects

Gastrointestinal

- Nausea (21-32% incidence)
  - Most common adverse effect leading to discontinuation
  - Usually occurs in the first week, with 15-20% experiencing nausea after 1-2 days of treatment [3].
  - Dose-related: Approximately 10% still experience nausea at treatment end with doses 10-20mg/day
  - Can be minimized by taking it with food
- Diarrhea (7-10% incidence)
- Dry mouth (7% incidence)
- Constipation (3-6% incidence)
- Vomiting (3-6% incidence)

Other common side effects

- Discontinuation syndrome
  - Lower risk compared to other antidepressants due to vortioxetine's 66-hour half-life [20,21]
  - Clinical trials and observational data suggest low incidence and/or similar to placebo [21,22]
  - For 15-20mg/day doses, a reduction to 10mg/day for one week before discontinuation is recommended [3]
- Antidepressant-induced sexual dysfunction
  - Lower rates of sexual dysfunction compared to other antidepressants [21,23]
    - However, spontaneous reporting likely underestimates actual prevalence [24]
  - Even though the effect is dose-dependent, treatment-emergent sexual dysfunction rates remain comparable to placebo [25]
  - May improve sexual function in patients switching from high-risk antidepressants (e.g., citalopram, paroxetine, or sertraline) [23]
  - Consider lower doses for patients concerned about sexual side effects

    - Use structured assessment tools like the ASEX rather than relying on spontaneous reporting
    - Monitor for dose-dependent effects
- Dizziness (6-9% incidence)
- Abnormal dreams (2-3% incidence)
- Pruritus (2-3% incidence)

Severe side effects

- Serotonin syndrome
    - Risk increases with other serotonergic drugs
    - Has also been reported in monotherapy [26]
    - Use caution when combining vortioxetine with serotonergic medications, especially during treatment initiation or dose adjustments [3].
- Bleeding risk
    - Serotonergic antidepressants (SSRIs, SNRIs) may increase bleeding risk, particularly with concurrent NSAIDs, antiplatelets or anticoagulants.
    - Vortioxetine may share this risk, though current evidence is limited
    - In healthy volunteers, coadministration with warfarin or aspirin did not alter coagulation parameters [27].
    - Clinical data in depressed populations remain sparse; monitor closely when combined with anticoagulants, especially at initiation [28].
- Hyponatremia
    - Antidepressant therapy can precipitate SIADH and clinically significant hyponatremia.
    - Ranking of risk [29]:
        - MAOIs > SNRIs > SSRIs > TCAs > Mirtazapine
        - Vortioxetine was not included in this meta-analysis, but cases have been documented [30–32].
    - Special caution in elderly patients, patients taking diuretics or who are otherwise volume-depleted

Use in special populations

Pregnancy

- First-trimester safety
    - Animal reproductive studies of vortioxetine show no evidence of increased congenital malformation risk during pregnancy.

    - Limited human data from a case series of 17 first-trimester exposures reported [33]
- Pregnancy complications
    - Late pregnancy exposure may be associated with [3]
        - Neonatal adaptation syndrome
        - Persistent pulmonary hypertension of the newborn (PPHN)
        - Similar to other serotonergic antidepressants

Breastfeeding

- Vortioxetine is present in breast milk.
- FDA prescribing information notes lack of data on effects on breastfed infants and milk production [3]
- Available case reports suggest minimal infant exposure, but few cases and limited follow-up data [34]
    - Relative infant dose: 1.1-1.7% of maternal dose
    - Based on data from only 3 women taking 10-20 mg/day
- One additional case report describes successful breastfeeding for one year while on medication [33]
    - No follow-up information provided on infant outcomes
- Breastfed infants should be monitored for
    - Sedation
    - Poor feeding patterns
    - Weight gain adequacy
    - Development

Hepatic impairment

- No dose adjustment needed

Renal impairment

- No dose adjustment needed

Elderly

- No dose adjustment recommended [3]
- Starting dose 5 mg/day recommended [35]
- Caution with doses >10 mg/day due to
    - Increased risk of hyponatremia
    - Higher exposure (up to 27%) compared to younger adults

Obesity

- Mean elimination half-life prolonged by 48% in patients with BMI ≥35 kg/m² compared to normal BMI
- Consider extended washout period when switching to MAOIs in patients with obesity [36]

Brand names

- US: Trintellix
- Canada: Trintellix
- Other countries/regions: Acsodix, Brintellix, Brivor, Depratiox, Fonksera, Kelac, Lupivor, Procetina, Torvox, Trivoxetin, Trintogen, Valquir, Vantaxa, Vectax, Vipca, Vormind, Vorpix, Vorsero, Vortica, Vortidif, Vortiox, Vortiray, Vorxetil, Voxigain, Voxitin, Vorellix, Vivirum, Vorti, Vorasan, Vurtuoso, Xomet

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