Serotonin modulators: Pharmacology, administration, and side effects

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INTRODUCTION

Advances in understanding brain neurophysiology have led to the development of serotonin modulators, including [1]:

- Nefazodone
- Trazodone
- Vilazodone
- Vortioxetine

The serotonin modulators are distinct from other classes of antidepressants that include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, tricyclics, and monoamine oxidase inhibitors. Serotonin modulators act as antagonists and agonists at postsynaptic serotonin receptors and inhibit reuptake of postsynaptic serotonin to varying degrees; effects upon norepinephrine reuptake are minimal.

The pharmacology, administration, and side effects of serotonin modulators are reviewed here. Choosing a regimen for the initial treatment of depression and treatment of resistant depression is discussed separately, as are other antidepressant drug classes:

- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

- (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Atypical antidepressants: Pharmacology, administration, and side effects".)
- (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)
- (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

GENERAL PRINCIPLES

Drug interactions and metabolism — Coadministration of serotonin modulators with another drug can decrease or increase the metabolism of the serotonin modulator, which may necessitate either adjusting the dose of the serotonin modulator or using a different antidepressant. Thus, prior to initiating or altering therapy with serotonin modulators, clinicians should check interactions with other medications using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate. The drug interaction tool provides specific dose recommendations for prescribing serotonin modulators concomitantly with drugs that affect the serotonin modulator's metabolism.

Serotonin modulators are metabolized by hepatic cytochrome P450 3A4 (CYP3A4) or 2D6 (CYP2D6) enzymes. Administering a serotonin modulator in conjunction with another drug that inhibits these enzymes can increase serum concentrations of the serotonin modulator, resulting in drug accumulation and toxicity. Prescribing a serotonin modulator concurrently with medications that induce the enzymes can decrease serum concentrations of the serotonin modulator and lead to therapeutic failure. The hepatic metabolism of the serotonin modulators includes the following:

- **Trazodone and vilazodone** – Trazodone and vilazodone undergo extensive hepatic metabolism by CYP3A4 [2,3]. Strong CYP3A4 inhibitors and inducers are listed in the table (table 1).
- **Vortioxetine** – Vortioxetine undergoes extensive metabolism by CYP2D6 and is also metabolized by other CYP enzymes [4]. Drug-drug interactions can occur when vortioxetine is coadministered with medications that inhibit CYP2D6 metabolism, or

medications that induce other CYP metabolic pathways. CYP2D6 inhibitors are listed in the table (table 2).

- **Nefazodone** – Although nefazodone seems to undergo extensive metabolism by CYP3A4 based upon in vitro data, this has not been well studied [5,6]. Strong CYP3A4 inhibitors and inducers are listed in the table (table 1).

  Nefazodone is itself a strong inhibitor of CYP3A4 and can elevate levels of comedications that are dependent upon CYP3A4 for clearance.

Serotonin modulators can also interact with other medications that elevate serotonin in the central nervous system, potentially resulting in the serotonin syndrome. These drug-drug interactions (eg, with monoamine oxidase inhibitors) can be severe and are described in more detail separately. (See "Serotonin syndrome (serotonin toxicity)".)

Guidelines to review with patients — Prior to prescribing serotonin modulators, clinicians should discuss:

- Drug interactions
- Side effects
- Time to response
- Stopping the medication

Common and serious side effects (table 3) and the need to take the medication as prescribed rather than on an as needed basis should be reviewed. Patients should also be informed that although some response often occurs within the first two weeks of treatment, it may take many weeks (eg, 8 to 14) for a full response (severity of illness and comorbid disease may affect how quickly depressed patients respond to treatment) [7].

Medical tests and plasma levels — No specific medical tests are required before starting serotonin modulators, and drug serum concentrations are not routinely monitored because they have not been shown to correlate with clinical response. However, levels can assess adherence and whether unresponsive patients are rapid metabolizers. Levels can also establish that it is safe to begin another serotonergic drug (eg, a monoamine oxidase inhibitor) after discontinuing a serotonin modulator, in order to avoid the serotonin syndrome (table 4). (See "Serotonin syndrome (serotonin toxicity)".)

Dosing — We suggest starting with a low dose in order to avoid side effects and slowly increasing the dose. Starting doses and target dose ranges of each serotonin modulator are listed in the table (table 5). Depressed patients with high levels of anxiety may tolerate the

medication better by starting with half of the suggested dose. Doses are adjusted according to patient response, tolerability, and clinical urgency.

Finding the effective dose of an antidepressant involves trial and error. After starting the drug and titrating up to the minimum effective dose, response should be monitored over the following two to four weeks. For patients who tolerate the antidepressant but do not respond, we continue titrating up the dose slowly (to avoid side effects) every two to four weeks. For unresponsive patients who do not tolerate the drug, we suggest switching to a different antidepressant. (See "Switching antidepressant medications in adults" and "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Next step treatment'.)

Patients who recover from an episode of major depression should generally receive maintenance treatment with the full dose that successfully resolved the episode, rather than a lower dose. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Dose'.)

Separate sections below discuss specific dose recommendations for each serotonin modulator.

Pregnancy — Treatment of pregnant women with antidepressants is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment".)

Serotonin syndrome — Serotonin modulators increase serotonergic neurotransmission and can cause the serotonin syndrome. (See "Serotonin syndrome (serotonin toxicity)".)

Suicide — The potential effect of antidepressants on suicidal ideation and behavior in adults is discussed separately. (See "Effect of antidepressants on suicide risk in adults".)

NEFAZODONE

Nefazodone is used to treat major depression and premenstrual syndrome. The drug is contraindicated in patients with elevated serum transaminases, active liver disease, or liver injury due to previous nefazodone treatment.

Pharmacology — Nefazodone is a phenylpiperazine whose structure resembles that of trazodone [1,8]. Nefazodone antagonizes and down regulates postsynaptic serotonin 5-HT2A receptors, and weakly inhibits presynaptic serotonin and norepinephrine reuptake; these actions increase activity at the serotonin 5-HT1A receptors [1,9,10]. The drug has little to no affinity for alpha-adrenergic receptors, cholinergic, dopamine D2, and histamine H1 receptors. The pharmacokinetic parameters of nefazodone are displayed in the table (table 6).

Administration, dose, and discontinuation — The usual starting dose of nefazodone for major depression is 100 mg twice daily (table 5) [9]. For patients who do not respond after two to four weeks, the dose is increased to 150 to 200 mg twice daily. The dose is increased further by increments of 100 to 200 mg per day every two to four weeks until the desired clinical response is achieved; the maximum dose is 300 mg twice daily. In clinically urgent situations, dose increases can occur once a week as tolerated. The effectiveness and tolerability of once daily and twice daily dosing may be comparable [11].

Based upon in vitro data, nefazodone seems to undergo extensive metabolism by cytochrome P450 3A4 (CYP3A4) enzymes. However, this has not been well studied and the manufacturer does not provide dose adjustment recommendations for use with CYP3A4 inhibitors or inducers [5,6]. Nevertheless, if nefazodone is co-prescribed with a strong inhibitor of CYP3A4, decreasing the dose of nefazodone may be warranted; if nefazodone is given concomitantly with a strong inducer, the dose of nefazodone may need to be increased. Strong CYP3A4 inhibitors and inducers are listed in the table (table 1).

Although abrupt discontinuation of nefazodone does not cause a withdrawal syndrome, we taper the drug over one week before stopping it, which is consistent with the preferred method of discontinuing any psychotropic medication. In two randomized trials, patients with major depression (n = 259 and 131) who received nefazodone for 16 weeks were randomly assigned to either continue the drug or abruptly stop it and start placebo (as part of relapse prevention studies); the incidence of discontinuation symptoms was comparable for the two groups [12,13]. Additional information about discontinuing antidepressants is discussed separately. (See "Discontinuing antidepressant medications in adults".)

Side effects — Nefazodone can injure the liver; the estimated incidence of hepatotoxicity based upon a national registry in Spain is 29 cases per 100,000 patients per year [14]. Adverse hepatic reactions can occur with doses as low as 100 mg per day and generally occur within six months of starting the drug [15]. These reactions include acute liver failure; the estimated incidence is 1 case per 200,000 to 300,000 patient years, which is three to four times greater than expected [16]. A 2010 study of the World Health Organization Programme for International Drug Monitoring database found 94 cases of acute liver failure attributed to nefazodone, including patients who received a liver transplant or died [17]. Thus, nefazodone is not commonly used in United States; generic versions are available, but the brand-name version is no longer manufactured. In addition, the drug has been withdrawn from the market in several countries. Patients receiving the drug should be monitored for signs and symptoms of liver failure (nausea, abdominal pain, jaundice, impaired synthetic function, coagulopathy, and delirium).

Although periodic liver function tests (eg, every two to six months) may possibly be useful, there is no evidence that testing prevents hepatic injury [12].

Nefazodone can cause several other side effects (table 3). A pooled analysis of randomized trials (n = 2185 patients, most with unipolar major depression) found that the incidence of discontinuing nefazodone because of side effects was 12 percent and for placebo was 7 percent [18]. Adverse effects that occurred more frequently with nefazodone included:

- Nausea – 21 percent of patients who received nefazodone
- Somnolence – 19 percent
- Dry mouth – 19 percent
- Dizziness – 12 percent
- Constipation – 11 percent
- Weakness – 11 percent
- Blurred vision – 6 percent

Each of these adverse effects, except dry mouth and weakness, appear to be dose related and less likely to occur at doses ≤300 mg per day [9].

Reduced systolic blood pressure (≤90 mmHg and ≥20 mmHg reduction from baseline) occurred in more patients who received nefazodone than placebo (5 versus 3 percent), but the incidence of syncope was comparable (0.02 and 0.03 percent) [18]. In addition, asymptomatic sinus bradycardia was detected by electrocardiogram in more patients who received nefazodone than placebo (1.3 versus 0.4 percent).

Sexual dysfunction with nefazodone and placebo appear to be comparable, based upon a meta-analysis [19] as well as a pooled analysis of randomized trials (n = 2185 patients) [18]. In addition, weight gain during treatment lasting between 3 to 13 months is comparable for nefazodone and placebo [18].

Compared with selective serotonin reuptake inhibitors, nefazodone is less activating and causes less gastrointestinal distress (eg, nausea, diarrhea, and anorexia), sexual dysfunction, and weight gain during long-term treatment (eg, 16 to 46 weeks), but causes more dry mouth, dizziness, constipation, visual disturbances, and confusion [9,20].

Overdose — The clinical features, toxicology, and management of overdoses with vilazodone are discussed separately. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)".)

TRAZODONE

Trazodone is used to treat major depression as well as functional dyspepsia. In addition, it is often used as a hypnotic to treat insomnia in the context of depression, as well as insomnia associated with antidepressants (eg, bupropion or fluoxetine) [21]. However, the efficacy of trazodone for insomnia in the absence of depression appears to be short-lived. (See "Pharmacotherapy for insomnia in adults", section on 'Trazodone'.)

Pharmacology — Trazodone is a triazolopyridine whose structure resembles that of nefazodone [8]. Trazodone acts upon postsynaptic serotonin 5-HT2A and 5-HT2C receptors and weakly inhibits presynaptic serotonin reuptake. The effects appear to be dose dependent such that at low doses the drug acts as a serotonin antagonist and at high doses as a serotonin agonist [8,22]. Effects on norepinephrine and dopamine reuptake are minimal. In addition, the drug blocks postsynaptic alpha-adrenergic receptors (which may account for the side effects of orthostatic hypotension and priapism) and histamine H1 receptors (which may explain its sedative effect) [8,22,23]. The drug does not affect cholinergic receptors.

The pharmacokinetic parameters of trazodone are displayed in the table (table 6).

Administration, dose, and discontinuation — Trazodone immediate release is typically dosed as follows for major depression (table 5). The drug is started at 50 mg twice daily, which is then increased by increments of 50 mg per day every three to seven days to a dose of 75 to 150 mg twice daily. The dose is subsequently increased by 50 to 100 mg per day every two to four weeks until the desired clinical response is achieved, to a maximum dose of 600 mg per day. Doses >400 mg per day warrant cautious use and additional monitoring, particularly in the elderly and other patients at risk for cardiovascular toxicity. The drug's sedative effects may be better tolerated if patients are given a smaller daytime dose and larger bedtime dose (eg, 100 mg in the morning and 200 mg at bedtime); some patients receive the entire dose at bedtime. An extended release preparation is available in a few countries, but no longer in the United States.

Patients with insomnia associated with antidepressants (eg, selective serotonin reuptake inhibitors) may benefit from immediate release trazodone 50 to 100 mg at bedtime [21]. When adjunctive trazodone is prescribed as a hypnotic for insomnia associated with depression, doses typically range from 50 to 300 mg at bedtime [24]. Although doses up to 600 mg at bedtime have been studied for insomnia in the context of depression, we rarely use more than 200 mg.

Trazodone undergoes extensive hepatic metabolism by hepatic cytochrome P450 3A4 (CYP3A4) enzymes [3]. If trazodone is co-prescribed with a strong inhibitor of CYP3A4, decreasing the

dose of trazodone may be warranted. If trazodone is given concomitantly with a strong inducer, the dose of trazodone may need to be increased. Strong CYP3A4 inhibitors and inducers are listed in the table (table 1).

We suggest tapering the drug over two to four weeks prior to discontinuation. Rapid or abrupt discontinuation of trazodone may be followed by withdrawal symptoms, including gastrointestinal distress, anxiety, and sleep disturbances [25]. Additional information about discontinuing antidepressants is discussed separately. (See "Discontinuing antidepressant medications in adults".)

Side effects — Trazodone can cause several side effects (table 3) [24,25]. A randomized trial that compared trazodone immediate release with placebo in 153 patients with major depression found that discontinuation of treatment due to side effects was greater in patients who received trazodone than placebo (23 versus 4 percent); trazodone caused a higher incidence of [26]:

- Sedation – 61 percent of patients who received trazodone
- Dizziness – 36 percent
- Dry mouth – 27 percent
- Nausea – 19 percent

Orthostatic hypotension and headache are also common with trazodone [27].

Rare but serious side effects of trazodone include:

- Priapism – Penile priapism secondary to trazodone is an emergency that should be evaluated immediately by a urologist (rare cases of clitoral priapism have also been reported) [28]. Trazodone induced priapism is estimated to occur 1 in 1000 to 1 in 10,000 patients, and has been reported at doses ranging from 50 to 400 mg per day. Although most cases occur within the first month of treatment, priapism may occur up to 18 months after onset of treatment. A prolonged erection during treatment may be a risk factor for subsequent priapism. Additional information about priapism is discussed separately. (See "Priapism".)

- Cardiac arrhythmias – A review identified case reports of atrial and ventricular arrhythmias in patients treated with trazodone [25]. Thus, the drug should be used with caution in patients with cardiac disease.

Trazodone appears to be weight neutral during treatment lasting 4 to 12 weeks, based upon a meta-analysis of three heterogeneous randomized trials (n = 155 patients treated with

trazodone for with major depression) [29].

Overdose — The clinical features, toxicology, and management of overdoses with vilazodone are discussed separately. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)".)

VILAZODONE

Vilazodone is used to treat major depression.

Pharmacology — Vilazodone is an indolalkylamine that inhibits presynaptic reuptake of serotonin and also acts as a partial agonist at postsynaptic serotonin 5-HT1A receptors [30]. Inhibition of norepinephrine and dopamine reuptake is minimal. The pharmacokinetic parameters of vilazodone are displayed in the table (table 6).

Administration, dose, and discontinuation — The usual starting dose of vilazodone for major depression is 10 mg per day at bedtime, for one week (table 5). The dose is then increased to 20 mg per day for week 2 [31]. This two-week titration schedule is intended to reduce gastrointestinal toxicity. The target dose is 20 to 40 mg per day. The drug should be taken with food to increase bioavailability. Dose adjustments are not required for patients with severe renal impairment [30]; use of the drug in patients with severe hepatic impairment has not been studied [32].

Concurrent use of vilazodone with other medications that inhibit or induce hepatic cytochrome P450 3A4 (CYP3A4) metabolism can alter vilazodone serum concentrations, which may necessitate adjusting the dose of vilazodone. Strong CYP3A4 inhibitors and inducers are listed in the table (table 1). Recommendations for specific vilazodone dose adjustments are as follows [2]:

- Vilazodone given with strong CYP3A4 inhibitors – Vilazodone dose should not exceed 20 mg once daily. If the CYP3A4 inhibitor is discontinued, readjust vilazodone to original dose.
- Vilazodone given with strong CYP3A4 inducers – Based upon clinical response, clinicians may need to increase the vilazodone dose two-fold when coadministered with CYP3A4 inducer for more than 14 days. Maximum daily dose of vilazodone is 80 mg. If the CYP3A4 inducer is discontinued, reduce vilazodone dose to the original dose over 7 to 14 days.

Specific interactions of serotonin modulators with other medications can be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Although withdrawal symptoms due to abrupt discontinuation of vilazodone have not been described, we taper drug doses of 20 to 40 mg per day for one to two weeks prior to discontinuation [30]; tapering is the preferred method of discontinuing any psychotropic medication. Additional information about discontinuing antidepressants is discussed separately. (See "Discontinuing antidepressant medications in adults".)

Side effects — Vilazodone can cause several side effects (table 3). A pooled analysis examined adverse effects in two randomized trials that compared vilazodone 40 mg per day with placebo for eight weeks in 891 patients with unipolar major depression; the following adverse effects occurred more often in patients who received vilazodone than placebo, and the incidence with vilazodone was as follows [33]:

- Diarrhea – 28 percent
- Nausea – 23 percent
- Sexual dysfunction – 16 percent of males and 5 percent of females
- Dizziness – 8 percent
- Insomnia – 6 percent
- Vomiting – 5 percent

Although discontinuation of treatment due to side effects was greater in patients who received vilazodone than placebo (7 versus 3 percent) [33], the clinical effect was small. A pooled analysis of two randomized trials lasting eight weeks (n = 891) compared vilazodone (40 mg/day) to placebo with regard to discontinuation of treatment due to adverse effects [34]. The analysis found that the number needed to harm was 27; this means that on average, a clinician would need to treat 27 patients with vilazodone and 27 patients with placebo before observing one more patient stopping vilazodone than placebo because of an adverse event.

Patients treated with vilazodone have reported the potentially life threatening serotonin syndrome. In premarketing studies of patients with unipolar major depression, symptoms of the syndrome were found in 0.1 percent [35]. The clinical features and management of the serotonin syndrome are discussed separately. (See "Serotonin syndrome (serotonin toxicity)".)

Concerns have been raised about the possibility that maternal use of vilazodone during pregnancy may cause persistent pulmonary hypertension of the newborn. (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes", section on 'Persistent pulmonary hypertension of the newborn'.)

Based upon placebo controlled trials, vilazodone appears to have little or no effect upon [32,33]:

- Vital signs
- Electrocardiogram parameters (including cardiac repolarization [corrected QT interval])
- Laboratory tests (including liver function tests)
- Body weight

Overdose — The clinical features, toxicology, and management of overdoses with vilazodone are discussed separately. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)".)

VORTIOXETINE

Vortioxetine is used to treat major depression [36-38]. In addition, improvement of cognitive dysfunction in patients with unipolar major depression may be greater with vortioxetine than other antidepressants (eg, duloxetine), and this benefit may be independent of resolving the depressive syndrome [39,40].

Pharmacology — Vortioxetine is a bis-aryl-sulphanyl amine that inhibits presynaptic reuptake of serotonin, which is considered the primary mechanism of action underlying the drug's antidepressant effect [41]. In addition, vortioxetine interacts with several serotonin receptor subtypes; the medication is a potent antagonist at serotonin 5-HT3 receptors, a weaker antagonist at 5-HT7 and 5-HT1D receptors, a partial agonist at 5-HT1B receptors, and a full agonist at 5-HT1A receptors [42-44]. The downstream pharmacodynamic effects include increased levels of serotonin, acetylcholine, dopamine, and norepinephrine in specific areas of the brain [45]. Although the clinical significance of the drug's effects upon the serotonin receptor subtypes is unknown [41,43], these effects may perhaps mediate the drug's therapeutic benefits and its side effect profile [40,43].

The pharmacokinetic parameters of vortioxetine are displayed in the table (table 6) [41,46].

Administration, dose, and discontinuation — We suggest starting vortioxetine at a dose of 10 mg once daily (table 5) [41]. For patients who tolerate the drug in week 1, the dose is increased to the target dose of 20 mg per day. However, a reasonable alternative is to initiate treatment with a dose of 5 mg/day for week 1 and then titrate up to 10 mg/day for week 2, followed by either 20 mg/day for week 3 or 15 mg/day for week 3 and 20 mg/day for week 4. In addition, it is reasonable to evaluate the effectiveness of each dose for two to four weeks before titrating up. (Multiple randomized trials found that vortioxetine 5, 10, 15, and 20 mg/day were each superior to placebo [37,47]).

Dose adjustments are not required for older patients (eg, age ≥65 years) and for patients with renal impairment or mild to moderate hepatic impairment; use of the drug in patients with severe hepatic impairment has not been studied [41,43].

Vortioxetine undergoes extensive metabolism by hepatic cytochrome P450 2D6 (CYP2D6) enzymes and is also metabolized by other CYP enzymes [4]. For patients who slowly metabolize CYP2D6 substrates, the maximum recommended dose is 10 mg/day. In addition, dose adjustments may be necessary if vortioxetine is coadministered with medications that inhibit CYP2D6 metabolism (table 2), or medications that induce other CYP metabolic pathways (eg, carbamazepine and phenytoin). Thus, prior to initiating or altering therapy with vortioxetine, clinicians should check drug-drug interactions with other medications using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate. The drug interaction tool provides specific dose recommendations for administering vortioxetine concomitantly with strong CYP2D6 inhibitors or with inducers of other CYP enzymes.

Although abrupt discontinuation of vortioxetine does not cause a withdrawal syndrome, we taper drug doses of 15 or 20 mg/day to 10 mg/day for one week before stopping it [41,46]; tapering is the preferred method of discontinuing any psychotropic medication. Evidence regarding the lack of discontinuation symptoms includes the following:

- Three randomized trials lasting eight weeks compared vortioxetine (10, 15, or 20 mg/day) with placebo in patients with acute unipolar major depression (n >1300), and then abruptly stopped the study drugs [48]. During the subsequent two weeks, the level of withdrawal symptoms was comparable for the two groups, which was probably due to the relatively long half-life of vortioxetine (table 6).

- A maintenance treatment study (n = 396 remitted patients) compared vortioxetine (5 or 10 mg/day) with placebo for up to 64 weeks and then abruptly stopped the study drugs [49]. During the subsequent two weeks, the level of withdrawal symptoms was comparable for the two groups.

Additional information about discontinuing antidepressants is discussed separately. (See "Discontinuing antidepressant medications in adults".)

Side effects — Although vortioxetine can cause several side effects, especially nausea (table 3), the drug is generally well tolerated [43,48]. As an example, a pooled analysis of 11 short-term (six or eight weeks) randomized trials compared vortioxetine (5 to 20 mg/day) with placebo in patients with unipolar major depression (n >4800) [34]. The analysis found that the number needed to harm, defined as discontinuing treatment due to side effects, was 43. This means that on average, a clinician would need to treat 43 patients with vortioxetine and 43

patients with placebo before observing one more patient stopping vortioxetine than placebo because of an adverse event. Nevertheless, randomized trials have demonstrated that the overall difference between vortioxetine and placebo, with regard to stopping treatment due to adverse effects, is statistically significant [36,50].

Based upon a pooled analysis of 11 short-term randomized trials that compared vortioxetine with placebo in depressed patients (n >4800), the absolute rate of discontinuing treatment due to adverse effects was as follows [48]:

- Placebo – 4 percent of patients
- Vortioxetine 5 mg/day – 5 percent
- Vortioxetine 10 mg/day – 5 percent
- Vortioxetine 15 mg/day – 8 percent
- Vortioxetine 20 mg/day – 7 percent

Comparable figures are found in longer studies. A maintenance trial included 396 patients who initially remitted with open-label vortioxetine and were then randomly assigned to vortioxetine (5 or 10 mg/day) or placebo for treatment lasting up to 64 weeks [49]. Discontinuation of treatment due to adverse events occurred in 8 and 3 percent of patients.

The side effect that most often causes patients to stop vortioxetine is nausea [48], and the most frequent side effect of vortioxetine is nausea [43]. A pooled analysis of 11 short-term randomized trials (n >4800 depressed patients) compared vortioxetine with placebo and found that the incidence of nausea was as follows [48]:

- Placebo – 8 percent of patients
- Vortioxetine 5 mg/day – 21 percent
- Vortioxetine 10 mg/day – 23 percent
- Vortioxetine 15 mg/day – 31 percent
- Vortioxetine 20 mg/day – 28 percent

Onset of nausea was most frequent in week 1 [41], and the median duration of nausea was 9 to 16 days, depending upon the dose [48]. Among patients taking 10 to 20 mg/day at the end of the short-term trials, nausea was present in 10 percent [41].

In addition, a study treated acutely depressed patients with open-label vortioxetine for 12 weeks and then randomly assigned remitted patients (n = 396) to vortioxetine (5 or 10 mg/day) or placebo for maintenance treatment lasting up to 64 weeks; the incidence of nausea was greater with vortioxetine than placebo (9 versus 3 percent of patients) [49].

Other side effects that occur more often with vortioxetine than placebo include vomiting and constipation [51]. However, the incidence of vomiting and constipation is relatively low, compared with the incidence of nausea. As an example, a pooled analysis of 11 short-term randomized trials (n >4800 depressed patients) found that the frequency of vomiting in patients treated with vortioxetine (5 to 20 mg/day) ranged from 3 to 6 percent, depending upon the dose; the rate with placebo was 1 percent [48]. Similarly, the frequency of constipation in patients treated with vortioxetine ranged from 3 to 6 percent, and the rate with placebo was 3 percent.

In multiple short-term randomized trials of acutely depressed patients, vortioxetine and placebo were comparable with regard to changes in electrocardiogram parameters, laboratory values (eg, complete blood counts, electrolytes, and liver function tests), and vital signs [48]. Similar results were found in one randomized trial that compared vortioxetine (5 or 10 mg/day) with placebo as maintenance treatment in patients (n = 396) [49]. In addition, patients who initially completed five short-term randomized trials (total n = 2587) were treated with vortioxetine in open-label extension studies; no clinically significant changes in electrocardiogram parameters, laboratory values, or vital signs were observed [52-56].

Other studies suggest that side effects are less problematic with vortioxetine than other antidepressants, such as agomelatine, duloxetine, and venlafaxine [57,58]. As an example, a meta-analysis of five randomized trials (n >2000 depressed patients) lasting eight weeks compared vortioxetine (2.5 to 20 mg/day) with duloxetine (60 mg/day) and found that adverse effects were less likely to occur with vortioxetine than duloxetine (relative risk 0.88, 95% CI 0.82-0.94), including nausea (relative risk 0.70, 95% CI 0.56-0.87) [59].

Overdose — The clinical features, toxicology, and management of overdoses with vilazodone are discussed separately. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Coping with high drug prices (The Basics)")
- Beyond the Basics topics (see "Patient education: Depression treatment options for adults (Beyond the Basics)" and "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

The National Institute of Mental Health also has educational material on the use of antidepressants, including SSRIs, entitled, "What medications are used to treat depression?" that is available online at the website. Material explaining the symptoms, causes, and treatment for depression is also available in a booklet entitled "Depression" that is available online at the website. Both publications can also be obtained through a toll-free number, 866-615-6464. The web site also provides references, summaries of study results in language intended for the lay public, and information about clinical trials currently recruiting patients.

The Depression and Bipolar Support Alliance (available at the website or 800-826-3632) is a national organization whose mission is to educate members about depression and how to cope with it. Other functions include increasing public awareness of the illness and advocating for more research and services. The organization is administered and maintained by patients and family members, and has local chapters.

The National Alliance on Mental Illness (available at the website or 800-950-6264) is a similarly structured organization devoted to providing education, support, and advocacy for patients with any mental illness. Depression is one of their priorities.

SUMMARY

- **Specific drugs** – Serotonin modulators include nefazodone, trazodone, vilazodone, and vortioxetine. (See 'Introduction' above.)
- **Pharmacokinetics** – The pharmacokinetic parameters of serotonin modulators are presented in the table (table 6). Nefazodone may inhibit the hepatic enzyme CYP3A4. (See 'Drug interactions and metabolism' above.)

- **What to discuss with patients** – Prior to prescribing serotonin modulators, clinicians should discuss drug interactions, side effects (table 3), time to response, and stopping the medication.

- **Medical tests and plasma levels** – No specific medical tests are required before starting serotonin modulators, and drug plasma levels are not routinely performed. (See 'General principles' above.)

- **Dosing** – We suggest starting with a low dose in order to avoid side effects (table 3) and slowly increasing the dose. Starting doses and target dose ranges of each serotonin modulator are listed in the table (table 5). (See 'Dosing' above.)

- **Adverse effects**

  - **Serotonin syndrome** – Serotonin modulators can cause the serotonin syndrome. (See "Serotonin syndrome (serotonin toxicity)".)

  - **Nefazodone** – Nefazodone can injure the liver and is contraindicated in patients with elevated serum transaminases, active liver disease, or liver injury due to previous nefazodone treatment. Other adverse effects include nausea, somnolence, dry mouth, dizziness, constipation, weakness, and blurred vision. (See 'Nefazodone' above.)

  - **Trazodone** – Common adverse effects of trazodone include somnolence, dry mouth, dizziness, fatigue, constipation, vision blurred, sexual dysfunction, orthostatic hypotension, and headache. Rare but serious side effects include priapism and cardiac arrhythmias. (See 'Trazodone' above.)

  - **Vilazodone** – Adverse effects of vilazodone include diarrhea, nausea, sexual dysfunction, dizziness, insomnia, and vomiting. (See 'Vilazodone' above.)

  - **Vortioxetine** – The primary adverse effect of vortioxetine is nausea. Other potential side effects include vomiting and constipation. (See 'Vortioxetine' above.)

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