Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects

AUTHOR: Craig Nelson, MD
SECTION EDITOR: Peter P Roy-Byrne, MD
DEPUTY EDITOR: David Solomon, MD

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INTRODUCTION

Serotonin-norepinephrine reuptake inhibitors (SNRIs) act primarily upon serotonergic and noradrenergic neurons, but have little or no effect upon cholinergic or histaminergic receptors [1]. SNRIs include:

- Desvenlafaxine
- Duloxetine
- Levomilnacipran
- Milnacipran
- Venlafaxine

The primary indications for SNRIs are depressive disorders (eg, unipolar major depression or persistent depressive disorder [dysthymia]) and anxiety disorders (eg, generalized anxiety disorder, panic disorder, or social anxiety disorder) [2,3]. SNRIs are also used for chronic pain syndromes, including diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain. In addition, clinicians use SNRIs to treat body dysmorphic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and premenstrual dysphoric disorder. Menopausal hot flashes (vasomotor symptoms), urinary incontinence, and vulvodynia may also respond to SNRIs. See other topic reviews.

This topic reviews the pharmacology, administration, and side effects of SNRIs. Choosing a regimen for the initial treatment of major 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 modulators: 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".)

EFFICACY FOR MAJOR DEPRESSION

The efficacy of serotonin-norepinephrine reuptake inhibitors for treating unipolar major depression is discussed separately in the context of choosing a regimen for the initial treatment of major depression and for treatment of resistant depression. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

PHARMACOLOGY

Structure — Desvenlafaxine (also called O-desmethylvenlafaxine) and venlafaxine are bicyclic phenylethylamine compounds with similar structures (removal of a methyl group from venlafaxine results in the active metabolite desvenlafaxine) [3,4]. Duloxetine is a naphthalene compound [5]. Milnacipran is a phenylacetamide compound and consists of two stereoisomers that are mirror images of each other and thus not identical in that they cannot be superimposed upon each other (similar to one's hands) [5]. One of the stereoisomers is levomilnacipran, which is the more active (potent) enantiomer of racemic milnacipran [6]. Although the mechanism of action for serotonin-norepinephrine reuptake inhibitors (SNRIs) is similar, the structures of duloxetine, milnacipran, and venlafaxine are dissimilar [3,5,7].

Pharmacodynamics — The SNRIs appear to treat depression by initially blocking presynaptic serotonin and norepinephrine transporter proteins [3,6,7]. This inhibits reuptake of these neurotransmitters, which changes various homeostatic mechanisms, and ultimately increases stimulation of postsynaptic receptors. However, the SNRIs vary in their affinity for the serotonin transporter and norepinephrine transporter. Desvenlafaxine, duloxetine, and venlafaxine are more potent inhibitors of serotonin reuptake than norepinephrine reuptake, whereas levomilnacipran and milnacipran preferentially block reuptake of norepinephrine [2,3,8,9].

SNRIs are often referred to as "dual action agents"; however, the degree to which reuptake of serotonin and norepinephrine is inhibited depends upon the dose administered. As an example, venlafaxine is essentially a selective serotonin reuptake inhibitor (SSRI) at 75 mg per day [1,10]. At higher doses, such as 225 mg/day and 375 mg/day, venlafaxine has significant effects on the norepinephrine transporter [11]. By contrast, low doses of levomilnacipran block reuptake of norepinephrine approximately two times more potently than serotonin [9]. However, levomilnacipran doses ≥40 mg per day inhibit 90 percent of norepinephrine reuptake and 80 percent of serotonin reuptake [6]. (All of these estimates are based upon indirect measures and group means.)

For treating unipolar major depression, drugs that block reuptake of both serotonin and norepinephrine appear to be more efficacious than SSRIs, but the advantage is small. A pooled analysis of 93 randomized trials (n>17,000 patients) compared dual action agents with SSRIs and found that response occurred in more patients treated with dual action drugs (64 versus 59 percent); although the difference was statistically significant, the magnitude was modest [12].

Choosing an antidepressant for treating major depression is discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

The SNRIs have little or no effect upon alpha1-adrenergic, cholinergic, dopaminergic, or histaminergic receptors [1,8]. However, the effects of SNRIs on norepinephrine receptors in the sympathetic nervous system lead to a relative decrease in parasympathetic tone; this can cause "pseudoanticholinergic" side effects (eg, constipation, dry mouth, and urinary retention), despite the lack of direct effects upon cholinergic receptors [13].

Pharmacokinetics — The pharmacokinetic parameters of SNRIs vary (table 1). Food decreases the rate but not the degree of absorption; administering the drugs with food may reduce nausea, which is generally the most common side effect of SNRIs [14]. Duloxetine is similar to SSRIs and tricyclics in that it is highly protein bound, clearance is primarily hepatic, and <1 percent of the drug is eliminated unchanged in the urine [7]. By contrast, the other

SNRIs are less protein bound, kidney excretion of the drugs plays a larger role in their clearance, more of the drug is excreted unchanged in urine, and dose adjustment is more likely to be required in the presence of kidney disease. As an example, levomilnacipran is only 22 percent bound to plasma proteins, and 58 percent is excreted unchanged in the urine [6]. Due to interindividual differences in the clearance of the SNRIs, steady state plasma concentrations of these drugs can vary substantially between individuals, resulting in the need for individual dose adjustments to attain the desired clinical effect. The dose of SNRIs is reduced in patients with hepatic or kidney disease. The suggested dose for each SNRI is discussed below in the sections that describe administration of a specific drug.

Drug-drug interactions — Duloxetine is a moderately potent inhibitor of the hepatic cytochrome P450 enzyme CYP2D6 (table 2) and may thus interact with other drugs [15,16]. As an example, CYP2D6 inhibition may block conversion of opiate prodrugs such as codeine, hydrocodone, and oxycodone to their active metabolite. By contrast, desvenlafaxine, levomilnacipran, milnacipran, and venlafaxine do not have clinically meaningful effects on P450 enzymes [3,16,17].

SNRIs are contraindicated in patients who received monoamine oxidase inhibitors (MAOIs) in the previous two weeks because of drug-drug interactions that can cause the serotonin syndrome and in some cases hypertensive crisis. Patients discontinuing SNRIs and starting MAOIs should wait two weeks between the last dose of the SNRI and the first dose of the MAOI. Switching antidepressants and the serotonin syndrome are discussed separately. (See "Switching antidepressant medications in adults" and "Serotonin syndrome (serotonin toxicity)".)

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

GENERAL PRINCIPLES

Guidelines to review with patients — Prior to prescribing serotonin-norepinephrine reuptake inhibitors (SNRIs), 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 may occur within the first two weeks of treatment, it may take many weeks (eg, 8 to 12) for a full response; severity of illness and comorbid disease may affect how quickly depressed patients respond to treatment. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar major depression in adults: Choosing initial treatment", section on 'Duration of an adequate trial'.)

In addition, clinicians should caution patients to not abruptly discontinue SNRIs, which may precipitate chills, dizziness, dysphoria, fatigue, gastrointestinal distress, and myalgias [18,19]. This discontinuation syndrome appears to be particularly common with venlafaxine and relatively uncommon with milnacipran. Additional information about the discontinuation syndrome and discontinuing SNRIs is discussed separately. (See "Discontinuing antidepressant medications in adults".)

Medical tests, plasma levels, and monitoring — No specific medical tests are required before starting SNRIs, and drug serum concentrations are not routinely monitored because therapeutic blood levels have not been established [20]. However, in nonresponsive patients, low drug levels can suggest poor adherence or ultrafast metabolism. High blood levels in intolerant patients can identify poor metabolizers.

Except for duloxetine, the SNRIs may increase blood pressure. Thus, blood pressure should be assessed prior to starting an SNRI and monitored during treatment. If blood pressure is elevated prior to treatment, appropriate antihypertensive treatment should be instituted or adjusted prior to starting the SNRI, or alternative antidepressants should be used. For patients receiving SNRIs, blood pressure is initially checked every one to two weeks for the first month of treatment, and then every one to two months for the next six months of treatment. Thereafter, monitoring occurs every three to six months. This schedule may be adjusted depending upon the SNRI and the dose; as an example, venlafaxine at a low dose (eg, 75 mg per day) would be expected to have minimal effects upon blood pressure.

Dose — We suggest starting SNRIs with a low dose to avoid side effects, and slowly increasing the dose to the lowest dose that provides the desired clinical response. This dosing schedule can be accelerated in patients who have demonstrated good tolerance with previous SSRIs or SNRIs.

The starting dose, titration schedule, and maximum dose vary by indication. For patients with depression, starting doses and target dose ranges of each SNRI are listed in the table (table 4). Depressed patients with comorbid anxiety disorders or insomnia, as well as older

adult patients, may tolerate the medication better by starting with half of the suggested dose or the lowest possible dose. Doses are adjusted according to patient response, tolerability, and clinical urgency.

Finding the effective dose of an antidepressant may involve successive drug trials. After starting the antidepressant and titrating up to the minimum target dose, response should be monitored over the next two to four weeks. For patients who tolerate the drug, but show no improvement, we increase the dose. For patients who show gradual improvement, we allow more time. If improvement plateaus prior to a satisfactory response, we again increase the dose within the therapeutic range. A full trial may take 6 to 12 weeks. The Sequenced Treatment Alternatives to Relieve Depression trial, one of the largest trials in the United States, found that two-thirds of the patients who responded (improvement from baseline ≥50 percent) did so in the first six weeks, but half of the patients who achieved remission did so during weeks 6 to 12 [21].

Fixed-dose randomized trials of venlafaxine indicate that efficacy in unipolar major depression increases with increased doses [3,22-25]. As an example, a dose-response meta-analysis included 10 fixed-dose randomized trials of venlafaxine lasting 6 to 12 weeks, with a total of 16 treatment groups [26]. Response (reduction of baseline symptoms ≥50 percent) with venlafaxine increased as the dose increased to approximately 75 to 150 mg/day, and response continued to increase more modestly at doses up to 375 mg/day. However, discontinuation of treatment due to adverse effects also increased as the dose of venlafaxine increased. While these data suggest more patients will respond at higher doses, optimal doses vary among individuals and reflect a balance between efficacy and adverse effects.

Flexible-dose trials suggest that doses at the higher end of the therapeutic range may be beneficial [27]. Flexible-dose trials better approximate clinical practice by allowing clinicians to titrate the dose according to response and tolerability. Although fixed-dose trials provide a rigorous means for assessing dose-response relationships, these trials can lead to early, intolerable side effects in patients assigned to relatively higher doses because the high dose is administered after a rapid or no dose titration.

Patients with a history of recurrent depression 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'.)

The specific dose for each SNRI is discussed below in the sections that describe administration of each drug.

Administration — Administering SNRIs with food may reduce nausea, which is the most common side effect [14,28].

Adverse effects — Common adverse effects spontaneously reported in randomized trials with SNRIs include (table 3):

- Nausea
- Dizziness
- Diaphoresis

Nausea appears to diminish over time.

Other adverse effects include the following:

- Blood pressure increase – Blood pressure can increase and this appears to be related to the potency of norepinephrine effects [29]. However, the number of patients who meet criteria for sustained hypertension is low.

- Headaches – Headaches are commonly reported during antidepressant trials but are also common in depressed patients before treatment and in patients receiving placebo.

- Sexual dysfunction – Sexual dysfunction, including decreased libido, erectile dysfunction, delayed ejaculation, and anorgasmia, is moderately common with SNRIs, but rates of spontaneously reported sexual impairment are usually lower than when systematically assessed.

In addition, observational studies suggest that SNRIs as a class may be associated with the following side effects; however, the data from these case-controlled or cohort studies should not deter clinicians from using SNRIs when indicated. Although observational studies are often relied upon when event rates are very low, observational studies are less compelling than randomized trials for answering questions about harms, due to potential confounding factors.

- Bleeding – SNRIs inhibit reuptake of serotonin, including serotonin transporter sites on platelets, and are associated with an increased risk of bleeding [30]. As an example:

    - A retrospective study of an administrative health care database identified patients who received a new prescription for an SNRI (n >50,000 patients) or an SSRI (n >220,000) [31]. The most frequently prescribed SNRI was venlafaxine (94 percent of patients) and the most common SSRI was citalopram (42 percent). Propensity scoring was used to match the two groups for potential confounders observed at baseline, and patients in both groups were followed on average for nearly a year. The risk of nonfatal ischemic

or hemorrhagic stroke was modestly greater with SNRIs than SSRIs (hazard ratio 1.2, 95% CI 1.1-1.3).

- A pooled analysis included 55 randomized trials that compared duloxetine with placebo (n >19,000) in patients with depression, pain, generalized anxiety disorder, or lower urinary tract disorders [32]. Bleeding (eg, ecchymosis, epistaxis, or gingival bleeding) occurred in more patients with duloxetine than placebo (1.8 versus 1.2 percent).

Although the risk of bleeding that is associated with SNRIs seems small [3], it may be of great concern to vulnerable patients, such as those already on anticoagulants.

- Bone resorption – SNRIs inhibit reuptake of serotonin on osteocytes, and are associated with an increased risk of bone resorption [30]. Although the absolute risk of bone resorption associated with SNRIs appears small [3], the risk may be of great concern to patients with osteoporosis.

- Hyponatremia – SNRIs appear to be associated with hyponatremia, particularly in patients who are older (eg, age >65 years), female, or have a prior history of hyponatremia [33-35]. In addition, the risk is substantially increased by concomitant medications such as diuretics, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and proton pump inhibitors [33,35]. While sodium levels <130 mmol/L are sometimes used to define hyponatremia, symptoms such as instability and falls, reduced cognitive function, osteoporosis, and increased morbidity and mortality can occur with levels <135 mmol/L [36]. In patients who are <65 years old and not on other medications associated with hyponatremia, the absolute risk of hyponatremia with SNRIs is low.

  Medications with any risk of hyponatremia are a concern in patients with a prior episode of hyponatremia [34]. In currently depressed patients with a history of hyponatremia from any cause, who are starting a new antidepressant, we suggest obtaining sodium levels at baseline and again one to two weeks afterwards, because if hyponatremia occurs, it is likely to occur early.

  Evidence regarding SNRIs and hyponatremia includes the following:

  - In a national registry study (n > 600,000 patients), duloxetine was prescribed to more than 4000 patients and venlafaxine to more than 13,000; hyponatremia was defined as a serum sodium level <135 mmol/L [36]. After adjusting for age, comorbid illnesses, and concurrent pharmacotherapy, the analyses found that hyponatremia was more likely to occur in patients treated with duloxetine or venlafaxine than in patients who received no antidepressant.

- A pharmacovigilance study in psychiatric inpatients (n >400,000) examined hyponatremia, which was defined as a sodium level of <130 mmol/L regardless of symptoms (57 percent were asymptomatic) [35]. The rate of hyponatremia with SNRIs was 0.09 percent. Age >65 years and female sex were associated with an increased risk. Concomitant medications including diuretics, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and proton pump inhibitors had a substantial effect, raising the risk of hyponatremia 10- to 40-fold.

Hyponatremia has not been well studied for desvenlafaxine, levomilnacipran, and milnacipran.

There is a possible association between SNRIs and stress cardiomyopathy, but a causal relationship has not been established. (See "Clinical manifestations and diagnosis of stress (takotsubo) cardiomyopathy", section on 'History'.)

The frequency of specific side effects for each SNRI is discussed below in the sections that describe each drug.

Pregnancy — Treatment of pregnant women with antidepressants, including SNRIs, is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment" and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors", section on 'Serotonin-norepinephrine reuptake inhibitors (SNRIs)'.)

Overdoses/acute poisoning — A rapid overview of the clinical features and management of SNRI overdoses is provided in the table (table 5). Additional information about acute poisoning (eg, overdoses) from SNRIs is reviewed elsewhere. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)".)

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

DESVENLAFAXINE

Desvenlafaxine is the active metabolite of venlafaxine. Like venlafaxine, it is more potent as a serotonin uptake inhibitor than a norepinephrine uptake inhibitor, but its norepinephrine potency is greater than that of the parent compound [37].

Formulations — Desvenlafaxine comes as an extended-release tablet that is intended to be swallowed whole and not divided, crushed, or chewed [38].

Administration — This section describes the typical starting dose, titration, and maximum dose of desvenlafaxine for patients with unipolar major depression. The administration of desvenlafaxine for other indications is discussed separately in other topics.

The starting dose of desvenlafaxine for unipolar major depression is 50 mg once daily (table 4). The target dose is 50 or 100 mg/day. For patients who do not respond to 50 mg/day after six weeks, the dose is increased to 100 mg once daily. Although doses of desvenlafaxine up to 400 mg/day have been studied, data regarding efficacy at high doses are limited and adverse events increase with dose. In clinically urgent situations (eg, during inpatient treatment), dose increases of 50 mg per day can occur as quickly as every seven days [39]. For patients with severe kidney impairment (creatinine clearance <30 mL/minute) or end-stage kidney disease, the recommended dose is 50 mg every other day [40]. For patients with hepatic impairment, the dose is limited to 100 mg per day.

Adverse effects — Desvenlafaxine 50 mg per day is generally well tolerated (table 3). Adverse effects that occurred at least twice as often with desvenlafaxine than placebo in randomized trials (n >900 patients with major depression) included [40]:

- Nausea – 22 percent of patients who received desvenlafaxine
- Dizziness – 13 percent
- Sweating – 10 percent
- Constipation – 9 percent
- Anorexia – 5 percent

In addition, the mean weight loss over eight weeks with desvenlafaxine 50 mg per day was approximately 0.4 kg, and with desvenlafaxine 100 mg per day was approximately 0.4 to 0.9 kg [39,41,42].

Although clinically significant increases in blood pressure are infrequent with desvenlafaxine, patients should nevertheless be checked at baseline and regularly thereafter (eg, every two to six months) [3]. In randomized trials:

- Desvenlafaxine 50 mg per day (n = 149 patients with unipolar major depression) caused a mean increase in supine systolic blood pressure of 2 mmHg, and diastolic pressure 1 mmHg [39]. Desvenlafaxine 100 mg per day (n = 109, 145, and 110 patients with unipolar major depression) caused a mean increase in supine systolic blood pressure of 2 to 4 mmHg, and diastolic pressure 1 to 2 mmHg [39,41,42].

- One trial found that among patients receiving desvenlafaxine 50 mg per day (n = 149), 100 mg per day (n = 145), or placebo, clinically significant increases in blood pressure occurred in one patient (<1 percent) in each group, and that none of the patients had sustained, clinically important increases [39]. A second trial found that in patients treated with desvenlafaxine 100 mg per day (n = 109), none of the patients had a clinically significant increase in blood pressure [41].

Desvenlafaxine may cause less sexual dysfunction than other serotonergic drugs. In a pooled analysis of three randomized trials (n>1500 patients with unipolar major depression, treated for eight weeks), the overall rate of sexual impairment with desvenlafaxine 50 mg per day, desvenlafaxine 100 mg per day, or placebo was comparable (54, 47, and 49 percent) [43]. However, small effects on sex drive and ease of erection/lubrication were observed.

Desvenlafaxine can also cause a small increase in pulse, and may be associated with other adverse effects, such as bleeding, bone resorption, and hyponatremia [3] (see 'Adverse effects' above). However, desvenlafaxine does not adversely affect cardiac conduction.

The incidence of intolerable side effects secondary to desvenlafaxine appears to be correlated with the dose [39-41]. A pooled analysis of nine randomized trials (1834 patients with unipolar major depression) found that discontinuation of treatment due to adverse effects occurred as follows [44]:

- Placebo – 3 percent of patients
- Desvenlafaxine 50 mg per day – 4 percent
- Desvenlafaxine 100 mg per day – 8 percent
- Desvenlafaxine 200 mg per day – 14 percent
- Desvenlafaxine 400 mg per day – 18 percent

Nausea is the most common reason for discontinuing desvenlafaxine and occurs most frequently during the first week of treatment [39,41].

Discontinuation — For patients who decide to stop the desvenlafaxine, we suggest tapering the drug over two to four weeks to reduce the risk of withdrawal symptoms such as dizziness, nausea, headache, irritability, insomnia, and diarrhea [10,45]. Multiple studies indicate that abrupt discontinuation of desvenlafaxine 50 mg/day and 100 mg/day can cause discontinuation symptoms [40,45]. As an example, a pooled analysis of acute, eight-week randomized trials in patients with unipolar major depression found that after the study drugs were abruptly stopped, at least one discontinuation symptom following treatment with desvenlafaxine 50 mg/day, 100 mg/day, or placebo occurred in 47, 43, and 27 percent [45].

General information about discontinuation syndromes is discussed separately. (See "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

Overdoses — A rapid overview of the clinical features and management of serotonin-norepinephrine reuptake inhibitor (SNRI) overdoses is provided in the table (table 5). Additional information about acute poisoning (eg, overdoses) from desvenlafaxine is reviewed elsewhere. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)", section on 'Desvenlafaxine'.)

DULOXETINE

Safety risks — Duloxetine is generally avoided in patients with severe kidney impairment (creatinine clearance <30 mL/minute), end-stage kidney disease, or hepatic impairment, and should be used cautiously in patients with angle closure glaucoma or chronic liver disease or alcohol abuse [46,47].

Administration — This section describes the typical starting dose, titration, and maximum dose of duloxetine for patients with unipolar major depression. The administration of duloxetine for other indications is discussed separately in other topics.

For patients with major depression, we typically start duloxetine at a dose of 30 mg daily to minimize side effects and usually increase the dose to 60 mg daily after one week. However, it is reasonable to start at 60 mg once per day, or with 30 mg twice per day [47]. Patients who have been taking a selective serotonin reuptake inhibitor can be switched directly to duloxetine 60 mg/day without a cross taper [48].

For patients who are tolerating 60 mg per day after four to six weeks and are demonstrating some but not sufficient improvement, it is reasonable to increase the dose by 30 mg per day every three or four weeks, to a maximum of 120 mg per day (either as a single daily dose or given as 60 mg twice per day) [2,49,50]. However, the benefit of this approach is not established. As an example, a trial recruited patients (n = 248) who did not remit after six weeks of initial treatment with duloxetine 60 mg per day, and randomly assigned them to continue 60 mg per day for eight more weeks or to increase the dose to 120 mg for eight weeks [51]. The rate of remission was nearly identical (approximately 30 percent), suggesting that additional time was the important factor.

Nevertheless, other studies support using duloxetine doses >60 mg per day for unipolar major depression [52]:

- A pooled analysis of four randomized trials compared duloxetine 120 mg per day with placebo as initial treatment in 348 patients, and found that improvement was superior with duloxetine 120 mg per day [53].

- Another trial randomized subjects (n = 299) to duloxetine 60 mg/day or placebo for 12 weeks [54]. Patients with insufficient response to duloxetine 60 mg could receive a dose increase to 120 mg/day for another 12 weeks under double blind conditions. Among 53 subjects who had not responded at 12 weeks and received a dose increase to 120 mg/day, 26 percent remitted. However, the trial did not randomize nonresponding subjects to 60 or 120 mg/day, which would control for additional time on treatment.

Adverse effects — Duloxetine can cause several side effects (table 3). As an example, a pooled analysis examined adverse effects in eight randomized trials that compared duloxetine (40 to 120 mg per day) with placebo for eight or nine weeks in patients with unipolar major depression (n>1900) [55]. Discontinuation of treatment due to side effects was greater in patients who received duloxetine than placebo (10 versus 4 percent). Adverse effects that occurred more frequently with duloxetine than placebo included:

- Nausea – 20 percent of patients who received duloxetine
- Dry mouth – 15 percent
- Constipation – 11 percent
- Insomnia – 10 percent
- Dizziness – 9 percent
- Fatigue – 8 percent
- Diarrhea – 8 percent
- Somnolence – 7 percent
- Diaphoresis – 6 percent
- Anorexia – 6 percent

Clinically significant weight change also occurred with duloxetine. Weight loss with duloxetine (n >1100 patients) during treatment lasting 8 to 9 weeks was 0.5 kg [55]. However, in studies lasting up to 34 weeks, weight gain ≥7 percent of baseline weight with duloxetine 80 mg per day (n = 186 patients) occurred in 9 percent of patients, with duloxetine 120 mg per day (n = 195) in 13 percent, and with placebo (n = 192) in 3 percent.

Duloxetine can cause sexual dysfunction as well. Among patients (approximately 350) without sexual dysfunction at baseline, sexual impairment was greater with duloxetine than placebo (46 versus 29 percent of patients) [55]. In addition, a network meta-analysis of randomized trials indirectly compared different drugs through their relative effect with a common comparator

(typically placebo) and found that sexual dysfunction was greater with duloxetine than nefazodone [56].

By contrast, blood pressure changes with duloxetine (n >1100 patients) were negligible; the mean increase in supine systolic and diastolic pressure were each <1 mmHg [55]. In addition, the incidence of clinically significant elevations of systolic or diastolic pressures in patients treated with duloxetine or placebo (n >700) was similar.

Duloxetine may be associated with other adverse effects, such as bleeding, bone resorption, and hyponatremia. (See 'Adverse effects' above.)

Despite its potential adverse effects, duloxetine is generally well tolerated. A pooled analysis of eight randomized trials lasting eight or nine weeks compared duloxetine (40 to 120 mg/day) with placebo in nearly 2000 patients with unipolar major depression [57]. The analysis found that the number needed to harm, defined as discontinuing treatment due to side effects, was 25. This means that on average, a clinician would need to treat 25 patients with duloxetine and 25 patients with placebo before observing one more patient stopping duloxetine than placebo because of an adverse event.

In addition, patients are more likely to benefit from duloxetine than be harmed by adverse effects. A pooled analysis of eight randomized trials found that patients treated with duloxetine were four times more likely to respond (reduction of baseline symptoms ≥50 percent) than to discontinue the drug because of side effects [57].

Discontinuation — For patients who discontinue duloxetine, we suggest tapering the dose over two to four weeks to reduce discontinuation emergent adverse events [10,58]. A pooled analysis examined discontinuation symptoms after treatment was stopped abruptly in six randomized trials that compared duloxetine (40 to 120 mg per day) with placebo for eight or nine weeks in 870 patients with unipolar major depression [58]. Discontinuation symptoms occurred in more patients who received duloxetine than placebo (44 versus 23 percent). Symptoms that occurred more often with duloxetine than placebo included dizziness, nausea, and headache.

General information about discontinuation symptoms is discussed separately. (See "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

Overdoses — A rapid overview of the clinical features and management of serotonin-norepinephrine reuptake inhibitor (SNRI) overdoses is provided in the table (table 5). Additional information about acute poisoning (eg, overdoses) from duloxetine is reviewed

elsewhere. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)", section on 'Duloxetine'.)

LEVOMILNACIPRAN

Safety risks — Levomilnacipran is not recommended in patients with end-stage kidney disease and should be used with caution in patients with angle closure glaucoma, or hypertension or cardiovascular conditions that would be aggravated by increases in blood pressure [59]. The drug has dose-dependent effects on urinary hesitancy, which may be more likely to occur in patients with a prior history of urinary obstructive disorder.

Formulation — Levomilnacipran is prepared as an extended-release formulation that is intended to be swallowed whole and not divided, crushed, or chewed [38].

Administration — This section describes the typical starting dose, titration, and maximum dose of levomilnacipran for patients with unipolar major depression. The administration of levomilnacipran for other indications is discussed separately in other topics.

Levomilnacipran is given once a day [8]. The drug is started at 20 mg per day and then increased within a few (eg, two) days to 40 mg per day. Based upon response and tolerability, the dose is increased further, in 20 mg increments every two to four weeks. The target dose is 40 to 80 mg per day; however, doses up to 120 mg per day have been used.

Efficacy of levomilnacipran was established in five acute phase trials (n >2500) [8]. Two of the trials employed fixed doses, and doses of 40, 80, and 120 mg/day were each more effective than placebo [60,61]. The magnitude of symptom change increased as the dose increased in one trial [60], but not in the other trial. In addition, four of the five trials found that improvement of functioning (work, social, and family) was greater with levomilnacipran than placebo, and that higher doses led to greater functional improvement.

For patients with moderate kidney impairment (creatinine clearance 30 to 39 mL/minute), the suggested maximum dose is 80 mg per day, and for patients with severe impairment (creatinine clearance 15 to 29 mL/minute), the suggested maximum dose is 40 mg per day. The drug is not used in patients with end-stage kidney disease.

Adverse effects — Levomilnacipran can cause several side effects (table 3). As an example, a pooled analysis examined adverse effects in five randomized trials that compared levomilnacipran (40 to 120 mg per day) with placebo for 8 or 10 weeks in unipolar major depression (nearly 2600 patients) [8]. Discontinuation of treatment due to side effects was

greater in patients receiving levomilnacipran than placebo (9 versus 3 percent). The only side effect that led to discontinuation of levomilnacipran in 1 percent or more of patients was nausea (1.5 percent for levomilnacipran versus 0.4 percent on placebo) [8]. The incidence of the most common adverse effects with levomilnacipran and placebo was as follows [8]:

- Nausea – 17 and 6 percent
- Headache – 17 and 13 percent
- Dry mouth – 10 and 7 percent
- Hyperhidrosis – 9 and 2 percent
- Constipation – 9 and 3 percent
- Dizziness – 8 and 5 percent
- Heart rate increased – 6 and 1 percent
- Erectile dysfunction – 6 and 1 percent

The incidence of nausea is likely to be reduced if given following food.

Erectile dysfunction and urinary hesitancy were dose dependent. On doses of 40 mg, 80 mg, and 120 mg per day, the incidence of erectile dysfunction was 6, 8, and 10 percent and urinary hesitancy was 4, 5, and 6 percent [8].

The cardiovascular effects of levomilnacipran include the following:

- Heart rate – In acute phase randomized trials, levomilnacipran increased heart rate by 7.4 beats per minute, whereas placebo decreased heart rate by 0.3 beats per minute [8]. While the heart rate increase is greater than that for the other serotonin-norepinephrine reuptake inhibitors (SNRIs), it is comparable to the eight beats per minute increase reported for the tricyclic nortriptyline [62]. An open-label, 48-week extension study suggested that levomilnacipran-induced increases in heart rate persist over time [63].

- Blood pressure – Randomized trials found that levomilnacipran (n >1500 patients) increased systolic and diastolic blood pressure by an average of 3.0 and 3.2 mmHg, whereas placebo (n >1000) decreased systolic blood pressure by 0.4 mmHg and did not change diastolic pressure [8]. Among patients on levomilnacipran or placebo, sustained, clinically significant blood pressure elevation occurred in 1.8 and 1.2 percent. Although the average increase in blood pressure with levomilnacipran was not large, blood pressure monitoring early in treatment will help detect blood pressure increases greater than average. An open-label extension study suggested that increases in blood pressure persist over time [63].

- QTc interval – In randomized trials that studied cardiovascular effects, levomilnacipran at usual doses and at 300 mg per day (2.5 times the maximum recommended dose) did not prolong the QTc interval (using the Fridericia correction, which adjusts for heart rate) [8].

Levomilnacipran appeared to be weight neutral in placebo-controlled randomized trials lasting 8 weeks, and in a 48-week open-label extension study [8,63,64].

Discontinuation due to adverse effects is relatively small. Tolerability was assessed in a pooled analysis of five randomized trials lasting 8 or 10 weeks that compared levomilnacipran (40 to 120 mg/day) with placebo in patients with unipolar major depression (n >2600) [57]. The analysis found that the number needed to harm, defined as discontinuing treatment due to side effects, was 19. This means that on average, a clinician would need to treat 19 patients with levomilnacipran to observe one patient stopping levomilnacipran who would not have discontinued treatment on placebo.

In addition, patients are more likely to benefit from levomilnacipran than be harmed by adverse effects. A pooled analysis of five randomized trials found that patients treated with levomilnacipran were two times more likely to respond (reduction of baseline symptoms ≥50 percent) than to discontinue the drug because of side effects [57].

Discontinuation — For patients who discontinue levomilnacipran, we suggest tapering the dose over one to two weeks before stopping the drug, consistent with procedures in the registration trials [60,61,65,66]. Randomized trials that used this approach found that the incidence of discontinuation symptoms in patients who stopped levomilnacipran or placebo was comparable (approximately 8 to 10 percent of patients).

General information about discontinuation symptoms is discussed separately. (See "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

Overdoses — A rapid overview of the clinical features and management of SNRI overdoses is provided in the table (table 5). Additional information about acute poisoning (eg, overdoses) from SNRIs is reviewed elsewhere. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)".)

MILNACIPRAN

Milnacipran is approved by the US Food and Drug Administration for use in fibromyalgia. However, it is not approved for depression in the United States. Randomized trials in depressed

subjects have demonstrated that milnacipran 50 and 100 mg twice/day are each superior to placebo [67], and other trials suggest that the efficacy of milnacipran and other antidepressants is comparable [68].

Safety risks — Milnacipran is generally avoided in patients with end-stage kidney disease and should be used cautiously in patients with angle closure glaucoma, and patients with chronic liver disease or alcohol abuse due to reports of increased liver enzymes and hepatic injury [10,46,69].

Administration — This section describes the typical starting dose, titration, and maximum dose of milnacipran for patients with unipolar major depression. The administration of milnacipran for other indications is discussed separately in other topics.

The initial starting dose of milnacipran for major depression is 12.5 mg once per day, which is titrated up to 12.5 mg twice daily on day 2 or 3 of treatment [14]. In the absence of significant side effects, the dose is increased to 50 mg twice daily by day 7 of treatment. For patients who do not respond after two to four weeks and are tolerating the drug, the dose can be increased up to 100 mg twice daily. After steady state serum concentrations have been achieved (in approximately two to three days), some clinicians administer the drug once per day [70]. For patients with severe kidney impairment (creatinine clearance <30 mL/minute), the dose should be limited to 50 mg twice daily.

Adverse effects — Milnacipran can cause several side effects (table 3). A pooled analysis of patients with major depression who received milnacipran 50 mg two times per day in randomized trials (n = 1871) found the following incidence of side effects [71]:

- Nausea – 11 percent of patients who received milnacipran
- Headache – 8 percent
- Dry mouth – 8 percent
- Abdominal pain – 7 percent
- Constipation – 7 percent
- Insomnia – 6 percent
- Vertigo/dizziness – 5 percent

A study of more than 4000 depressed patients found that tolerability of milnacipran was better at 50 mg twice daily than 100 mg twice daily [72]. Among patients followed for up to 12 months, most side effects emerged within the first 3 months.

Blood pressure may increase in patients treated with milnacipran and should thus be checked at baseline and regularly thereafter (eg, every two to six months) [10]. Although data from

depressed patients (n >1800) treated with milnacipran 50 mg twice per day indicated that the average blood pressure increase was less than 1 mmHg [72], more recent trials (n >4000 patients with fibromyalgia randomly assigned to milnacipran or placebo) showed that milnacipran increased both systolic and diastolic pressure by 3 mmHg [14]. Among fibromyalgia patients with baseline hypertension, the average increase in systolic pressure was more than 15 mmHg greater with milnacipran than placebo.

Discontinuation — We suggest tapering milnacipran over one to two weeks prior to discontinuation [14]. In one study, abruptly stopping milnacipran 50 mg twice daily after six weeks of treatment for major depression (n = 46 patients) was associated with at least one discontinuation symptom (eg, anxiety) in 13 percent [73]. In patients who were initially treated for 24 weeks (n = 20), 30 percent reported at least one discontinuation symptom.

General information about discontinuation symptoms is discussed separately. (See "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

Overdoses — A rapid overview of the clinical features and management of serotonin-norepinephrine reuptake inhibitor (SNRI) overdoses is provided in the table (table 5). Additional information about acute poisoning (eg, overdoses) from milnacipran is reviewed elsewhere. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)", section on 'Milnacipran'.)

VENLAFAXINE

Safety risks — Venlafaxine should be used cautiously in patients with angle closure glaucoma and patients at risk of bleeding (eg, taking anticoagulants) [74].

Formulations — Although an immediate-release formulation of venlafaxine is available, the once-daily extended-release formulation is commonly used because of ease of administration and decreased nausea. Plasma concentrations of the two formulations appear to be comparable at equivalent doses. As an example, 37.5 mg twice daily of the immediate-release formulation results in approximately the same plasma concentration as 75 mg daily of the extended-release formulation [75].

The venlafaxine extended-release tablets and capsules are intended to be swallowed whole and not divided, crushed, or chewed [38]. However, the extended-release capsules can be opened, and the pellets can be sprinkled on food (eg, applesauce), which should be swallowed immediately without chewing.

Administration — This section describes the administration of venlafaxine for patients with unipolar major depression. The typical starting dose, titration, and maximum dose for other indications is discussed separately in other topics.

For patients with major depression, we typically start venlafaxine extended release with a single morning dose of 37.5 mg. If this is well tolerated, the dose is increased within four to seven days to 75 mg once daily and it is reasonable to continue this dose for four to six weeks to assess efficacy. If response is insufficient, the dose can be increased to 150 mg per day for four weeks, and if needed, to a recommended maximum of 225 mg once daily. Some clinicians prefer to increase the dose more quickly if the patient has minimal side effects, based upon the logic that getting to a high dose quickly will improve chances for response and that testing the efficacy of intermediate doses is not necessary. The dose titration can be accelerated, with increases occurring as quickly as every four days if needed and tolerated. For patients with hepatic impairment, severe renal impairment (creatinine clearance <30 mL/minute), or end-stage kidney disease, the dose is increased by increments of 37.5 mg per day, to a maximum of 112.5 to 150 mg once daily.

The immediate-release form of venlafaxine is typically started at 37.5 mg twice daily. For patients unresponsive after four to six weeks, the dose is increased by 37.5 mg twice daily every week, to a recommended maximum of 375 mg per day, in two to three divided doses. In clinically urgent situations, the dose is increased by increments of 37.5 mg twice daily every four days. For patients with hepatic impairment, severe renal impairment, or end-stage kidney disease, the starting dose is 37.5 mg once daily, and the dose is increased by increments of 37.5 mg per day, to a maximum of 187.5 mg per day, given in two divided doses.

Pharmacokinetics — The pharmacokinetic parameters of venlafaxine are described in the table (table 1).

Polymorphism in the hepatic cytochrome P450 enzyme CYP2D6, which converts venlafaxine to the active metabolite desvenlafaxine, may possibly influence the efficacy of venlafaxine. A pooled analysis of four randomized trials compared the efficacy of venlafaxine in 464 patients with unipolar major depression who all received the drug and were classified as extensive or poor metabolizers based upon the plasma concentration ratio of desvenlafaxine to venlafaxine [76]. Remission was greater in patients who were extensive metabolizers compared with poor metabolizers (56 versus 37 percent); the venlafaxine dose and tolerability were comparable for the two groups. A possible explanation for this counterintuitive effect is that extensive metabolizers convert more venlafaxine to desvenlafaxine, and desvenlafaxine may have a greater antidepressant effect. However, two head-to-head randomized trials indicate that the efficacy of venlafaxine and desvenlafaxine is comparable [77]. In addition, it is not known

whether the effectiveness of venlafaxine is diminished by medications that inhibit CYP2D6, such as bupropion. Desvenlafaxine and drug-drug interactions involving serotonin-norepinephrine reuptake inhibitors (SNRIs) are discussed elsewhere in this topic. (See 'Desvenlafaxine' above and 'Drug-drug interactions' above.)

Adverse effects — Venlafaxine can cause several side effects (table 3), which were examined in a pooled analysis of eight randomized trials that compared venlafaxine with placebo for six or eight weeks in 1348 patients with unipolar major depression [78]. (Venlafaxine was administered as either the extended-release formulation 75 to 225 mg per day or the immediate release formulation 75 to 375 mg per day.) Discontinuation due to adverse effects occurred in more patients who received venlafaxine than placebo (9 versus 2 percent). The frequency of specific side effects in patients treated with venlafaxine compared with placebo was as follows:

- Nausea – 24 versus 16 percent
- Dizziness – 13 versus 9 percent
- Dry mouth – 12 versus 10 percent
- Insomnia – 11 versus 11 percent
- Diaphoresis – 10 versus 5 percent
- Constipation – 9 versus 9 percent

Venlafaxine may increase the risk of upper gastrointestinal bleeding, but the absolute risk appears to be small. A nested case control study found that use of venlafaxine was nearly three times greater in 1321 patients with upper gastrointestinal tract bleeding, compared with 10,000 controls with no bleeding (odds ratio 2.9, 95% CI 1.5-5.6); use of venlafaxine occurred in 1.1 percent of the cases [79]. The risk of bleeding may be elevated by concomitant use of nonsteroidal anti-inflammatory drugs, particularly among patients not using acid-suppressing agents.

Another adverse effect that can occur with venlafaxine is increased blood pressure, especially at higher doses [3]. Thus, blood pressure should be checked at baseline, and regularly monitored (eg, every two to six months) in patients receiving venlafaxine at relatively high doses (eg, >300 mg per day). In a meta-analysis of 27 randomized trials that compared venlafaxine with placebo for six weeks in 3424 patients with major depression, the mean increase in supine diastolic blood pressure with venlafaxine was 1 mmHg, which was statistically significant but clinically small, compared with placebo [29]. However, the incidence of supine diastolic blood pressure ≥90 mmHg (elevated blood pressure) was greater in patients who received venlafaxine than placebo (11 versus 6 percent). In addition, elevated blood pressure occurred in more patients who received venlafaxine at doses >300 mg per day, compared with placebo (9 and 2 percent);

by contrast, the frequency of elevated blood pressure was comparable for venlafaxine ≤300 mg per day and placebo (3 and 2 percent of patients).

Venlafaxine can also cause a small increase in pulse [3]. However, venlafaxine does not adversely affect cardiac conduction.

A pooled analysis of randomized trials and observational studies lasting 4 to 12 weeks suggested that short-term treatment with venlafaxine is associated with a weight loss of 0.5 kg [80]. However, a retrospective study of 49 patients treated for an average of 18 months found that the mean weight gain was 7 kg [81].

In addition, a pooled analysis of randomized trials and observational studies suggest that venlafaxine impairs sexual function (at a rate comparable to selective serotonin reuptake inhibitors [SSRIs]) [82].

Venlafaxine may be associated with other adverse effects, such as bleeding, bone resorption, and hyponatremia [3]. (See 'Adverse effects' above.)

Adverse effects often lead patients to discontinue venlafaxine. A pooled analysis of four randomized trials lasting six or eight weeks compared venlafaxine (75 to 375 mg/day) with placebo in nearly 1000 patients with unipolar major depression [57]. The analysis found that the number needed to harm (NNH), defined as discontinuing treatment due to side effects, was eight. This means that on average, a clinician would need to treat only eight patients with venlafaxine to have one patient discontinue treatment with an adverse event that would not have occurred with placebo. This relatively low (unfavorable) NNH may be related to the high doses of venlafaxine that were used.

Nevertheless, patients are more likely to benefit from venlafaxine than be harmed by adverse effects. A pooled analysis of four randomized trials found that patients treated with venlafaxine were 1.4 times more likely to respond (reduction of baseline symptoms ≥50 percent) than to discontinue the drug because of side effects [57].

Discontinuation — For patients who discontinue venlafaxine, we suggest tapering the dose by 37.5 to 75 mg per day each week to reduce the incidence of discontinuation emergent adverse events [10]. Due to venlafaxine's relatively short half-life, discontinuation can cause symptoms [3]. A review found that stopping the drug abruptly can lead to withdrawal symptoms, such as anxiety, dizziness, headache, insomnia, nausea, and weakness [83]. In addition, a small, eight-week randomized trial that compared venlafaxine with placebo found that after the study drugs were tapered and discontinued, discontinuation symptoms occurred in more patients treated with venlafaxine than placebo (7 in 9 versus 2 in 9 patients [78 versus 22 percent]) [84].

Additional information about discontinuation symptoms and discontinuing venlafaxine is discussed separately. (See "Discontinuing antidepressant medications in adults".)

Overdoses — A rapid overview of the clinical features and management of SNRI overdoses is provided in the table (table 5). Additional information about acute poisoning (eg, overdoses) from venlafaxine is reviewed elsewhere. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)", section on 'Venlafaxine'.)

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 explaining the symptoms, causes, and treatment for depression in a booklet entitled “Depression,” which is available online at the website, or by calling a toll-free number, 866-615-6464. The website 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 serotonin-norepinephrine reuptake inhibitors (SNRIs)** – SNRIs include desvenlafaxine, duloxetine, levomilnacipran, milnacipran, and venlafaxine. (See 'Desvenlafaxine' above and 'Duloxetine' above and 'Levomilnacipran' above and 'Milnacipran' above and 'Venlafaxine' above.)

- **Efficacy** – SNRIs can be efficacious for treating unipolar major depression. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

- **Pharmacodynamics** – SNRIs appear to treat depression by initially blocking presynaptic uptake of serotonin and norepinephrine. This leads to a cascade of events that increases synaptic transmission of the two neurotransmitters. (See 'Pharmacodynamics' above.)

- **Pharmacokinetics** – The pharmacokinetic parameters of SNRIs vary (table 1). Like most other antidepressants, duloxetine is highly protein bound and cleared mainly by hepatic metabolism. The other SNRIs exhibit lower protein binding and have more extensive renal clearance. (See 'Pharmacokinetics' above.)

- **Educating patients** – Prior to prescribing SNRIs, clinicians should discuss drug interactions, side effects (table 3), time to response, and stopping the medication. (See 'Guidelines to review with patients' above.)

- **Baseline assessments** – No specific medical tests are required before starting SNRIs, although assessing baseline blood pressure is advisable for several of the SNRIs. Drug serum concentrations are not routinely performed. (See 'Medical tests, plasma levels, and monitoring' above.)

- **Dose** – We suggest starting SNRIs at a low dose to assess tolerance, and within a week, advancing to the minimal effective dose. Thereafter, the dose can be increased in

nonresponsive patients who tolerate the drug. Starting doses and target dose ranges of each SNRI are listed in the table (table 4). (See 'Dose' above.)

- **Administration** – Administering SNRIs with food may reduce nausea, which is the most common side effect. (See 'Administration' above.)

- **Adverse effects** – SNRIs can cause side effects; nausea is most common. Other side effects include constipation, dizziness, dry mouth, and sweating. With the exception of duloxetine, the SNRIs can raise blood pressure, which should be monitored. All drugs that inhibit serotonin uptake can cause sexual dysfunction. Prolonged use (eg, ≥6 months) of SNRIs can lead to substantial weight gain (eg, 5 kg). In addition, SNRIs are associated with an increased risk of bleeding, bone resorption, and hyponatremia. (See 'Adverse effects' above.)

- **Discontinuation** – Abrupt discontinuation of SNRIs can cause discontinuation symptoms; thus, we advise tapering these drugs before stopping them. Although levomilnacipran and milnacipran are less likely to cause discontinuation symptoms, tapering is still preferred if time permits. (See 'Desvenlafaxine' above and 'Duloxetine' above and 'Levomilnacipran' above and 'Milnacipran' above and 'Venlafaxine' above and "Discontinuing antidepressant medications in adults".)

- **Overdose** – Venlafaxine may perhaps be more lethal in overdose than SSRIs. (See 'Overdoses' above.)

  A rapid overview of the clinical features and management of SNRI overdoses is provided in the table (table 5). Additional information about acute poisoning (eg, overdoses) from SNRIs is reviewed elsewhere. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)".)

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