Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects

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INTRODUCTION

The selective serotonin reuptake inhibitors (SSRIs) include:

- Citalopram
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline

SSRIs are frequently used as first-line antidepressants because of their efficacy and tolerability, as well as their general safety in overdose. In addition, SSRIs are indicated for anxiety disorders, eating disorders, menopausal hot flashes, obsessive-compulsive and related disorders, posttraumatic stress disorder, premature ejaculation, premenstrual dysphoric disorder, and somatic symptom disorder [1].

This topic reviews the pharmacology of SSRIs, their administration for treating unipolar depression in adults, and their side effects. Sexual dysfunction associated with SSRIs, the serotonin syndrome, and management of SSRI overdose are discussed separately. In addition, choosing initial treatment of depression in adults and managing treatment resistant depression are discussed separately.

- (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management".)
- (See "Serotonin syndrome (serotonin toxicity)".)
- (See "Selective serotonin reuptake inhibitor poisoning".)
- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

PHARMACOLOGY

Structure — The selective serotonin reuptake inhibitors (SSRIs) vary considerably in their chemical structure and activity [1]. As examples, paroxetine and sertraline exist as single isomers, whereas citalopram and fluoxetine are racemic mixtures of two stereoisomers that are mirror images of each other.

Citalopram and escitalopram — Citalopram 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) [2]. One of the stereoisomers, S-citalopram (escitalopram), more potently inhibits reuptake of serotonin compared with the other stereoisomer.

Pharmacodynamics — SSRIs appear to treat depression by increasing serotonergic activity [1-4]. They are selective in that they have relatively little affinity for other types of receptors.

Serotonin (5-hydroxytryptamine or 5-HT) is an indoleamine neurotransmitter released in the brain from neurons originating in the brainstem raphe nuclei [1,3,4]. Serotonergic neurotransmission in the brain involves at least 14 different types of pre- and postsynaptic serotonin receptors. All SSRIs potently decrease the action of the presynaptic serotonin reuptake pump, by as much as 90 percent [3]. This increases the length of time that serotonin is available in the synapse and increases postsynaptic serotonin receptor occupancy.

However, reuptake inhibition does not appear to be sufficient for treating depression. Reuptake inhibition occurs soon after SSRIs are started, and the full therapeutic effects of SSRIs may not appear for three to eight (or more) weeks after treatment has started. The full clinical response may require additional "downstream" effects [5]. As an example of one such effect, the initial increase in synaptic serotonin eventually leads to increased production of neuroprotective proteins such as brain-derived neurotrophic factor and Bc1-2 [6]. In addition, treatment with an SSRI for weeks modifies the serotonergic receptors; the changes vary depending upon the serotonin receptor subtype [1,4].

The relatively benign side effect profile of the SSRIs is due to their selectivity [1,3,4]. None of the SSRIs significantly affect alpha-adrenergic, histaminic, or cholinergic receptors, except for paroxetine, which weakly antagonizes the cholinergic receptor. Side effects that occur with SSRI treatment are attributed primarily to their effects upon serotonin receptors.

Pharmacokinetics — The absorption, distribution, metabolism, and elimination of the SSRIs are well described [7-10].

SSRIs are well absorbed in the gastrointestinal tract and reach peak plasma levels within one to eight hours [2,4,5,7]. Food generally does not affect absorption, except for sertraline, which is absorbed more quickly when taken with food. Following absorption, SSRIs bind to plasma proteins and are widely distributed throughout the body, including the brain, because they are lipophilic.

Metabolism and elimination occur largely in the liver [7]. Metabolism of each SSRI except fluvoxamine produces pharmacologically active metabolites [5]. However, only fluoxetine yields a metabolite (norfluoxetine) that potently inhibits reuptake of serotonin and has antidepressant activity.

The elimination half-life for the SSRIs is as follows [1-5]:

- Citalopram – 36 hours
- Escitalopram – 36 hours
- Fluoxetine – 4 to 6 days (active metabolite norfluoxetine 4 to 16 days)
- Fluvoxamine – 15 hours
- Paroxetine – 24 hours
- Sertraline – 26 to 32 hours

Drug-drug interactions — Some SSRIs are moderate to potent inhibitors of hepatic cytochrome P450 drug metabolism and can cause drug-drug interactions by altering blood levels of other medicines that depend on these enzymes for clearance or activation. Citalopram and escitalopram inhibit liver enzymes less than other SSRIs and are thus the SSRIs of choice for situations in which drug-drug interactions are a concern [7,11]. Sertraline is a reasonable alternative [12].

The specific cytochrome enzymes that each drug and their metabolites potently or moderately inhibit are as follows:

- Citalopram – none
- Escitalopram – none

- Fluoxetine – CYP2D6 (potent) and 2C19 (moderate)
- Fluvoxamine – CYP1A2 (potent) and 2C19 (moderate)
- Paroxetine – CYP2D6 (potent)
- Sertraline – none

All SSRIs weakly inhibit one or more other cytochrome P450 drug metabolizing enzymes. However, weak inhibition of CYP450 metabolism rarely alters the levels or activity of other medications to a degree that is clinically significant. Additional information about each drug and its inhibition of hepatic enzymes can be found in the individual Lexicomp drug information topics in the section on Metabolism/Transport Effects.

Among the many potential drug-drug interactions that may occur with SSRIs is the interaction between fluoxetine or paroxetine and tamoxifen. Tamoxifen is used to treat or prevent recurrence of breast cancer, and is a prodrug that is metabolized by cytochrome P450 2D6 to the active metabolite. Although concerns have been raised that paroxetine or fluoxetine may interact with tamoxifen and interfere with tamoxifen treatment of breast cancer, the clinical significance of the drug-drug interactions is not clear. Nevertheless, we prefer to avoid using CPY2D6 inhibitors with tamoxifen if alternative strategies are available. (See "Mechanisms of action of selective estrogen receptor modulators and down-regulators", section on 'Patients taking SSRIs'.)

Another example is the interaction between SSRIs and prodrug opioids. Prodrug opioids, such as codeine, hydrocodone, and tramadol, are converted to active metabolites (eg, morphine) by hepatic CYP2D6; by contrast, other opioids, such as fentanyl, morphine, and oxycodone, are effective without metabolism. A nine-year retrospective study of surgical patients with depression (n >4300) found that postoperative pain control was worse in patients who were treated with prodrug opioids plus SSRIs, compared with patients who received prodrug opioids but no SSRIs, non-prodrug opioids plus SSRIs, or non-prodrug opioids but no SSRIs [13].

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

PRESCRIBING SSRIs

Treating depression with selective serotonin reuptake inhibitors (SSRIs) requires use of general pharmacotherapy principles as well as knowledge about the proper dose.

SSRIs are contraindicated in patients with hypersensitivity, as well as patients who received a monoamine oxidase inhibitor (MAOI) in the previous two weeks, because SSRIs and MAOIs can

interact to cause the serotonin syndrome. In addition, clinicians should exercise caution in prescribing SSRIs with other serotonergic medications (eg, lithium or serotonin-norepinephrine reuptake inhibitors) (table 1), which may also cause the serotonin syndrome. (See "Serotonin syndrome (serotonin toxicity)".)

Choosing a specific SSRI is based upon individual patient tolerance, cost, and clinician experience, because efficacy across SSRIs appears to be comparable [1,3,4].

General principles

Guidelines to review with patients — Prior to prescribing SSRIs, clinicians should discuss side effects, time to response, drug interactions, and stopping the medication. (See 'Side effects' below.)

Clinicians should review common side effects and the need to take the medication as prescribed rather than on an as needed basis. Patients should also be informed that although some response may occur within the first two weeks of treatment, it may take up to eight weeks to reach full clinical effect.

Possible drug interactions should also be reviewed, including other drugs that increase serotonergic activity (eg, MAOIs) (table 1) and the possibility of the potentially fatal serotonin syndrome. (See 'Drug-drug interactions' above and "Serotonin syndrome (serotonin toxicity)".)

In addition, clinicians should discuss abrupt discontinuation of SSRIs, which may precipitate dysphoria, dizziness, gastrointestinal distress, fatigue, chills, and myalgias. The discontinuation syndrome associated with suddenly stopping SSRIs is discussed separately. (See "Discontinuing antidepressant medications in adults", section on 'SSRIs'.)

Medical tests and plasma levels — No specific medical tests are required before starting an SSRI [12].

SSRI serum concentrations are rarely performed. Although several indications for serum levels have been proposed, clinical judgment can usually resolve the issue and avoid the problems that are associated with serum concentrations, including uncertainty about their clinical significance, as well as cost and patient inconvenience. As an example, drug levels can theoretically be used to establish that it is safe to begin another serotonergic drug (eg, an MAOI) after discontinuing an SSRI, to avoid the serotonin syndrome [14]. However, clinicians can instead wait for five or more elimination half-lives of the discontinued SSRI or its metabolite, whichever is longer (see 'Pharmacokinetics' above), to elapse before starting the new drug [1], unless the depressive syndrome is severe and time is of the essence. Other

proposed indications for serum levels include assessing adherence, determining whether patients who do not respond to initial treatment or who relapse during maintenance treatment are rapid metabolizers, determining whether concomitant drugs are affecting SSRI serum concentrations, and monitoring special populations (eg, children and adolescents; patients with intellectual disability; older adult, pregnant, or breastfeeding patients; and patients with hepatic disease or abnormally high or low body weight) [14]. Another possible indication may be problems that occur when switching between a brand-name and generic preparations.

Although measuring SSRI serum concentrations is not standard practice, several studies have attempted to correlate plasma levels and therapeutic effects. Therapeutic reference ranges suggested by one practice guideline are as follows [14]:

- Citalopram – 50 to 110 ng/mL
- Escitalopram – 15 to 80 ng/mL
- Fluoxetine plus norfluoxetine – 120 to 500 ng/mL
- Fluvoxamine – 60 to 230 ng/mL
- Paroxetine – 20 to 65 ng/mL
- Sertraline – 10 to 150 ng/mL

Response time — Many depressed patients treated with an SSRI respond within one or two weeks, while other patients require several more weeks of treatment (eg, a total of 8 to 12 weeks) [15-17]. Severity of illness, comorbid disease, pharmacodynamic factors, and psychosocial factors may affect how quickly depressed patients respond to treatment with SSRIs.

Time to response was evaluated in the following studies:

- In the Sequenced Treatment Alternatives to Relieve Depression study, which included 2876 outpatients; more than 75 percent of the patients had recurrent or chronic depression, and most had multiple comorbid medical and psychiatric illnesses [17]. The average mean time to response (reduction in baseline depression rating scale score ≥50 percent) to citalopram was six weeks. Among patients who eventually responded, 56 percent did so at or after eight weeks of treatment. The average mean time to remission was seven weeks.

- An open-label study of 384 outpatients with major depression, treated with fluoxetine for eight weeks, evaluated time to sustained response, defined as a 30 percent decrease from the baseline depression rating scale score, which persisted and led to a 50 percent decrease by week 8 [16]. None of the patients had previously failed an adequate antidepressant trial during the current episode. Among the 182 patients who responded,

56 percent responded at week 2, 25 percent at week 4, and 9 percent at week 6 (the cumulative probabilities of response were thus 56, 80, and 90 percent).

- A meta-analysis of 28 randomized trials (5872 patients with unipolar depression) found that SSRIs begin to have a small clinically beneficial effect beyond the effect of placebo by the end of the first week of treatment [15]. Incremental improvement attributable to the SSRI continued at a decreasing rate for the next five weeks. A second analysis of five studies (1365 patients) showed that response (≥50 percent reduction in baseline depression rating scale score) by week 1 was 60 percent more likely in patients who received an SSRI compared with patients who received placebo (relative risk 1.6, 95% CI 1.2-2.3).

Pregnancy — The safety of antenatal SSRIs, individually as well as a class, is discussed separately. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors".)

The role of SSRIs and other antidepressants for antenatal depression is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment".)

Administration — The frequency and timing of each dose varies between SSRIs.

The entire dose of an SSRI is generally taken once a day because the elimination half-life averages approximately 24 hours [1,4,8]. Fluvoxamine is taken in two divided doses when the total daily dose exceeds 100 mg, because it has a shorter half-life [5].

Clinicians usually advise patients to take SSRIs in the morning to minimize insomnia, although there is no evidence that this side effect is related to dose timing. Fluvoxamine is usually taken at bedtime at doses of 100 mg or less, and patients who experience drowsiness with any SSRI can take the drug at bedtime.

Sertraline is the only SSRI whose absorption is increased when taken with food. Although taking the other SSRIs on a full stomach will not improve absorption, it may help prevent gastrointestinal distress [3].

Dose — We suggest starting with the lowest minimal effective dose to avoid side effects. Equipotent starting doses for the SSRIs for unipolar major depression are as follows (table 2):

- Citalopram – 20 mg
- Escitalopram – 10 mg
- Fluoxetine – 20 mg
- Fluvoxamine – 50 to 100 mg

- Paroxetine – 20 mg
- Sertraline – 50 mg

In patients who are sensitive to side effects, it may help to start at a subtherapeutic dose for a few days to improve tolerability and then increase the dose to the minimum therapeutic dose. As an example, depressed patients with a comorbid anxiety disorder may tolerate the medication better by starting with half of the suggested dose.

Dose adjustments are made slowly, with increases as needed according to patient response, tolerability, and clinical urgency. Target doses vary depending upon the patient's specific disorder.

Finding the effective dose involves a process of trial and error. In the absence of intolerable side effects, a trial of two to six weeks (often four weeks) at the minimum therapeutic dose is often appropriate to assess response before adjusting the dose or implementing other treatment options. The dose can generally be increased every one to four weeks, depending upon response and tolerability. More frequent titration (eg, every three to six days) may be appropriate in urgent cases with close monitoring, such as inpatients. Although genotype testing (eg, CYP2D6 and CYP2C19 polymorphisms) is available to guide choosing a specific SSRI and dosing the drug [18], the tests are not standard practice and we suggest not using them because of the preliminary nature of the data that underlie the tests and lack of compelling evidence that they affect outcomes in clinical practice.

Fixed dose randomized trials of SSRIs indicate that efficacy in unipolar major depression increases with increased doses, but that tolerability decreases. As an example, a dose-response meta-analysis included 66 randomized trials of SSRIs that generally lasted six to eight weeks and evaluated various fixed doses in a total of 99 active treatment arms [19]. Doses for the different SSRIs were converted to fluoxetine equivalents. Response (reduction of baseline symptoms ≥50 percent) with SSRIs increased as the dose increased to approximately 20 to 40 mg/day fluoxetine equivalents, with no further benefit up to 80 mg/day fluoxetine equivalents. However, as the dose of SSRIs increased, discontinuation of treatment due to adverse effects also increased, suggesting that the optimal balance between response and tolerability may be achieved at 20 to 40 mg/day fluoxetine equivalents.

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 high doses because the protocols call for rapid- or no-dose titration. By contrast, flexible-dose trials better approximate clinical practice by allowing clinicians to titrate the dose according to both response and tolerability.

Flexible-dose trials also indicate that higher doses within the therapeutic range can be beneficial [20]. As an example, a meta-analysis examined 40 randomized trials of SSRIs, including flexible-dose trials, with 49 active treatment arms [21]. The results found that a dose greater than 50 mg/day fluoxetine equivalents was modestly superior to 20 mg/day fluoxetine equivalents (odds ratio 1.3, 95% CI 1.1-1.5).

Patients who recover from an episode of major depression should 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'.)

Citalopram — We suggest an initial dose of 20 mg in the morning (table 2). Older patients and those sensitive to side effects can be started at a dose of 10 mg. The target dose range is 20 to 40 mg once per day [22-24]. The dose can be titrated up in increments of 10 or 20 mg per day, every one to four weeks.

The maximum dose of citalopram is nearly always 40 mg/day, based upon recommendations from the US Food and Drug Administration (FDA) [25]. The FDA issued a warning that citalopram can cause dose-dependent prolongation of the corrected QT interval, which can lead to a life-threatening cardiac arrhythmia, torsade de pointes [25]. A subsequent warning recommended a maximum dose of 20 mg per day in patients with risk factors for increased serum concentrations of citalopram [26]:

- Hepatic impairment.
- Age >60 years.
- CYP2C19 variants that slowly metabolize citalopram.
- Concomitant medications that inhibit CYP2C19. Specific interactions of citalopram with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Furthermore, citalopram should be avoided in patients with congenital long QT syndrome, persistent corrected QT measurements >500 milliseconds, bradycardia, hypokalemia, hypomagnesemia, recent myocardial infarction, or uncompensated heart failure, as well as patients taking other drugs that prolong the QT interval.

It may be reasonable to prescribe doses greater than those recommended by the FDA, such as patients who achieve an incomplete response to citalopram after failing other antidepressants [2,27,28]. Nevertheless, clinicians should exercise great care when exceeding the FDA guidance.

If clinicians prescribe citalopram at doses >40 mg/day, or >20 mg per day in patients at risk for increased serum concentrations, we suggest first reviewing a baseline electrocardiogram (ECG) [28]. In addition, we suggest an ECG when starting citalopram in any patient receiving concurrent medications that can prolong the QTc interval and patients who are suffering palpitations or syncope. Additional information about the cardiac effects of citalopram and other SSRIs is discussed elsewhere in this topic. (See 'Cardiac' below.)

The FDA does not make any recommendation about testing for CYP2C19 poor metabolizers, nor is it standard practice to test patients who will receive citalopram.

A liquid concentrate formulation is available.

Escitalopram — We suggest an initial dose of 10 mg in the morning (table 2). Older patients and those sensitive to side effects can be started at a dose of 5 mg.

The standard dose range for unipolar major depression is 10 to 20 mg once per day [22-24]. The dose can be titrated up in increments of 5 or 10 mg per day, after one to four weeks. Doses up to 30 mg per day have been used.

Escitalopram is a single isomer formulation of citalopram, and the FDA has issued warnings that citalopram causes dose-dependent QT interval prolongation that can lead to arrhythmias (see 'Citalopram' above) [25,26]. Although an analysis of a randomized trial by the FDA found that escitalopram also caused dose-dependent QT interval prolongation, the finding was not deemed clinically significant, and no warning was issued regarding escitalopram. Cardiac effects of escitalopram and other SSRIs and the structural relationship between escitalopram and citalopram are discussed elsewhere in this topic. (See 'Cardiac' below and 'Citalopram and escitalopram' above.)

A liquid concentrate formulation is available.

Fluoxetine — We suggest an initial dose of 20 mg in the morning (table 2). Older patients and those sensitive to side effects can be started at a dose of 10 mg.

In addition, patients with clinically significant anxiety/agitation or insomnia can be started at a dose of 5 mg.

The standard dose range for unipolar major depression is 20 to 60 mg once per day [22-24]. The dose can be titrated up in increments of 10 or 20 mg per day, every four weeks. Doses up to 80 mg per day have been used.

Other formulations of fluoxetine are available, including a liquid concentrate. In addition, there is a 90 mg delayed release capsule taken once per week. Patients must be stabilized on fluoxetine 20 mg daily prior to switching to once-weekly dosing. The manufacturer recommends waiting seven days after the last 20 mg daily dose of fluoxetine before beginning the once weekly regimen with the 90 mg delayed release formulation.

Fluvoxamine — We suggest an initial dose of 50 mg at bedtime (table 2). Older patients and those sensitive to side effects can be started at a dose of 25 mg.

The standard dose range for unipolar major depression is 100 to 200 mg per day [22,23,29-31]. The dose can be titrated up from the starting dose of 50 mg by increments of 25 or 50 mg per day, every several days to two weeks. When the dose exceeds 100 mg per day, it should be given in two divided doses. The two doses may be either equal, or a larger portion may be given at bedtime. The dose may be increased further by increments of 50 mg per day, every several days to two weeks. Doses up to 300 mg per day have been used.

It is also available in an extended-release formulation (100 and 150 mg) for once per day dosing at higher doses.

Paroxetine — We suggest an initial dose of 20 mg in the morning (table 2). Older patients and those sensitive to side effects can be started at a dose of 10 mg.

The standard dose range for unipolar major depression is 20 to 40 mg once per day [22-24]. The dose can be titrated up in increments of 10 or 20 mg per day, every one to four weeks. The maximum dose is 50 mg per day.

Other formulations of paroxetine are available, including a liquid concentrate. In addition, there is an enteric coated, controlled-release formulation. It may cause less nausea than the immediate release formulation for patients who are experiencing this adverse effect; otherwise, there is no compelling reason to change from one formulation to the other. The controlled-release formulation has less bioavailability, thus, a 12.5 mg dose of the controlled-release formulation is equivalent to 10 mg of regular release paroxetine. The recommended starting dose of the controlled-release formulation is 25 mg/day; the maximum dose may be as high as 75 mg/day, depending upon the indication.

Sertraline — We suggest an initial dose of 50 mg in the morning (table 2). Older patients and those sensitive to side effects can be started at a dose of 25 mg.

The standard dose range for unipolar major depression is 50 to 200 mg once per day [22-24]. The dose can be titrated up in increments of 25 or 50 mg per day, every one to four weeks.

Doses up to 300 mg per day have been used.

A liquid concentrate formulation is available.

Sertraline reaches its peak plasma concentration sooner when taken with food [4].

SIDE EFFECTS

Overview — The selective serotonin reuptake inhibitors (SSRIs) tend to have similar side effect profiles [1]. However, certain SSRIs may be more likely to cause specific side effects (table 3) [32]. Thus, some patients who cannot tolerate one SSRI may do well with another [12].

The SSRIs are often first-line treatment for depression because they are better tolerated than tricyclics or monoamine oxidase inhibitors [1,4,12,32,33]. In three-arm randomized trials, discontinuation of treatment because of an adverse event was typically lowest for placebo (5 to 10 percent), intermediate for the SSRI (10 to 20 percent), and highest for the tricyclic (30 to 35 percent) [1]. However, it is not clear that SSRIs are better tolerated than other antidepressant classes, such as atypical antidepressants (eg, bupropion and mirtazapine) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Based upon randomized trials, the most frequent and troublesome adverse effects of SSRIs include [1-5]:

- Nausea – Most common
- Dry mouth
- Headache
- Insomnia
- Loose stools/diarrhea
- Sexual dysfunction
- Somnolence
- Sweating
- Tremor
- Weight change

Additional information about sexual dysfunction and weight change are described elsewhere. (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management" and 'Weight change' below.)

Other SSRI side effects identified in randomized trials and observational studies include anxiety, asthenia (daytime sedation associated with malaise, diminished mental energy, or emotional

blunting), bleeding, coagulopathy, bone fractures, dizziness, extrapyramidal symptoms (eg, akathisia, dystonias, and parkinsonism), and hyponatremia [1-5,32-34]. (See 'Bleeding' below and "Drugs that affect bone metabolism", section on 'Antidepressants' and 'Hyponatremia' below.)

While any SSRI can cause side effects, there are a few general trends in side effect frequency [3,32,35]. Nausea and sedation may be more likely to occur with paroxetine and fluvoxamine, diarrhea with sertraline, activation may be more likely to occur with fluoxetine and sertraline, and sexual dysfunction may be more likely with paroxetine. Weight gain and anticholinergic side effects most common with paroxetine.

Although side effects that occur at the onset of treatment can persist beyond three months of treatment [33], many are transient and remit [1]. Reducing the dose may help alleviate the problem if the dose was previously titrated up. Dividing the dose during the day may also help. Nausea, which is the most common side effect and is often distressing, can be mitigated by starting the drug at a relatively low dose and administering the drug with food [3].

Additional information about SSRI adverse effects are described elsewhere. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Side effects'.)

Suicide risk — There is no clear evidence that treating depressed patients with SSRIs, or antidepressants in general, increases or decreases the risk of suicidality (suicidal ideation, preparatory act, attempt, or death) [36,37]. However, there may be an age-specific effect of antidepressants upon suicidality. Antidepressants in general may raise the risk of suicidal ideation slightly in patients age 18 to 24 years, have no effect upon patients age 25 to 30 years, and may lower the risk in patients 31 years and older. In addition, untreated depression can lead to suicidality. Some studies suggest that the risk of suicidality among different SSRIs is comparable [3] and that the risk of suicidality is comparable with SSRIs and placebo [2,4].

Suicidal ideation and behavior in adults and the potential effect of SSRIs on suicidal ideation and behavior in adults and children are discussed separately. (See "Suicidal ideation and behavior in adults" and "Effect of antidepressants on suicide risk in adults" and "Effect of antidepressants on suicide risk in children and adolescents".)

Cardiac — SSRIs are generally safe with regard to adverse cardiac effects and are considered the safest antidepressants for treating patients with comorbid cardiovascular disease (table 3) [38].

Although SSRIs can prolong the QT interval (corrected for heart rate), the clinical effect is often small. In a meta-analysis of 10 trials (n = 2599 patients) that compared SSRIs with placebo, SSRIs

were associated with an increase in the corrected QT interval of 6 milliseconds, and prolongation was dose dependent [39]. The SSRI with the highest value for QTc prolongation was citalopram. (See 'Citalopram' below.)

Other studies suggest that QT prolongation in patients treated with SSRIs is generally not clinically serious. A study of an administrative health care database included patients with a first diagnosis of depression (n >230,000) who were followed for a median of five years [40]. After adjusting for potential confounding factors (eg, age, smoking, severity of depression, and general medical illnesses such as hypertension and diabetes), the analyses found that the risk of a first diagnosis of arrythmia was comparable in patients treated with SSRIs and patients not treated with antidepressants.

Risk factors for a serious arrhythmia due to drug-induced QTc prolongation include [28]:

- Baseline QT prolongation
- Underlying heart disease (particularly heart failure, myocardial infarction [MI], and left ventricular hypertrophy)
- Bradycardia
- Electrolyte derangements (especially hypokalemia and hypomagnesemia)
- Concurrent use of more than one drug that can prolong the QT interval
- Female sex
- Advanced age (eg, >60 years)

Specific interactions of SSRIs with other medications that may increase the risk of QTc prolongation can be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate. In addition, an internet resource with updated lists of specific drugs that prolong the QT interval is available at the University of Arizona Center for Education and Research on Therapeutics website.

Additional information about QT prolongation is discussed separately. (See "Acquired long QT syndrome: Definitions, pathophysiology, and causes" and "Acquired long QT syndrome: Clinical manifestations, diagnosis, and management".)

Multiple studies indicate that SSRIs are not associated with onset of coronary heart disease (eg, MI):

- In a meta-analysis of 16 observational studies that included more than 750,000 subjects with no history of coronary heart disease, the risk of coronary heart disease for patients treated with SSRIs and controls was comparable [41].

- A subsequent study of an administrative health care database included patients with a first diagnosis of depression (n >230,000) who were followed for a median of five years [40]. In year 1 of follow-up, the risk of a first diagnosis of MI was lower in patients treated with SSRIs than patients not treated with antidepressants (adjusted hazard ratio 0.6, 95% CI 0.4-0.8). Over five years of follow-up, the risk of a first diagnosis of MI in patients treated with SSRIs and patients not treated with antidepressants was comparable.

Citalopram — Citalopram causes dose-dependent QT interval prolongation, which potentially may lead to a life-threatening cardiac arrhythmia, torsade de pointes (a form of polymorphic ventricular tachycardia):

- An analysis by the US Food and Drug Administration (FDA) of a randomized trial (n = 119) found that the maximum mean prolongation in the individually corrected QT intervals was longer for citalopram 60 mg per day (18.5 milliseconds, 90% CI 16.0-21.0) compared with 20 mg per day (8.5 milliseconds, 90% CI 6.2-10.8) [25,26,42].

- In addition, a randomized trial compared citalopram (target dose 30 mg per day) with placebo in patients with Alzheimer disease and agitation (n = 48; mean age approximately 78 years) [43]. Increases in corrected QT interval were greater with citalopram and an increase >30 milliseconds occurred in more patients who received citalopram than placebo (7 versus 1 patient).

- Multiple retrospective studies have also found an association between increasing doses of citalopram and corrected QT interval prolongation [42,44,45].

Based upon the finding that citalopram causes dose-dependent QT prolongation, the FDA issued a safety warning about using doses >40 mg/day and also warned that citalopram should be avoided in patients with congenital long QT syndrome, persistent corrected QT measurements >500 milliseconds, bradycardia, hypokalemia, hypomagnesemia, recent MI, or uncompensated heart failure, as well as patients taking other drugs that prolong the QT interval (see 'Citalopram' above). Warnings about citalopram and QT prolongation have been issued by other regulatory agencies, including Medicines and Healthcare Products Regulatory Agency of the United Kingdom, Health Canada, and the Therapeutic Goods Administration of Australia [28].

However, the warnings about citalopram are controversial, due to the magnitude of the prolongation in corrected QT intervals (approximately 10 to 20 milliseconds), which are clinically insignificant in the absence of other risk factors for arrythmias [28]. In addition, multiple retrospective studies of administrative health care databases suggest that relatively high doses of citalopram (eg, >40 mg/day) are not associated with cardiac arrhythmias [46]:

- Data from the United States Veterans Health Administration:
  - One study identified depressed patients who were prescribed citalopram (n >610,000) and found that after adjusting for potentially confounding sociodemographic and clinical factors, the risk of ventricular arrhythmia was less with daily doses >40 mg compared with doses ≤20 mg (hazard ratio 0.7, 95% CI 0.6-0.8) [47]. In addition, the risk of cardiac mortality was comparable for the two dose regimens.
  - Another study included patients who were prescribed citalopram at a dose >40 mg/day prior to the FDA safety warnings; subsequently, the doses were reduced to 40 mg/day or less (n >14,000) over one year, or were not reduced (n >14,000) [48]. After adjusting for the probability (propensity) of a dose reduction and for potential confounders observed at baseline, the analyses showed that the composite outcome of arrythmia-related hospitalizations or all-cause deaths was comparable in the two groups.
- Data from other health care databases:
  - One study included primary care patients with a first diagnosis of depression (n >230,000) who were followed for a median of five years [40]. After adjusting for potentially confounding factors (eg, age, smoking, severity of depression, and general medical illnesses such as hypertension and diabetes), the analyses found that the risk of a first diagnosis of arrythmia was comparable in patients treated with citalopram ≥40 mg/day and patients not treated with antidepressants.
  - A 14-year study examined sudden cardiac death as a proxy for proarrhythmic effects in patients (total n >54,000) who were prescribed relatively high doses of SSRIs: citalopram, fluoxetine, or paroxetine >40 mg/day, or sertraline >150 mg/day, prior to the FDA safety warnings [49]. After adjusting for potentially confounding factors (eg, age, other medications, and general medical illnesses), the analyses found that the risk of sudden cardiac death was comparable among the four SSRIs.

Problems that undermine the validity of these low-quality studies include residual confounding and selection bias (eg, prescribing clinicians may have prescribed lower doses to patients at greater risk of arrhythmia) [50,51].

Escitalopram — Escitalopram, the single isomer formulation of citalopram, may also prolong the corrected QT interval [45]. In a randomized trial (n = 113 healthy volunteers), the FDA found that the maximum mean prolongation in the individually corrected QT intervals was longer for escitalopram 30 mg per day (10.7 milliseconds, 90% CI 8.7-12.7) compared with 10 mg per day

(4.5 milliseconds, 90% CI 2.5-6.4); however, the FDA concluded that the finding was not clinically significant and did not justify a warning [28]. (See 'Escitalopram' above.)

Randomized trials suggest that escitalopram, at doses less than 30 mg/day, does not cause clinically significant QT prolongation [42]:

- A meta-analysis of 14 randomized trials, lasting 8 to 12 weeks, evaluated electrocardiograms in 3689 patients with psychiatric disorders who were randomly assigned to escitalopram (5 to 20 mg/day) or placebo [52]. The difference between the two groups in the mean change in the corrected QT interval was only 3.5 milliseconds. In three other randomized trials (total n = 670 patients), lasting 24 weeks, the difference between the two groups was 0.8 milliseconds.

- A one-year randomized trial compared escitalopram 10 mg/day with placebo as prophylaxis against depression in patients with recent acute coronary syndrome (n = 240) [53]. Each of the cardiovascular safety measures, including the length of the corrected QT intervals as well as the incidence of ventricular arrythmia and episodes of ST-segment depression, was comparable in the two groups.

In addition, low-quality data also indicate that escitalopram is not associated with clinically significant QT prolongation. As an example, a 14-year retrospective study of an administrative health care database examined sudden cardiac death as a proxy for proarrhythmic effects in patients (total n >54,000) who were prescribed relatively high doses of SSRIs: escitalopram >20 mg/day, fluoxetine or paroxetine >40 mg/day, or sertraline >150 mg/day, prior to the FDA safety warnings about citalopram (see 'Citalopram' above) [49]. After adjusting for potentially confounding factors (eg, age, concurrent medications, and general medical illnesses), the analyses found that the risk of sudden cardiac death was comparable among the four SSRIs.

However, other low-quality data suggest that escitalopram at therapeutic doses may possibly be associated with greater QT prolongation than previously appreciated. Cases of clinically significant QTc prolongation with escitalopram have been reported [54,55]; small, prospective observational studies found QT prolongation and variability [56,57]; and a World Health Organization pharmacovigilance database received reports that suggested an increased likelihood of QT prolongation with escitalopram and citalopram relative to other SSRIs [58].

Other SSRIs — There is no compelling evidence that fluoxetine, fluvoxamine, paroxetine, and sertraline cause QT prolongation, and they appear to be unlikely to cause serious arrhythmia when used in usual recommended doses and in patients without other risk factors [28,42]. The SSRIs with the lowest risk of QT prolongation may be fluoxetine [40] and paroxetine [3].

Serotonin syndrome — Serotonin syndrome is a potentially lethal condition caused by overstimulation of central and peripheral serotonin receptors. It typically results from an interaction between multiple medications that increase serotonergic neurotransmission (table 1). However, the syndrome can occur after initiating or increasing a single serotonergic drug. Clinical features include anxiety, agitation, delirium, diaphoresis, tachycardia, hypertension, hyperthermia, gastrointestinal distress, tremor, muscle rigidity, myoclonus, and hyperreflexia. It is not known whether SSRIs differ in their likelihood to cause this syndrome.

A rapid overview of the clinical features and management of the serotonin syndrome is provided in the table (table 4). Additional information about the serotonin syndrome is discussed separately. (See "Serotonin syndrome (serotonin toxicity)".)

Sexual dysfunction and infertility — SSRIs can cause sexual dysfunction. The incidence, assessment, and management of SSRI induced sexual dysfunction is discussed separately. (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management".)

It is not known if SSRIs interfere with fertility. One review examined whether SSRIs adversely affected fecundability in women, and identified only two relevant studies that yielded conflicting results [59]. The review also identified seven studies that examined whether SSRIs impacted fertility in males, and found that in six of the studies, SSRIs were associated with abnormal semen parameters. However, all seven studies were observational studies rather than randomized trials, including two studies that were case reports with a total of three patients, and two other studies with a total sample of 60 patients. In addition, some of these six studies failed to account for the potential confounding effect of depression.

Weight change — The effect of SSRIs upon weight depends upon the specific medication prescribed and the length of treatment. Short-term treatment for two to three months with SSRIs usually causes little or no weight change [60-66]. However, short-term therapy is not clinically appropriate for most patients.

Although treatment with SSRIs for longer periods of time may result in weight gain, in some cases it is not clear if this is a true medication side effect or the result of recovery from depression and the reversal of undesired weight loss. The evidence suggests that fluoxetine may be the least problematic SSRI regarding undesired weight gain and that paroxetine may the most problematic [67-69]. Studies lasting between 6 and 30 months have reported the following weight effects:

- Fluoxetine leads to small weight changes ranging from a loss of 0.2 percent of body weight at baseline [70] to a gain of 0.9 percent [60]. A one-year randomized trial showed a

mean weight gain of 3.0 kg (6.6 lb) for fluoxetine, compared with 3.2 kg (7.0 lb) for placebo [61].

- Citalopram leads to weight changes ranging from none [71] to a mean gain of 2.5 percent of baseline body weight [60].
- Fluvoxamine leads to a mean weight gain of 2.6 percent of baseline body weight [60].
- Paroxetine leads to weight gain in 6 percent of patients [72], ranging from 1.6 to 3.6 percent of baseline body weight [60,70].
- Sertraline leads to a mean weight gain ranging from 1.0 to 1.6 percent of baseline body weight [60,70]. A randomized trial showed a mean weight gain of 1.5 kg (3.3 lb) for sertraline, compared with 1.8 kg (4.0 lb) for placebo [73].

Most studies have evaluated patients suffering from major depressive disorder. It is not clear whether weight change caused by SSRIs differs according to different demographic profiles such as age or sex.

A review found that weight gain during treatment with SSRIs may be due to remission of major depression, improved appetite, increased carbohydrate craving, and changes in serotonin 2C receptor activity [74]. In addition, weight gain during SSRI treatment is significantly related to poor appetite at the beginning of treatment [61], and there may be a genetic component involving polymorphisms in the catechol-O-methyltransferase gene [75].

Weight gain due to long-term treatment with SSRIs may lead to diabetes mellitus. An observational study of patients with depression found that use of moderate to high daily doses of SSRIs for periods greater than 24 months was associated with a two-fold increased risk of developing diabetes mellitus, compared with not using antidepressants (incidence rate ratio 2.06, 95% CI 1.20-3.52) [76]. Analysis of individual antidepressants found an increased risk estimate for paroxetine (incidence rate ratio 1.33, 95% CI 1.02-1.73), suggesting the possibility that the increased risk for SSRIs might have been primarily due to paroxetine.

Bleeding — SSRIs may be associated with bleeding [1,38], but the evidence is not compelling and we suggest that clinicians should generally not change their practice with regard to using SSRIs [77]. Among the different SSRIs, there is little indication that any specific SSRI is more strongly associated with bleeding [78].

Although many observational studies have found that SSRIs are associated with abnormal bleeding [78-80], the increased risk is typically small and serious events are rare [81]. In addition, observational studies provide low-quality evidence. The association between SSRIs and

bleeding in observational studies may be confounded by many factors, such as intracranial small vessel disease, diabetes mellitus, smoking, and alcohol abuse. In addition, depressed patients who received SSRIs may have been compared with healthy controls; thus, observed associations between SSRI exposure and bleeding may be confounded by exposure to depression (confounding by indication).

By contrast, high-quality studies (randomized trials) suggest that SSRIs do not cause bleeding [82,83]. However, these studies are too small to identify a low-risk event.

Bleeding complications of SSRIs identified in observational studies include serious events such as upper gastrointestinal bleeding, stroke, postpartum hemorrhage, and perioperative bleeding, as well as less serious problems such as easy bruising, petechiae and purpura, epistaxis, and hematomas [84,85]. A meta-analysis of 42 observational studies (n >1.4 million patients) found that the risk of serious bleeding was greater in SSRI users than controls (odds ratio 1.4, 95% CI 1.3-1.6) [86]. The association between SSRI exposure and abnormal bleeding across multiple studies appears to be more consistent with upper gastrointestinal bleeding than perioperative bleeding or stroke [84-86]. In addition, the risk of bleeding generally appears to be limited to the time of current use of SSRIs rather than recent or past use, and the risk may be greatest relatively early during SSRI treatment, such as the first 30 days.

The association between SSRIs and bleeding in observational studies can be amplified by other medications that can cause bleeding, such as nonsteroidal anti-inflammatory drugs (NSAIDs; eg, aspirin, ibuprofen, or naproxen), other antiplatelet agents (eg, clopidogrel), or anticoagulants (eg, warfarin) [80,84,85,87]:

- A retrospective study compared the risk of intracranial hemorrhage in patients exposed to antidepressants plus NSAIDs with patients exposed to antidepressants alone (total n >4,000,000) [88]. Antidepressants consisted of SSRIs, SNRIs, and tricyclics; propensity scoring was used to match the two groups for observed potential confounders (eg, age, comorbidity, and exposure to other medications). The risk of bleeding within 30 days of drug use was higher with antidepressants plus NSAIDs compared with antidepressants alone (hazard ratio 1.6, 95% CI 1.3-1.9).

- A meta-analysis of five studies (number of patients not reported) found that intracranial bleeding was greater in patients treated with SSRIs plus oral anticoagulants than oral anticoagulants alone (relative risk 1.6, 95% CI 1.3-1.8) [89].

Nevertheless, other observational studies of patients treated with SSRIs found that concomitant use of antiplatelet agents or anticoagulants did not increase the risk of bleeding [78].

The biological plausibility of the association between SSRIs and increased bleeding is supported by the finding that SSRIs can block the serotonin transporter, inhibit serotonin uptake into platelets, and decrease intraplatelet serotonin concentrations, which may reduce platelet aggregation [84,85]. SSRIs may also increase gastric acid secretion, which can render patients more susceptible to gastrointestinal bleeding.

In addition, multiple studies suggest that the risk of bleeding may perhaps be greater with antidepressants that bind more tightly to the serotonin transporter and are relatively strong inhibitors of serotonin reuptake, compared with weak inhibitors of serotonin reuptake [85]. As an example, one retrospective study found that the bleeding occurred more often with strong inhibitors of serotonin reuptake (eg, fluoxetine, paroxetine, and sertraline), compared with weak inhibitors of serotonin reuptake (eg, agomelatine, desipramine, and nortriptyline) [78].

Bleeding may be associated with antidepressants other than SSRIs, which supports the idea that depression rather than SSRIs is associated with bleeding:

- A prospective observational study of individuals who underwent baseline brain imaging and subsequent imaging after a mean of four years (n >2100) found that the risk of asymptomatic, subclinical cerebral bleeding between scans was comparable in individuals who used SSRIs or non-SSRI antidepressants between scans [90].

- In a retrospective study (n >4,000,000 patients) that found the risk of intracranial hemorrhage was higher with antidepressants plus NSAIDs compared with antidepressants alone, the increased risk was comparable in patients treated with SSRIs, SNRIs, or tricyclics [88].

- A retrospective study identified patients who received new prescriptions for an SSRI (n >200,000) or an SNRI (n >50,000); after using propensity scores to match the two groups on baseline characteristics (eg, age, sex, and comorbidities), the analyses found that the risk of nonfatal stroke was greater with SNRIs than SSRIs (hazard ratio 1.2, 95% CI 1.1-1.3) [91].

- A systematic review evaluated bleeding with mirtazapine and bupropion, which have relatively low affinity for the serotonin transporter and are weak inhibitors of serotonin reuptake [92]. As part of the review, a meta-analysis of five studies found that the risk of bleeding in patients treated with either SSRIs or mirtazapine (total n >60,000) was comparable. Likewise, a meta-analysis of three studies found that the risk of bleeding in patients treated with either SSRIs or bupropion (total n >14,000) was comparable.

The association between exposure to SSRIs and postpartum hemorrhage is discussed separately. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors", section on 'Postpartum hemorrhage'.)

Upper gastrointestinal bleeding — Although SSRIs are associated with an elevated risk of upper gastrointestinal bleeding, the absolute risk is small and on par with the risk of bleeding in patients taking low doses of NSAIDs [93]. However, the likelihood of upper gastrointestinal hemorrhage is greater in patients with risk factors such as older age (eg, >65 years); smoking or alcohol consumption; use of NSAIDs, other antiplatelet agents (eg, clopidogrel), or anticoagulants (eg, warfarin); thrombocytopenia; platelet dysfunction (eg, von Willebrand disease); liver cirrhosis with coagulopathy; and prior history of upper gastrointestinal bleeding [84,93].

Meta-analyses of observational studies suggest that SSRIs are associated with upper gastrointestinal bleeding [84,86,94]; however, the absolute effect is low [93,95]. As an example:

- A meta-analysis 15 observational studies identified patients who developed upper gastrointestinal bleeding and controls who did not (total n >390,000) [96]. Treatment with SSRIs was more likely in patients with bleeding than controls (odds ratio 1.7, 95% CI 1.4-1.9). In addition, the study estimated that among low-risk patients (eg, no prior history of upper gastrointestinal bleeding), the number needed to harm was 3177. This means that on average, for every 3177 patients treated with SSRIs and every 3177 patients not treated with SSRIs, one additional episode of bleeding occurred with SSRIs. Among high-risk patients (eg, prior history of upper gastrointestinal bleeding), the number needed to harm was 881. The study also found that the risk of bleeding was further elevated with use of SSRIs plus NSAIDs (odds ratio 4.3, 95% CI 2.8-6.4).

- Another meta-analysis compared the risk of upper gastrointestinal bleeding in SSRI users with the risk in non-SSRI users, pooling data from 22 observational studies (n >1,000,000 individuals, including more than 56,000 cases of bleeding) [97]. Exposure to SSRIs was associated with an increased risk of bleeding (odds ratio 1.6, 95% CI 1.4-1.8). The risk was even greater in the subgroup of patients who took SSRIs plus NSAIDs (odds ratio 3.7, 95% CI 3.0-4.7). By contrast, a separate subgroup analysis found that the risk of bleeding was comparable for patients who took SSRIs plus NSAIDs plus acid suppressing drugs and for patients who were not exposed to SSRIs.

Based upon these findings, some clinicians use non-SSRI antidepressants in patients at high risk for bleeding (eg, prior history of upper gastrointestinal bleeding), or prescribe a proton pump

inhibitor when SSRIs are used in conjunction with NSAIDs; however, this is not standard practice.

Although SSRIs are often temporarily withheld in patients with peptic ulcer bleeding, doing so may not be necessary. A national registry study identified patients hospitalized for peptic ulcer bleeding who were using SSRIs (n >1800) or were not (n >12,000) [98]. After adjusting for potential confounding factors (eg, alcohol consumption, use of aspirin or anticoagulants, and American Society of Anesthesiologists physical status classification), the analyses showed that endoscopy-refractory bleeding, rebleeding, and 30-day mortality were each comparable in the two groups.

Perioperative bleeding — Although SSRIs may be associated with perioperative bleeding, the evidence is weak at best and the clinical relevance is unknown [84]. Thus, we suggest that clinicians should generally not stop SSRIs prior to surgery.

Multiple studies suggest that SSRIs may perhaps be associated with a marginally increased risk of perioperative bleeding. As an example, a meta-analysis of eight observational studies examined perioperative bleeding in patients who underwent different types of surgery and were either taking SSRIs prior to surgery or were not (total n >560,000) [99]. Transfusion rates were modestly higher in patients taking SSRIs than controls (odds ratio 1.2, 95% CI 1.1-1.3). However, reoperation for a bleeding event was comparable in the two groups.

Subsequent studies have failed to find an association between SSRIs and perioperative bleeding. A retrospective study identified patients who underwent cardiac surgery, including patients who were taking SSRIs or SNRIs at the time of surgery, and controls who were not (total n >1400) [100]. The two groups were matched for potentially confounding factors, including age, type of operation, and preoperative hemoglobin and platelet count. Postoperative bleeding was defined as chest tube output and reoperation for bleeding, each of which was comparable for patients treated with SSRIs/SNRIs and controls. Transfusion rates were also comparable for the two groups.

Stroke — Although meta-analyses of observational studies suggest that SSRIs are associated with new onset stroke [81], the clinical significance of these findings is not clear because the magnitude of the increased risk is small [85]:

- In a meta-analysis of 16 studies that compared patients who received SSRIs with controls who did not (total n >500,000), the risk of intracranial hemorrhage was elevated (relative risk 1.7, 95% CI 1.2-3.0) [89]. However, heterogeneity across studies was moderate, and the absolute risk of any stroke in patients using SSRIs was thought to be very low; it was estimated that SSRIs may lead to one additional intracerebral hemorrhage for every

10,000 patients treated for one year [81,89,101]. In addition, SSRI use was associated with a trend toward a protective effect against subarachnoid hemorrhage (relative risk 0.6, 95% CI 0.4-1.0).

- A second meta-analysis included four studies that controlled for confounding by depression and compared SSRI users with nonusers (total n >13,000) [102]. The risk of stroke was greater in SSRI users, but the magnitude of the increased risk was small (odds ratio 1.2, 95% CI 1.1-1.3). These results are similar to a third meta-analysis that compared SSRI users with nonusers (eight studies, sample size not reported), which found that SSRIs were associated with a marginally increased risk of intracerebral hemorrhage (odds ratio 1.16, 95% CI 1.01-1.33) [86].

- A subsequent retrospective study of an administrative health care dataset identified new users of antidepressants without a history of stroke, including patients who eventually suffered an intracranial hemorrhage (n >3000) and controls who did not (n >89,000); the two groups were matched for age, sex, and duration of follow-up [78]. After adjusting for potentially confounding factors (eg, alcohol abuse, smoking, and general medical comorbidities), the analyses found that the risk of intracranial hemorrhage was marginally greater with SSRIs than tricyclics (relative risk 1.17, 95% CI 1.02-1.35).

However, other studies suggest that the relative risk of stroke with SSRIs may be higher. As an example, an eight-year, retrospective study of an administrative health care dataset included patients who were exposed to SSRIs (n >14,000) or were not (n >394,000) [103]. After adjusting for potentially confounding factors such as age, sex, and diseases comorbid with stroke, the analyses found that the risk of stroke was more than twice as great among SSRI users (hazard ratio 2.6, 95% CI 2.4-2.7).

Multiple studies suggest that the association between SSRIs and stroke may be greatest relatively early during SSRI treatment, such as the first 30 days [78] or the first three years [103].

Aside from strokes, SSRIs may also be associated with asymptomatic, subclinical cerebral bleeding (microbleeds). A prospective observational study used magnetic resonance imaging to identify individuals with no prior history of microbleeds (n >2100, age ≥45 years); brain imaging was repeated after a mean of four years, and use of SSRIs between scans was assessed [90]. After adjusting for the probability (propensity) of SSRI use between scans and for potential confounders observed at baseline, the analyses showed first-time microbleeds were more likely to occur in SSRI users than nonusers (odds ratio 2.4, 95% CI 1.1-5.3). However, reverse causality may explain the association, such that microbleeds may lead to psychiatric symptoms and use of SSRIs.

Multiple randomized trials in patients with a recent stroke have evaluated the benefit of SSRIs for functional outcomes. (See "Initial assessment and management of acute stroke", section on 'Ischemic stroke management'.)

Recurrence of stroke — Use of SSRIs in patients with a prior history of stroke may be associated with an increased risk of recurrence of stroke. One prospective observational study enrolled patients who survived an intracerebral hemorrhage (n >1200) and followed them for a median of 53 months [104]. After adjusting for potentially confounding factors (eg, education, location of prior intracerebral hemorrhage, and apolipoprotein E genotype), the analyses showed that recurrence of intracerebral hemorrhage was modestly greater in SSRI users than nonusers (hazard ratio 1.3, 95% CI 1.1-1.6). In addition, the association between SSRIs and recurrence was greater in patients at high risk of recurrence (eg, prior history of hemorrhages) compared with non-high-risk patients, and was greater in patients treated with high doses of SSRIs than low doses.

Mortality after stroke — Most evidence suggests that SSRIs do not increase the risk of death in patients with strokes:

- Among patients who use SSRIs and subsequently suffer a stroke, it is not clear whether SSRIs are associated with increased mortality due to contradictory results across observational studies:
  - A prospective, five-year study of patients who suffered a stroke included patients who were taking an SSRI at the time of the stroke (n = 55) and patients who were not (n = 1082) [105]. Mortality in the two groups was comparable. However, depression three months after the stroke was associated with an increased risk of death (hazard ratio 1.4, 95% CI 1.1-1.7).
  - A national registry study identified patients who had suffered hemorrhagic strokes and used SSRIs in the 90 days before the stroke (n = 626), and patients with strokes who had not used SSRIs (n = 626) [106]. Propensity scoring was used to match the two groups with regard to observed potential confounders (eg, age, sex, history of general medical illnesses, and exposure to other medications). Prestroke SSRI use was associated with an elevated risk of death in the 30 days after the stroke (odds ratio 1.6, 95% CI 1.2-2.2).
- Based upon randomized trials, the risk of death is not increased in patients who suffer a stroke and are subsequently treated with SSRIs. As an example, a meta-analysis of 46 trials compared SSRIs with control conditions in patients who suffered strokes (n >3000) [82,83]. Mortality was comparable in the two groups.

Hyponatremia — SSRIs are associated with the syndrome of inappropriate antidiuretic hormone secretion and hyponatremia, but the absolute rate is low [1-4,107]. Risk factors include older age (eg, >65 years), concurrent diuretics, and prior history of hyponatremia [107-109]. The literature emphasizes the increased morbidity that can occur with serum sodium concentrations below 135 mmol/L, such as instability and falls, reduced cognitive function, and osteoporosis; mortality is also increased [110].

> Medications with any risk of hyponatremia are concerning in patients with prior hyponatremia [107]. In currently depressed patients with a history of hyponatremia from any cause, who are starting an SSRI, we suggest obtaining sodium levels at baseline and again two weeks afterwards, because if hyponatremia occurs, it is likely to occur early. One study that examined the association between antidepressants and hyponatremia found that the risk of hyponatremia was greatest within the first two weeks of treatment [109,110]. Another study found that among psychiatric inpatients who developed hyponatremia attributed solely to SSRIs, the median time to onset was 11 days [108], and a third study found that paroxetine-induced hyponatremia in older adult patients occurred within a mean of 9 days [109].

Retrospective studies suggest that SSRIs are strongly associated with hyponatremia:

- In a registry study that included more than 600,000 patients, SSRIs were prescribed to more than 93,000 patients; hyponatremia was defined as a serum sodium level <135 mmol/L [110]. After adjusting for potentially confounding factors such as age, comorbid illnesses, and concurrent pharmacotherapy, the analyses found that two weeks after SSRIs were initiated, hyponatremia was far more likely to occur in patients treated with SSRIs than patients who received no antidepressant (incidence rate ratio 8.7, 95% CI 8.9-9.5). The incidence rate ratio (95% CI) for the association between each specific SSRI and hyponatremia was as follows:
  - Citalopram – 7.8 (7.4-8.2)
  - Escitalopram – 3.7 (3.3-4.2)
  - Fluoxetine – 5.6 (4.5-7.0)
  - Paroxetine – 6.2 (5.3-7.2)
  - Sertraline – 4.5 (4.0-5.1)
- Another registry study identified patients with a first-ever hospitalization for hyponatremia (cases; n >14,000) and controls matched for age and sex with no lifetime history of hyponatremia (n >57,000); hyponatremia was defined as a serum sodium level <135 mmol/L [111,112]. Newly initiated treatment with an SSRI was far more likely to have

occurred in the cases hospitalized for hyponatremia than in controls, as indicated by the following odds ratios (95% CI):

- Citalopram – 6.5 (5.4-7.8)
- Escitalopram – 3.0 (1.8-5.1)
- Sertraline – 6.8 (5.0-9.3)
- Other SSRIs – 4.5 (2.2-9.2)

- A study of administrative health care databases identified two groups of individuals older than 65 years: patients with depressive or anxiety disorders who received a new prescription for an SSRI or another second-generation antidepressant, and controls who did not start an antidepressant (n >138,000 in each group) [107]. The two groups were matched on the probability (propensity) of receiving an antidepressant and on potentially confounding factors such as sex, general medical disorders, and pharmacotherapy. Hospitalization for hyponatremia occurred in far more SSRI users than controls, as indicated by the following risk ratios (95% CI):

  - Citalopram – 5.8 (4.1-8.0)
  - Escitalopram – 4.8 (2.6-8.7)
  - Paroxetine – 8.0 (3.7-17.6)
  - Sertraline – 7.3 (3.3-16.1)

However, the absolute rate of hyponatremia associated with SSRIs is low (which means large samples are required to estimate the risk). In addition, rates vary with the study population, definition of hyponatremia (eg, hospitalization or serum sodium <130 mmol/L or <135 mmol/L), and with the length of exposure [109]:

- A drug surveillance program of psychiatric inpatients found that among those treated with SSRIs (n >50,000), hyponatremia (serum sodium <130 mmol/L) occurred in 0.06 percent [108]. Among patients who received an SSRI plus an angiotensin converting enzyme inhibitor (n >4000), the rate of hyponatremia was 4.5 times larger (0.27 percent).

- A retrospective study of administrative health care databases identified two groups of individuals older than 65 years: patients who received a new prescription for an SSRI or another second-generation antidepressant, and controls who did not start an antidepressant (n >138,000 in each group) [107]. The two groups were matched on the probability (propensity) of receiving an antidepressant and on potentially confounding factors observed at baseline. Hospitalization for hyponatremia occurred in more antidepressant users than controls (0.33 versus 0.06 percent).

Other — The literature suggests that SSRIs may possibly be associated with other adverse effects. However, the evidence often consists of low-quality studies with small effect sizes, and the results should generally not deter clinicians from using SSRIs when indicated:

- Bone fractures – Many observational studies have found an association between SSRI use and bone fractures. (See "Drugs that affect bone metabolism", section on 'Antidepressants'.)

- Ophthalmic

  - Cataracts – Exposure to SSRIs is marginally associated with developing cataracts [113]. As an example, a meta-analysis of seven observational studies included patients with cataracts (n >400,000) and controls without cataracts (n >1,500,000) [114]. Use of SSRIs was slightly greater in cataract patients than controls (odds ratio 1.12, 95% CI 1.06-1.19).

  - Glaucoma – A meta-analysis of seven observational studies, which included SSRI users (n >160,000) and nonusers (630,000), found that after adjusting for potentially confounding factors (eg, age, general medical disorders, eye diseases, and depressive symptoms), the risk of glaucoma was comparable for the two groups, suggesting that SSRIs do not cause glaucoma [115].

- Seizures – The risk of seizures with SSRIs is low and may be reduced compared with placebo [116]. However, seizures may occur with large overdoses. In addition, some SSRIs can increase serum levels of concomitant medicines, which may secondarily increase the risk of seizures. (See 'Drug-drug interactions' above.)

- Violent behavior – A national registry study included more than 780,000 patients who were treated with an SSRI, and compared the rate of conviction for violent crime (eg, manslaughter, harassment, and assault) during periods on versus off treatment with the SSRI; the mean follow-up time was seven years [117]. After adjusting for potentially confounding factors (sex, lifetime diagnoses, and history of violent crime), the analyses found a nominal association between current use of SSRIs and violent crime conviction (hazard ratio 1.10; 95% CI 1.06-1.13) [117]. However, the observed association between SSRI exposure and violent behavior may be confounded because the disorders that were treated with SSRIs are also associated with violent behavior (confounding by indication).

EFFICACY FOR MAJOR DEPRESSION

The efficacy of selective serotonin 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-resistant depression. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

OVERDOSE

A single-substance selective serotonin reuptake inhibitor (SSRI) overdose rarely causes death or serious sequelae. SSRIs (except for citalopram and escitalopram) have a wide therapeutic window, such that overdoses of up to 30 times the usual daily dose typically produce minor or no symptoms, while larger ingestions may cause drowsiness, tremor, and vomiting. Nearly all fatalities from SSRI overdoses involve extremely large doses or coingestion of other substances. A rapid overview of the clinical features and management of SSRI overdoses is provided in the table (table 5). Additional information about acute poisoning from SSRIs is reviewed elsewhere. (See "Selective serotonin reuptake inhibitor poisoning".)

Among different SSRIs, relatively low-quality evidence suggests that citalopram may be more lethal in overdose than other SSRIs [118]. A retrospective study examined reports to the United States Poison Control Centers that included exposures to SSRIs (n >180,000) over a 15-year period [119]. The mortality risk per 10,000 exposures was three times greater for citalopram than paroxetine, and five times greater for citalopram than escitalopram, fluoxetine, and sertraline. The increased fatality observed with citalopram may be related to dose-dependent QT prolongation. (See 'Citalopram' above.)

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 depressive and bipolar disorders and how to cope with them. Other functions include increasing public awareness of the illnesses and advocating for more research and services. The organization has local chapters and is administered and maintained by patients and family members.

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 and indications** – The selective serotonin reuptake inhibitors (SSRIs) include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. SSRIs are frequently first-line agents for depressive disorders because of their efficacy, tolerability, and general safety in overdose. Other indications include anxiety disorders, eating disorders, obsessive-compulsive and related disorders, and posttraumatic stress disorder. (See 'Introduction' above.)

- **Pharmacodynamics** – SSRIs inhibit the serotonin reuptake pump and increase postsynaptic serotonin receptor occupancy. This initial action may cause subsequent changes involved in treating depression. SSRIs are selective in that they have relatively little affinity for other types of receptors, although they have secondary effects on neurotransmission involving norepinephrine and dopamine. (See 'Pharmacodynamics' above.)

- **Avoiding drug-drug interactions** – The SSRIs may inhibit hepatic cytochrome P450 enzymes that metabolize other medications and cause drug-drug interactions. Citalopram and escitalopram inhibit liver enzymes less than other SSRIs and are usually the SSRIs of choice for situations in which drug-drug interactions are a concern. (See 'Drug-drug interactions' above.)

- **Dose** – SSRIs should generally be started at their minimal effective dose (table 2). A process of trial and error is used to find the effective dose. Dose adjustments are made according to patient response, tolerability, and clinical urgency.

  For citalopram, the maximum dose is nearly always 40 mg/day because of dose-dependent QT interval prolongation. In addition, the recommended maximum dose is 20 mg/day in patients with risk factors for increased serum concentrations, including hepatic impairment and age >60 years. Citalopram should be avoided in patients with congenital long QT syndrome, persistent corrected QT measurements >500 milliseconds, bradycardia, hypokalemia, hypomagnesemia, recent myocardial infarction, or uncompensated heart failure, as well as patients taking other drugs that prolong the QT interval. (See 'Dose' above and 'Cardiac' above.)

- **Side effects** – Common SSRI side effects (table 3) include nausea, dry mouth, headache, insomnia, loose stools, sexual dysfunction, somnolence, sweating, tremor, and weight change. In addition, SSRIs may increase the risk of bleeding, bone fractures, dizziness, extrapyramidal symptoms, and hyponatremia. (See 'Side effects' above.)

- **Overdose** – A single-substance SSRI overdose rarely causes death or serious sequelae. Except for citalopram and escitalopram, overdoses of SSRIs of up to 30 times the usual daily dose typically produce minor or no symptoms. Nearly all fatalities from SSRI overdoses involve extremely large doses or coingestion of other substances. (See 'Overdose' above.)

  A rapid overview of the clinical features and management of SSRI overdoses is provided in the table (table 5). (See "Selective serotonin reuptake inhibitor poisoning".)

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