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Discontinuing antidepressant medications in adults

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INTRODUCTION

Patients who stop their antidepressants are at risk for the antidepressant discontinuation syndrome, especially if they abruptly stop the drug, taper it too quickly, or switch to a new antidepressant with a different pharmacodynamic profile [1-5]. Although discontinuation symptoms are generally mild and self-limiting, in some cases they are severe [6], which has given rise to online forums such as Surviving Antidepressants.

This topic discusses the antidepressant discontinuation syndrome and discontinuing antidepressants without switching to another drug. Choosing an alternative treatment for patients with depression, as well as switching antidepressant drugs, are discussed separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression" and "Switching antidepressant medications in adults".)

INDICATIONS FOR DISCONTINUATION

Following a clinical assessment and discussion with the patient, discontinuing antidepressant medications may be indicated for the following reasons:

- Lack of efficacy – Patients with acute psychiatric disorders who do not respond satisfactorily to an antidepressant drug may switch to another antidepressant medication, psychotherapy, or neuromodulation. This topic discusses discontinuing antidepressants without switching to another drug. Choosing an alternative treatment for patients with

depression, as well as switching antidepressant drugs, are discussed separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression" and "Switching antidepressant medications in adults".)

- Serious adverse effect.
- Unintended pregnancy.
- Imminent surgery or medical emergency.
- Sequential treatment – Patients with unipolar major depression who successfully complete acute phase pharmacotherapy may switch to psychotherapy for maintenance treatment; this strategy is called sequential treatment. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Sequential treatment'.)
- Successful acute and maintenance treatment – Acute and maintenance phase treatment may be successful such that patients recover for a substantial length of time (eg, two years). At that point, it is reasonable for patients who are not at an elevated risk of recurrence to discontinue pharmacotherapy. Risk factors for recurrence of unipolar major depression are discussed separately. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Indications'.)

ADVERSE CONSEQUENCES

Stopping antidepressants may lead to the antidepressant discontinuation syndrome. Among patients who are successfully treated with antidepressants, another risk of stopping the medication is recurrence of the underlying disorder.

Discontinuation syndrome — The antidepressant discontinuation syndrome is characterized by sudden onset of symptoms shortly after stopping the antidepressant or tapering it too quickly; the syndrome is typically self-limited when untreated, and resolves after restarting the antidepressant [4]. The morbidity and management of the antidepressant discontinuation is described in the subsections below.

Recognition of the antidepressant discontinuation syndrome extends as far back as 1959 [7]. As an example, an observational study of 85 patients who were treated with imipramine for depressive syndromes found that discontinuation symptoms occurred in 18 percent [8]. The symptoms included restlessness and nausea, were generally mild, and lasted approximately three days in the absence of treatment.

Overview — There is no standard definition for the antidepressant discontinuation syndrome. Nevertheless, it is generally thought that the syndrome comprises one or more adverse effects, such as dizziness, fatigue, headache, and nausea, which can occur when antidepressants that have been taken continuously for at least several (eg, four) weeks are discontinued [1-5,9-14]. The syndrome is especially likely to occur if patients:

- Abruptly stop antidepressants
- Taper antidepressants too quickly (eg, for two to seven days)
- Switch to a new antidepressant with a different pharmacodynamic profile
- Skip a few (eg, three or four) consecutive doses of antidepressants with relatively short half-lives or nonlinear pharmacokinetics, such as paroxetine or venlafaxine

In addition, it is conceivable that discontinuation symptoms may arise if the patient switches from a branded formulation to a generic, due to differences in bioequivalence [15].

All antidepressant classes can cause the antidepressant discontinuation syndrome, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, serotonin modulators, tricyclics, and monoamine oxidase inhibitors [3-5,9-11,16,17]. Although discontinuation symptoms have been best characterized in patients with unipolar depression who abruptly stop SSRIs, they can occur in patients taking antidepressants regardless of diagnosis [5,9-11,14].

It appears that many patients abruptly discontinue their antidepressant. In a retrospective study of 66 patients who were treated with SSRIs for at least two months, more than 20 percent abruptly stopped their medication; this was usually on their initiative rather than the advice of their clinician [18].

The pathophysiology of the antidepressant discontinuation syndrome is not clear. For SSRIs, the association between shorter elimination half-life and increased frequency and severity of discontinuation symptoms suggests that reduced availability of serotonin in the brain is involved in the syndrome [14,19]. During SSRI treatment, the density and sensitivity of serotonin receptors are downregulated, which may leave patients vulnerable to a deficiency of serotonin when SSRIs are stopped [9]. Other neurotransmitters such as acetylcholine, dopamine, glutamate, and norepinephrine may also be involved in the discontinuation syndrome, given the wide range of symptoms that can occur as part of the syndrome (see 'Clinical features' below), and that serotonergic neurons affect other neurotransmitter systems [9,14,19]. In addition, polymorphisms in hepatic enzyme genes that affect the rate of

antidepressant metabolism, and polymorphisms in neurotransmitter receptor genes, may possibly be related to discontinuation symptoms [3,20]. Psychologic factors, including negative expectations that amplify discontinuation symptoms (nocebo effects), may also have a role [9,21,22].

Clinicians can assess discontinuation symptoms by asking open-ended questions such as, "How have you felt since stopping the drug, have you had any new problems?" [10]. The value of this assessment is increased by establishing the patient's clinical status prior to discontinuing the drug. For patients who report new onset symptoms, clinicians should rule out other causes, such as psychiatric disorders, general medical conditions, or concurrent drugs [3,14].

In many studies of the discontinuation syndrome, investigators used the Discontinuation-Emergent Signs and Symptoms checklist, which includes 43 items and is administered by the clinician or self-report [10,23]. Some studies have defined the discontinuation syndrome as the presence of a minimum number of signs and symptoms (eg, at least two or four) [6]; however, there is no standardized cutoff and using this instrument is not part of routine clinical practice.

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) describes the clinical features of the antidepressant discontinuation syndrome in the section entitled "Medication-Induced Movement Disorders and Other Adverse Effects of Medication" [3]. However, DSM-5 does not provide specific criteria for diagnosing the syndrome. Some studies use the term "withdrawal reaction" or "withdrawal syndrome" instead of discontinuation syndrome [6,13].

Evidence regarding the antidepressant discontinuation syndrome is limited in part because many of the studies consist of case reports rather than prospective studies [14]. In addition, many randomized trials of antidepressants were not designed to assess discontinuation symptoms, and the trials often lasted only six weeks, which may not be long enough to generate discontinuation effects in some patients.

Incidence and risk factors — Although the reported incidence of the antidepressant discontinuation syndrome varies widely [3,6,9,14], many studies suggest the syndrome occurs in approximately 30 percent of patients who stop an antidepressant. As an example, a meta-analysis of nine randomized trials of SSRIs and venlafaxine (sample size not reported) indicates that discontinuation symptoms occur in 31 percent of patients; however, heterogeneity across studies is large [24]. In addition, a review in the National Institute for Health and Care Excellence practice guideline for depression found that symptoms occur in approximately 30 percent of patients [5]. A prior meta-analysis, which included 14 randomized trials and observational studies (n >4000 patients), found that the incidence was 56 percent [6]. However,

this estimate appears to be excessive, given that more than 75 percent of the patients were assessed with online surveys, in which the incidence of discontinuation effects was self-defined and probably affected by attributional bias [24,25].

Although some studies suggest the frequency of specific symptoms varies across different antidepressant classes [4], this is not established.

Risk factors for the antidepressant discontinuation syndrome include [1-5,9,14,15,26-29]:

- Abrupt discontinuation or tapering the medication too quickly (eg, over two to seven days)
- Shorter antidepressant elimination half-life (eg, <24 hours)
- Nonlinear antidepressant pharmacokinetics
- Lack of an active metabolite
- Lower receptor binding affinity of the antidepressant
- Anxiety symptoms at the onset of antidepressant treatment
- Higher antidepressant doses and serum concentrations prior to discontinuation
- Longer duration of treatment at therapeutic doses (eg, at least four to eight weeks)
- Prior history of discontinuation symptoms
- Concurrent centrally acting medications (eg, antihypertensives, antihistamines, or antipsychotics)

Sociodemographic factors such as age and sex do not appear to be risk factors for discontinuation symptoms.

Clinical features — The antidepressant discontinuation syndrome is characterized by a wide range of new onset somatic and neuropsychiatric symptoms that can occur in any combination; some reviews have identified approximately 50 to 80 symptoms across 10 organ systems [3-5,9,11,12,14]. None of the symptoms are pathognomonic.

Based upon results from multiple studies, the most common discontinuation symptoms appear to be [1-4,6,9-12,14,15,26,30]:

- Dizziness
- Fatigue

- Headache
- Nausea

Other common discontinuation symptoms include [1-4,6,9-12,14,15,26,30]:

- Agitation
- Anxiety
- Chills without fever
- Diaphoresis
- Dysphoria
- Electric shock-like sensations (“brain zaps”)
- Insomnia
- Irritability
- Myalgias
- Paresthesias
- Rhinorrhea
- Tremor
- Vivid dreams

Less common or rare symptoms, such as those described in case reports, include loss of balance [4,9,10,15], cognitive impairment [4,9,10,30], loose stools/diarrhea [4,6,9,10,14], extrapyramidal symptoms [4], hypertension [31], hypomania and mania [32,33], psychosis (eg, auditory and visual hallucinations) [34-36], sexual dysfunction [37], suicidal ideation [6], tinnitus [3,11], and vomiting [2,4,9,10,12].

Onset of the antidepressant discontinuation syndrome typically occurs within a few (eg, one to four) days of abruptly stopping antidepressants or tapering them too quickly [1-5,11,14,15,27,34,38,39]. However, symptoms may not emerge until one or more weeks has elapsed since the last dose, especially for drugs with relatively long elimination half-lives, such as fluoxetine.

The antidepressant discontinuation syndrome is usually mild and dissipates spontaneously over one to three weeks; however, distressing symptoms can persist for a month or longer, and some studies report protracted cases lasting for one year and beyond [3-6,9,11,12,14,30]. Symptoms can interfere with functioning, and may rarely lead to hospitalization, particularly if discontinuation occurs abruptly. Some patients may be reluctant to discontinue their antidepressant because symptoms are aversive, whereas other patients may become alarmed and refuse subsequent treatment with antidepressants.

Although the adverse effects of stopping antidepressants (eg, dysphoria, insomnia, and nausea) can overlap with symptoms that arise from stopping addictive substances such as alcohol, opioids, or stimulants, the antidepressant discontinuation syndrome differs from substance-related and addiction disorders [1-5,19,34]. Antidepressants are not addictive in that they do not cause reinforcing or euphoric effects, and patients do not neglect important occupational or social activities due to using antidepressants; rather, antidepressants typically improve functioning. In addition, patients do not crave antidepressants, spend a large amount of time obtaining or using antidepressants, or escalate the dose unless directed to do so by the prescribing clinician. Nor do antidepressants have street market value among individuals with substance-related and addictive disorders. Rather, the antidepressant discontinuation syndrome is a normal physiologic response that can occur after patients are treated with an antidepressant for a sufficient length of time (eg, four weeks) and then stop the medication [3].

Some symptoms of the antidepressant discontinuation syndrome, including dysphoria, fatigue, and insomnia, can also occur in patients with recurrences of anxiety and depressive disorders [3-5,9,11,14,15]. However, other symptoms of the discontinuation syndrome, such as dizziness, electric-like shock sensations, nausea, and paresthesias, are not characteristic of anxiety and depressive disorders. Furthermore, resuming the discontinued antidepressant generally resolves the discontinuation syndrome within days (eg, one to three), whereas relapses of anxiety and depressive disorders often require weeks or months to remit after reintroducing the antidepressant or may require a different treatment.

In addition, discontinuation symptoms may be mistaken for other general medical conditions [5,14,15]. One case report described discontinuation symptoms from paroxetine that were initially mistaken for stroke [40] and another case report described evaluation and treatment by a neurologist and otolaryngologist for symptoms induced by stopping fluoxetine [41].

Prevention and management — Strategies for preventing the antidepressant discontinuation syndrome include educating patients to not abruptly stop their medication and to not taper medications too quickly. (See 'General approach to discontinuing antidepressants' below.)

For patients who develop the antidepressant discontinuation syndrome after abruptly stopping treatment, we resume the medication at the dose that was used prior to discontinuation [3,4,9,14]. However, if restarting the same antidepressant is contraindicated (eg, it was abruptly stopped due to rash or patient declines), we suggest using another antidepressant with a similar pharmacodynamic profile. As an example, fluoxetine can be substituted for sertraline. When the discontinuation symptoms abate, we discontinue the antidepressant using the general approach. (See 'General approach to discontinuing antidepressants' below.)

If the discontinuation syndrome occurs in the context of tapering the antidepressant according to the general approach, management depends upon the severity of symptoms and time of onset [4,5,9,15,29,38,39,42-45]:

- Mild discontinuation symptoms that occur during a two- to four-week taper are usually managed with reassurance and watchful waiting.

- If moderate to severe discontinuation symptoms occur during a two- to four-week taper, clinicians can extend the duration of the taper (eg, discontinue the antidepressant over 6 to 12 weeks). In addition, the antidepressant dose can be tapered by a fixed percent (eg, approximately 25 percent) rather than fixed amount. Thus, the absolute amount of each dose decrease is progressively smaller, until the last several doses, at which point the same small decrements are prescribed. As an example, sertraline 150 mg/day can be tapered using a liquid formulation as follows:

  - Week 1 – 110 mg/day
  - Week 2 – 80 mg/day
  - Week 3 – 60 mg/day
  - Week 4 – 45 mg/day
  - Week 5 – 35 mg/day
  - Week 6 – 25 mg/day
  - Week 7 – 15 mg/day
  - Week 8 – 10 mg/day
  - Week 9 – 5 mg/day
  - Week 10 – 5 mg/day
  - Week 11 – Stop

  Liquid formulations are available for slowly tapering other SSRIs, including citalopram, escitalopram, fluoxetine, and paroxetine.

  Alternatively, if moderate to severe discontinuation symptoms occur during a two- to four-week taper, patients may choose to abruptly stop the drug. Some patients may prefer more severe symptoms for a relatively short time, rather than less intense symptoms for a longer time.

- If moderate to severe symptoms arise after the drug is tapered and stopped, the antidepressant is restarted at the dose at which there were no symptoms; the discontinuation syndrome should resolve within a few days (eg, one to three). The taper is then recommenced at a slower pace (eg, 6 to 12 weeks) than the initial taper, and the

antidepressant dose can be decreased by a fixed percent (eg, 25 percent) with each reduction until the last several doses, at which point small decrements are prescribed.

- For patients who have difficulty tapering off of an SSRI (eg, paroxetine) or venlafaxine, a reasonable alternative is to immediately switch to fluoxetine 10 to 20 mg per day; fluoxetine can then be tapered over one to two weeks. (See 'SSRIs' below.)

- If patients refuse to restart an antidepressant, it is reasonable to prescribe a short course (eg, one to two weeks) of a benzodiazepine such as clonazepam or lorazepam [44,46]. Clonazepam is started at 0.25 to 0.5 mg once or twice daily and titrated up to 1 mg two or three times daily, based upon response and side effects. Following resolution of discontinuation symptoms, clonazepam is tapered by 20 to 25 percent every week.

Rarely, patients with episodes of the antidepressant discontinuation syndrome require hospitalization, especially if it includes severe symptoms such as mania and/or psychosis [4]. For manic or psychotic symptoms, we suggest using standard treatments, such as a second-generation antipsychotic (eg, olanzapine or quetiapine). (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation", section on 'Clinical manifestations'.)

Recurrence of underlying disorder — Among patients who are successfully treated by antidepressants, recurrence of the disorder that prompted treatment can occur if the drug is discontinued, and may be more likely if discontinuation occurs abruptly [3,23,26,27,47-50]. In one study, patients with acute unipolar major depression were initially treated with open-label fluoxetine 20 mg/day for 12 weeks; those who responded (n = 395) were randomly assigned to abruptly stop the drug and substitute placebo, or to continue fluoxetine [27]. Recurrence of depression occurred in more than twice as many patients who abruptly stopped fluoxetine, compared with patients who did not (39 versus 17 percent).

Additional information about recurrence in the absence of maintenance treatment is discussed separately. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Relapse/recurrence in the absence of treatment'.)

GENERAL APPROACH TO DISCONTINUING ANTIDEPRESSANTS

Education about the potential for and nature of the antidepressant discontinuation syndrome at the onset of treatment may prevent patients from skipping doses or abruptly stopping antidepressants on their own and help reduce anxiety should adverse discontinuation effects occur [4,14,15,38,39,42]. Patients may be reassured to learn that discontinuation symptoms are

not unique to antidepressants and do not indicate that antidepressants cause addiction or dependence.

For patients who are treated with an antidepressant for at least several (eg, four to eight) weeks, and are stopping the drug without switching to another antidepressant, the general approach for minimizing discontinuation symptoms is to progressively taper the dose by a fixed amount or percent for at least two to four weeks [4,14,42,51]. For patients who are treated with antidepressants for a briefer time period (eg, two to three weeks), the drug can be tapered over one to two weeks, and for patients treated for less than two weeks, the drug can be abruptly stopped. This general approach is consistent with multiple treatment guidelines [5,38,39,52,53].

The specific duration of the taper depends primarily upon the clinical urgency and the drug's elimination half-life. Abrupt discontinuation may be necessary in some situations (eg, severe adverse effect, unintended pregnancy, or urgent surgery). Drugs with a longer half-life (eg, ≥24 hours) can generally be tapered over two to three weeks, whereas drugs with shorter half-lives (eg, <24 hours) are tapered over four weeks if it is practical. Although some studies report tapering schedules lasting for nine months or longer [9], this is not standard practice.

For patients who suffer discontinuation symptoms despite a gradual taper, the duration of the taper is extended beyond four weeks; the pace depends upon what the patient can tolerate. (See 'Prevention and management' above.)

Evidence supporting the general approach to discontinuing antidepressant drugs is limited:

- A small, randomized trial compared tapering over three days with tapering over 14 days in patients who were treated with citalopram, fluoxetine, paroxetine, or venlafaxine (n = 28), and found that the incidence of discontinuation and depressive symptoms was comparable (approximately 46 percent in each group) [26].

- A retrospective study of patients treated with SSRIs for at least two months found that the mean number of discontinuation symptoms was greater in 14 patients who abruptly stopped their antidepressant, compared with 52 patients who tapered the drug over 2 to 16 weeks (12 versus 6 symptoms) [18].

- A prospective observational study of euthymic patients who discontinued their antidepressants (n = 224) found that the median time to recurrence of depression was shorter in patients who discontinued their antidepressant over one to seven days, compared with patients who discontinued their antidepressant over 14 or more days (three versus eight months) [54].

Discontinuing an antidepressant may necessitate dose adjustments of co-prescribed medications because some antidepressants affect the metabolism of other drugs. As an example, fluoxetine potently inhibits the hepatic cytochrome enzyme CYP2D6. Specific interactions of antidepressants with other medications may be determined using the Lexicomp drug interactions tool included in UpToDate.

SPECIFIC DRUGS

Each subsection below describes aspects of the antidepressant discontinuation syndrome that are specific to individual antidepressants within each antidepressant class. In addition, aspects of the standard approach that vary for individual antidepressants are discussed below. The individual antidepressants that constitute each drug class are listed in the table (table 1).

SSRIs — Discontinuation symptoms can occur with any selective serotonin reuptake inhibitor (SSRI), and for each SSRI, the incidence and severity varies widely across different studies [9,14]. One review estimated that the incidence of clinically significant discontinuation symptoms with SSRIs was approximately 40 percent [14].

Randomized trials and observational studies indicate that the risk of discontinuation symptoms differs according to the drug's elimination half-life [2-5,9-12,14,23,26,27,47-50,54-56]:

- Least risk – Fluoxetine
- Intermediate risk – Citalopram, escitalopram, and sertraline
- Greatest risk – Fluvoxamine and paroxetine

As an example, across different randomized trials in which an SSRI was abruptly stopped after 12 weeks of treatment, the incidence of discontinuation symptoms in patients treated with fluoxetine or paroxetine was 7 and 35 percent [11]. In addition, an observational study of clinician initiated reports of adverse events found that discontinuation symptoms occurred 10 times more often with paroxetine than sertraline and 100 times more often with paroxetine than fluoxetine [34]. Other observational studies suggest that the risk of discontinuation symptoms with fluvoxamine is high and comparable to that of paroxetine [10,57,58]. As an example, a retrospective study found that among patients treated with fluvoxamine (n = 43) or paroxetine (n = 50), the frequency of discontinuation symptoms was comparable (14 and 20 percent of patients) [59]. Other factors that affect the frequency and severity of discontinuation symptoms are discussed elsewhere in this topic. (See 'Clinical features' above.)

To prevent onset of the antidepressant discontinuation syndrome with SSRIs, tapering over two to four weeks prior to discontinuation works well for the large majority of patients. (See

'General approach to discontinuing antidepressants' above.)

However, fluoxetine can be tapered over one to two weeks due to the relatively long elimination half-life of the drug (four to six days) and its active metabolite norfluoxetine (4 to 16 days). Alternatively, it is reasonable to abruptly stop fluoxetine [2,14,29]. Support for abrupt discontinuation includes randomized trials that found discontinuation symptoms were comparable for fluoxetine and placebo when placebo was abruptly substituted for fluoxetine [23,47]. In one trial, acutely depressed patients (n = 395) who responded to 12 weeks of fluoxetine 20 mg/day were randomly assigned to either continue fluoxetine or to abruptly switch to placebo [27]. During six weeks of follow-up, the incidence of adverse events in the two groups was similar. A subsequent, randomized trial in patients treated with fluoxetine (n = 37; mean dose 29 mg/day), for an average duration of one year, found that placebo substitution did not cause any discontinuation symptoms [48].

Paroxetine is discontinued over three to four weeks because it is most likely to cause discontinuation symptoms [1]. As an example, paroxetine 50 mg per day is tapered to 40 mg per day for week 1, 30 mg per day for week 2, 20 mg per day for week 3, and 10 mg per day for week 4. The drug is then stopped, unless discontinuation symptoms persist, in which case 5 mg/day can be prescribed for at least one or two additional weeks.

Patients who have difficulty tapering off of paroxetine or other SSRIs may benefit from immediately switching to fluoxetine 10 to 20 mg per day [38,39,42,43]. Patients switched to fluoxetine 20 mg per day continue the dose for one to two weeks after the discontinuation symptoms have abated, decrease the dose to 10 mg per day for one to two weeks, and then stop the drug. Patients switched to fluoxetine 10 mg per day continue the dose for one to two weeks after the discontinuation symptoms have resolved, after which fluoxetine is stopped. For patients who have difficulty discontinuing fluoxetine 10 mg per day, a liquid formulation is available for administering 5 mg per day for one to two weeks before stopping the drug.

The pharmacology, administration, and side effects of SSRIs are discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

SNRIs — Abrupt discontinuation of serotonin-norepinephrine reuptake inhibitors (SNRIs), or tapering them too quickly, often causes the antidepressant discontinuation syndrome (see 'Discontinuation syndrome' above) [17]. To prevent discontinuation symptoms, SNRIs are usually tapered gradually prior to discontinuation. (See 'General approach to discontinuing antidepressants' above.)

- **Desvenlafaxine** – Abrupt discontinuation of desvenlafaxine 50 mg/day or 100 mg/day may cause the discontinuation syndrome [60,61]. For patients treated with higher doses

who decide to stop the medication and are not switching to another antidepressant, we suggest tapering the drug over two to four weeks to reduce the risk of discontinuation symptoms (such as dizziness, headache, insomnia, irritability, and nausea) [61].

- **Duloxetine** – Based upon multiple randomized trials, we suggest tapering duloxetine over two to four weeks to reduce discontinuation symptoms. A pooled analysis of six randomized trials, lasting eight or nine weeks, compared duloxetine (40 to 120 mg/day) with placebo in patients with acute unipolar major depression (n = 870) [51]. Following abrupt discontinuation of treatment, the incidence of one or more discontinuation symptoms was greater with duloxetine than placebo (44 versus 23 percent). Symptoms that occurred more often with duloxetine included dizziness, nausea, and headache.

  However, a subsequent trial suggests that tapering duloxetine for one to two weeks may be a reasonable alternative [29]. A 10-week randomized trial compared duloxetine (mean dose 108 mg/day) with placebo for 10 weeks in patients with acute generalized anxiety disorder [62]. Afterwards, pharmacotherapy was tapered and stopped over one to two weeks, depending upon the dose. Among the 194 patients who entered the drug-tapering phase, the incidence of one or more discontinuation symptoms was comparable with duloxetine and placebo (19 and 15 percent).

- **Levomilnacipran** – We suggest that doses greater than 20 mg per day be tapered and discontinued over two to four weeks, consistent with procedures in the registration trials [63].

- **Milnacipran** – We suggest tapering milnacipran over two to four weeks prior to discontinuation [64]. In a randomized trial that included 46 patients with acute unipolar major depression who were treated with milnacipran 50 mg twice daily for six weeks, abrupt discontinuation caused at least one discontinuation symptom (eg, anxiety) in 13 percent; among patients who were treated for 24 weeks (n = 20), at least one discontinuation symptom occurred in 30 percent [65].

- **Venlafaxine** – We suggest tapering the daily dose of venlafaxine by 37.5 to 75 mg each week over four weeks to reduce discontinuation symptoms [15,29]. This schedule applies to both the immediate- and extended-release formulations. As an example, patients starting at 300 mg can be tapered by increments of 75 mg each week, whereas patients starting at 150 mg can be tapered by 37.5 mg each week. Patients starting at 225 mg can initially be tapered by 75 mg each week and then switch to 37.5 mg each week. Patients who have difficulty tapering off of venlafaxine may benefit from switching to fluoxetine 10

to 20 mg per day; the fluoxetine can then be tapered off, typically without discontinuation effects [38,39,42,43]. (See 'SSRIs' above.)

Abrupt discontinuation of venlafaxine commonly causes discontinuation symptoms due to its relatively short elimination half-life and that of its active metabolite desvenlafaxine [26,28,54,66-68]. Although venlafaxine extended-release has a longer elimination half-life than venlafaxine immediate release, the extended formulation half-life is nonetheless relatively short. The half-lives are approximately as follows:

- Venlafaxine immediate-release – 5 hours
- Desvenlafaxine immediate-release – 11 hours

- Venlafaxine extended-release – 11 hours
- Desvenlafaxine extended-release – 13 hours

The antidepressant discontinuation syndrome seen with venlafaxine is similar to that seen with SSRIs, but can be more severe. As an example, an eight-week randomized trial that compared venlafaxine extended-release (mean dose 95 mg/day) with escitalopram (mean dose 12 mg/day) in 288 patients with acute unipolar major depression found that after the drugs were abruptly stopped, the average number of discontinuation symptoms was greater with venlafaxine than escitalopram (five versus two) [55]. In addition, the incidence of 11 symptoms was greater in the venlafaxine group, including agitation, cognitive impairment, diaphoresis, dizziness, fatigue, nausea, restlessness, tremor, and unsteady gait. By contrast, escitalopram did not lead to a greater incidence of any discontinuation symptoms.

Discontinuation symptoms may perhaps be more likely to occur with desvenlafaxine or venlafaxine than other SNRIs [5,38,39]. A 10-week randomized trial compared venlafaxine extended-release (mean dose 184 mg/day), duloxetine (108 mg/day), and placebo in patients with acute generalized anxiety disorder [62]. Afterwards, pharmacotherapy was tapered and stopped over one to two weeks, depending upon the dose. Among the 298 patients who entered the drug-tapering phase, the incidence of one or more discontinuation symptoms was greater with venlafaxine than placebo (27 versus 15 percent). By contrast, the incidence was comparable with duloxetine and placebo (19 and 15 percent of patients) and with venlafaxine and duloxetine.

The pharmacology, administration, and side effects of SNRIs are discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

Atypical antidepressants — Atypical antidepressants include drugs that are not related to each other or to other drug classes.

- **Agomelatine** – Abrupt cessation of agomelatine 25 mg per day does not cause discontinuation symptoms [69]. For patients taking agomelatine 50 mg per day, we suggest tapering the dose to 25 mg for one week before stopping the drug.

- **Bupropion** – Although discontinuation symptoms from bupropion are uncommon, nevertheless, we taper the drug over two weeks before stopping it, consistent with prudent care (see 'General approach to discontinuing antidepressants' above). One case report described discontinuation symptoms, including anxiety, headache, insomnia, irritability, and myalgias [70]. (See 'Discontinuation syndrome' above.)

- **Mirtazapine** – We suggest tapering the dose over two to four weeks. One report described a case in which abrupt cessation of mirtazapine led to discontinuation symptoms, including anxiety, dizziness, insomnia, nausea, and paresthesias [71]; another case report described severe anxiety in the form of new onset panic attacks when mirtazapine was abruptly withdrawn [72].

The pharmacology, administration, and side effects of atypical antidepressants are discussed separately. (See "Atypical antidepressants: Pharmacology, administration, and side effects".)

Serotonin modulators

- **Nefazodone** – We suggest tapering the dose over one to two weeks to reduce discontinuation symptoms. However, the evidence indicates that a reasonable alternative is to abruptly stop the drug. In one study, patients with acute unipolar major depression who responded to 16 weeks of nefazodone (n = 259) were randomly assigned to maintenance treatment with nefazodone or abrupt placebo substitution [73]. Assessments 14 days after randomization found that the incidence of at least one new-onset or worsened adverse effect was comparable in patients who received active drug or placebo (17 and 21 percent of patients). At day 28, the incidence was again comparable with placebo and nefazodone (29 and 31). (See 'Discontinuation syndrome' above.)

- **Trazodone** – Trazodone is gradually tapered over two to four weeks prior to discontinuation. Rapid or abrupt discontinuation may be followed by discontinuation symptoms, including anxiety, headache, myalgia, nausea, and weakness [74,75].

- **Vilazodone** – Discontinuation symptoms due to abrupt discontinuation of vilazodone have not been described. Nevertheless, for patients who take 20 to 40 mg per day, we suggest

tapering the dose down to 10 mg per day over one to two weeks, prior to discontinuation [76].

- **Vortioxetine** – Clinicians can abruptly discontinue vortioxetine 10 mg per day, consistent with procedures in the registration trials [77]. For patients taking 15 or 20 mg per day, we suggest decreasing the dose to 10 mg per day for one week before stopping the drug, consistent with prescribing information in the vortioxetine label.

  Evidence regarding minimal discontinuation symptoms with vortioxetine includes the following:

  - A review of registration trials by the US Food and Drug Administration found that abrupt discontinuation of vortioxetine 10 mg per day did not cause discontinuation symptoms [77]. However, abruptly discontinuing a dose of 15 or 20 mg per day caused dizziness, headache, mood lability, muscle tension, and/or rhinorrhea in approximately 5 percent of patients.

  - Three randomized trials lasting eight weeks compared the efficacy of vortioxetine (10, 15, or 20 mg/day) with placebo in patients with acute unipolar major depression (n >1300), and then abruptly stopped the study drugs [78]. During the subsequent two weeks, a pooled analysis found that the level of discontinuation symptoms was comparable for the two groups.

  - A maintenance treatment study compared vortioxetine (5 or 10 mg/day) with placebo for up to 64 weeks in patients who remitted from unipolar major depression (n = 396), and then abruptly stopped the study drugs [79]. During the subsequent two weeks, the level of discontinuation symptoms was comparable for the two groups.

  The safety of vortioxetine regarding the antidepressant discontinuation syndrome is probably due in part to its relatively long elimination half-life, which is 66 hours (table 2) [53].

  The pharmacology, administration, and side effects of serotonin modulators are discussed separately. (See "Serotonin modulators: Pharmacology, administration, and side effects".)

Tricyclics — Tricyclic (and tetracyclic) antidepressants are generally tapered over two to four weeks [29,80] (see 'General approach to discontinuing antidepressants' above). Abrupt discontinuation can cause discontinuation symptoms, including agitation, anxiety, chills, diaphoresis, headache, insomnia, irritability, malaise, myalgia, and nausea (see 'Clinical

features' above), and may rarely cause akathisia, cardiac arrhythmia, and parkinsonism [10,81,82].

The pharmacology, administration, and side effects of tricyclics are discussed separately. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

MAOIs — Monoamine oxidase inhibitors (MAOIs) are generally tapered for at least four weeks prior to stopping the drug [29]. Moderate to severe discontinuation symptoms that arise while tapering phenelzine or tranylcypromine are managed by resuming the daily dose at which there were no symptoms, and then tapering the dose more slowly (eg, phenelzine by 15 mg or tranylcypromine by 10 mg every two weeks [29,81]). Abruptly stopping MAOIs can cause discontinuation symptoms, including anxiety, agitation, insomnia, chills, diaphoresis, headache, irritability, malaise, and nausea [16,44,57,81] (see 'Clinical features' above). In addition, reports have described more serious discontinuation symptoms, including delirium, myoclonic jerks, and psychosis.

The pharmacology, administration, and side effects of MAOIs are discussed separately. (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

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

SUMMARY

- **Indications for discontinuation** – Indications for discontinuing antidepressant medications include lack of efficacy, serious adverse effect, unintended pregnancy, and imminent surgery. (See 'Indications for discontinuation' above.)
- **Antidepressant discontinuation syndrome** – The antidepressant discontinuation syndrome comprises one or more adverse effects that can occur if patients discontinue antidepressants that have been taken continuously for at least several (eg, four) weeks, especially if the medication is stopped abruptly or tapered too quickly. All antidepressant classes can cause the discontinuation syndrome. (See 'Overview' above.)
  - **Incidence and risk factors** – Multiple studies suggest the discontinuation syndrome occurs in approximately 30 percent of patients who stop an antidepressant. Risk factors include shorter antidepressant elimination half-life (eg, <24 hours), higher antidepressant doses, and longer duration of treatment at therapeutic doses (eg, at least four to eight weeks). (See 'Incidence and risk factors' above.)
  - **Clinical features** – The most common discontinuation symptoms appear to be:
    - Dizziness
    - Fatigue
    - Headache
    - Nausea

    Other common symptoms include agitation, anxiety, chills, diaphoresis, dysphoria, electric shock-like sensations, insomnia, irritability, myalgias, paresthesias, rhinorrhea, tremor, and vivid dreams.

    Onset of the antidepressant discontinuation syndrome typically occurs within a few days of abruptly stopping antidepressants or tapering them too quickly. The syndrome

is usually mild and dissipates spontaneously over one to three weeks; however, symptoms can persist for a month or longer. (See 'Clinical features' above.)

- **Prevention and management** – Strategies for preventing the antidepressant discontinuation syndrome include educating patients to not abruptly stop their medication, and not tapering medications too quickly. For patients who develop the antidepressant discontinuation syndrome after abruptly stopping treatment, we generally resume the medication at the dose that was used prior to discontinuation. If the discontinuation syndrome occurs despite using a relatively gradual tapering schedule to stop the antidepressant, management of the syndrome depends upon the severity of symptoms and time of onset. (See 'Prevention and management' above.)

- **General approach for discontinuing antidepressants** – For most patients who are discontinuing an antidepressant after at least four to eight weeks of use, and are stopping the drug without switching to another antidepressant, we suggest tapering the dose over two to four weeks (**Grade 2C**). Exceptions include fluoxetine, which can be stopped abruptly, and monoamine oxidase inhibitors (MAOIs), which are generally tapered for at least four weeks before stopping the drug.

  Patients who are treated with an antidepressant for less time (eg, two to three weeks) can taper the drug over one to two weeks, and patients treated for less than two weeks can abruptly stop the drug. (See 'General approach to discontinuing antidepressants' above.)

- **Specific drugs** – The general approach for discontinuing antidepressants may vary for individual antidepressants; the specific antidepressants that constitute each drug class below are listed in the table (table 1).

  - **Selective serotonin reuptake inhibitors (SSRIs)** – Tapering SSRIs over two to four weeks prior to stopping the drug works well for a large majority of patients. However, fluoxetine can be tapered over one to two weeks due to the relatively long elimination half-life of the drug and its active metabolite. Alternatively, it is reasonable to abruptly stop fluoxetine. (See 'SSRIs' above.)

  - **Serotonin-norepinephrine reuptake inhibitors (SNRIs)** – SNRIs are usually tapered and discontinued over two to four weeks. Discontinuation symptoms may perhaps be more likely to occur with desvenlafaxine or venlafaxine than other SNRIs. (See 'SNRIs' above.)

  - **Atypical antidepressants and serotonin modulators** – Discontinuation symptoms and tapering schedules vary among atypical antidepressants and serotonin

modulators. (See 'Atypical antidepressants' above and 'Serotonin modulators' above.)

- **Tricyclics** – Tricyclic antidepressants are generally tapered over two to four weeks. (See 'Tricyclics' above.)
- **MAOIs** – MAOIs are generally tapered for at least four weeks before stopping the drug. (See 'MAOIs' above.)

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