Pediatric unipolar depression and pharmacotherapy: Choosing a medication

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INTRODUCTION

There have been several phases of pharmacotherapy studies for unipolar depression in children and adolescents [1]:

- Initial studies
- Tricyclic antidepressant phase
- Second-generation antidepressant phase, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)
- The era of the US Food and Drug Administration boxed warning about antidepressants and suicidal ideation and behavior (see "Effect of antidepressants on suicide risk in children and adolescents")

The initial studies that investigated pharmacotherapy for pediatric depression occurred in the 1960s and were limited by several problems (eg, mixed diagnostic groups and different outcome measures across studies). Nonetheless, these studies established that properly monitored patients could safely tolerate antidepressants, which was necessary for conducting the randomized trials that ushered in the subsequent eras.

This topic reviews the choice of acute pharmacotherapy for children and adolescents with depressive disorders and the use of continuation and maintenance treatment, as well as the indications and efficacy of selective SSRIs, SNRIs, tricyclic antidepressants, and other antidepressants in depressed youth. Separate topics discuss the general principles for prescribing pharmacotherapy for pediatric depression, the effect of antidepressant medications on suicide risk in children and adolescents, psychosocial treatments for adolescent depression, an overview of treating pediatric depression, and the pharmacology, administration, and side effects of antidepressants in adults.

- (See "Pediatric unipolar depression and pharmacotherapy: General principles".)
- (See "Effect of antidepressants on suicide risk in children and adolescents".)
- (See "Pediatric unipolar depression: Psychotherapy".)
- (See "Overview of prevention and treatment for pediatric depression".)
- (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Serotonin modulators: Pharmacology, administration, and side effects".)
- (See "Atypical antidepressants: Pharmacology, administration, and side effects".)
- (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

CHOICE OF MEDICATION FOR ACUTE TREATMENT

Decisions about using pharmacotherapy in pediatric depression must be individualized after discussing the benefits and risks with patients and families. Additional information about choosing a treatment regimen is discussed separately. (See "Overview of prevention and treatment for pediatric depression", section on 'Choice of therapy'.)

First-line — For children and adolescents with acute depressive disorders, first-line pharmacotherapy is fluoxetine [2]. There is more consistent, high-quality evidence for the efficacy of fluoxetine than other antidepressants [3,4]. The efficacy of fluoxetine is discussed elsewhere in this topic. (See 'Fluoxetine' below.)

Choosing an antidepressant other than fluoxetine as first-line treatment may be reasonable for reasons that include:

- Desire to avoid specific adverse effects (table 1)
- Response to a different antidepressant during a prior depressive episode

- Response to a different antidepressant by parent or sibling
- Known hypersensitivity to fluoxetine in the patient or family
- Patient and/or family preference
- Potential drug-drug interactions

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

Second-line — Acute pediatric depressive episodes do not remit with fluoxetine in approximately 30 percent of patients [3]. For these treatment-resistant patients, we suggest sertraline [2]; however, escitalopram or citalopram are reasonable choices, based upon their efficacy in randomized trials [5]. Another reasonable alternative is venlafaxine, which appears to be comparable to selective serotonin reuptake inhibitors (SSRIs) in treatment-resistant patients [6]. We typically do not use paroxetine for pediatric depression because of its lack of demonstrated efficacy [5,7]. The efficacy of sertraline, escitalopram, citalopram, venlafaxine, and paroxetine is discussed elsewhere in this topic. (See 'Other specific SSRIs' below and 'Indications and efficacy' below.)

Third-line — When third-line therapy is necessary for pediatric depression, we recommend consultation with or referral to a child and adolescent psychiatrist.

For children and adolescents with acute depressive disorders who do not respond to fluoxetine as well as a second trial with a different SSRI and a third trial with venlafaxine, we suggest bupropion or duloxetine, based upon randomized trials in adults and low-quality studies in youth. The evidence supporting the use of these medications is discussed elsewhere. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Antidepressants' and 'Other antidepressants' below.)

CONTINUATION AND MAINTENANCE TREATMENT

Based upon randomized trials, children and adolescents with unipolar major depression who remit with pharmacotherapy should continue the same regimen for at least another 6 to 12 months [8]. Relapse frequently occurs in pediatric patients who stop their antidepressants soon after their depressive syndromes improve [9-11]. (See "Overview of prevention and treatment for pediatric depression".)

Evidence for the efficacy of continuation and maintenance pharmacotherapy includes a meta-analysis of three randomized trials (164 children and adolescents with unipolar major depression who remitted with treatment) that compared pharmacotherapy (fluoxetine or

sertraline) with placebo for 24 to 52 weeks [12]. Relapse was less likely in patients who received medications than placebo (odds ratio 0.3, 95% CI 0.2-0.6). In the biggest trial (n = 102), relapse occurred in fewer patients who received fluoxetine than placebo (42 versus 69 percent) [13]. In addition, randomized trials in depressed adults who remitted with antidepressants have established that recurrence is less frequent in patients who continue and maintain pharmacotherapy. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Antidepressant medications'.)

Based upon adult studies and clinical experience with youth, maintenance pharmacotherapy beyond 6 to 12 months for children and adolescents is often indicated in the following situations [8]:

- The presenting depressive episode included:
  - Psychotic features (eg, delusions or hallucination)
  - Moderate to severe suicidal ideation or behavior
  - Moderate to severe functional impairment
  - Treatment resistance
  - A duration ≥2 years
  - An unsuccessful prior attempt to taper the antidepressant
- The course of illness includes three or more episodes of unipolar major depression

Maintenance studies extending beyond one year have not been conducted in youth, and thus the long-term effects of antidepressants on maturation and development in pediatric patients are unknown.

PSYCHOTIC DEPRESSION

Pediatric patients with psychotic features (eg, delusions and hallucinations) are typically referred to mental health clinicians for evaluation and treatment. (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis" and "Unipolar major depression with psychotic features: Acute treatment".)

OVERVIEW OF EFFICACY

For children and adolescents with depressive disorders, randomized trials have shown that antidepressants collectively are beneficial [14-16]. However, other analyses indicate that the efficacy of antidepressants varies among different classes. As an example, selective serotonin reuptake inhibitors (SSRIs) collectively have been found to be efficacious (see 'Efficacy' below), whereas tricyclic antidepressants often fail to demonstrate any benefit. (See 'Efficacy' below.)

In addition, within a single antidepressant class, the efficacy of individual antidepressants for childhood and adolescent depression may vary. One such example is the SSRIs; fluoxetine has demonstrated efficacy in multiple meta-analyses of randomized trials, whereas the efficacy of paroxetine is less well established. However, no head to head trials have compared one SSRI with another. (See 'Efficacy' below.)

Outcomes in pharmacotherapy studies of depressed youth can vary because of methodologic issues. As an example, lower placebo response rates are more likely to occur in trials that are conducted at only a few sites (eg, 3) rather than many sites (eg, 10) [17]. In addition, it may be easier to demonstrate the benefits of antidepressants in studies that are conducted by experienced investigators at university settings with more severely ill patients.

All antidepressants — Antidepressants as a class are efficacious for pediatric depressive disorders. A pooled analysis of 29 randomized trials (3069 patients, age ≤20 years, treated for a median of eight weeks) compared antidepressants (primarily SSRIs or tricyclics) with placebo, and found that response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received antidepressants than placebo (60 versus 49 percent) [14].

Although a network meta-analysis concluded that among 14 different antidepressants, only fluoxetine was efficacious [18], we disagree with this conclusion. The study was rigorous and included 34 randomized trials with more than 5000 pediatric patients with acute major depression; nevertheless, the conclusion that only fluoxetine is effective is not justified for several reasons [2]:

- Prior to the network meta-analysis, the investigators initially conducted standard meta-analyses of randomized trials to directly compare one drug with placebo or another active drug. The standard meta-analyses found that escitalopram, fluoxetine, nefazodone, and sertraline were each superior to placebo. In addition, paroxetine was superior to clomipramine (and fluoxetine was superior to nortriptyline).

- Next, the authors performed a network meta-analysis using direct comparisons between two drugs or between a drug and placebo, as well as indirect comparisons of the drugs through their relative effect with a common comparator (typically placebo). The network meta-analysis found that for the primary outcome of improvement in depressive

symptoms, only fluoxetine was better than placebo; however, this may be due to the questionable assumption that variability (heterogeneity) was the same in each pairwise comparison. In addition, for the secondary outcome of response (reduction of baseline symptoms ≥50 percent), duloxetine and nefazodone, as well as fluoxetine, were each superior to placebo.

- Many patients who are treated with antidepressants have severe and chronic depressive symptoms; these patients may be more likely to respond to active drugs than placebo, but are nearly always excluded from clinical trials. In addition, the network meta-analysis excluded studies of patients with treatment-resistant patients (eg, patients who do not respond to initial treatment with psychotherapy).

Second-generation antidepressants — Second-generation antidepressants include SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants (eg, mirtazapine), and serotonin modulators (eg, vilazodone and vortioxetine), which were developed after the first-generation of antidepressants (tricyclics and monoamine oxidase inhibitors). Based upon randomized trials, second-generation antidepressants collectively are effective for juvenile unipolar major depression:

- A meta-analysis of 15 trials (n >2900 patients) compared antidepressants (SSRIs or venlafaxine) with placebo and found that remission or response occurred in more patients treated with antidepressants (risk ratio 1.2, 95% CI 1.1-1.3) [5]. In addition, antidepressants improved functioning, and subgroup analyses indicated that antidepressants were beneficial for both children (aged 6 to 12 years) and adolescents (aged 13 to 18 years). However, adverse effects occurred in more patients who received antidepressants than placebo (risk ratio 1.11, 95% CI 1.05-1.17).

  Subsequently, the same investigators conducted a network meta-analysis of 26 trials in youth aged 6 to 18 years (n >6400), using direct comparisons between two drugs or between a drug and placebo, as well as indirect comparisons of the drugs through their relative effect with a common comparator such as placebo (conventional meta-analyses use only direct comparisons) [4]. The results suggested that most newer antidepressants may reduce depressive symptoms compared with placebo, and that among most antidepressants, there were small differences in the reduction of depressive symptoms. The investigators concluded that first-line options include fluoxetine, as well as sertraline, escitalopram, and duloxetine.

- A pooled analysis of 13 randomized trials compared antidepressants (SSRIs, mirtazapine, nefazodone, or venlafaxine) with placebo in 2910 children and adolescents treated for a

median of eight weeks [15]. Response occurred in more patients treated with antidepressants than placebo (61 versus 50 percent). However, antidepressants appeared to be less efficacious for longer episodes of depression. In addition, subgroup analyses found that for adolescents (age ≥12 years), antidepressants were superior to placebo; in children (age <12 years), there was a trend for a greater rate of response with antidepressants.

The risk of suicidal ideation and behavior with second-generation antidepressants are discussed separately. (See "Effect of antidepressants on suicide risk in children and adolescents", section on 'Randomized trials'.)

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The selective serotonin reuptake inhibitors (SSRIs) include [19]:

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

The pharmacology of SSRIs (including their structure, pharmacodynamics, pharmacokinetics, and drug-drug interactions) is discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Pharmacology'.)

Indications — SSRIs are indicated for children and adolescents with moderate to severe unipolar major depression (table 2) as well as other depressive disorders accompanied by moderate to severe functional impairment. However, these drugs are generally not prescribed for patients who have subsyndromal depressive symptoms or mild depressive disorders.

Efficacy

SSRIs as a class — SSRIs as a class are effective for pediatric depressive disorders:

- In a pooled analysis of 12 randomized trials (2220 patients with depressive disorders, age ≤20 years, treated for 7 to 12 weeks) that compared SSRIs (citalopram, fluoxetine, paroxetine, and sertraline; two trials examined venlafaxine) with placebo, response (reduction of baseline symptoms ≥50 percent) occurred in more patients treated with

SSRIs than placebo (59 versus 51 percent) [14]. Among the antidepressants, fluoxetine had the largest pooled efficacy.

- SSRIs are more efficacious than tricyclics for pediatric depression. A meta-analysis of five randomized trials (422 depressed patients, mean age 15 years) compared SSRIs with tricyclics and found a significant, clinically moderate effect favoring SSRIs over tricyclics [20]. Heterogeneity across studies was moderate.

- A meta-analysis of 13 randomized trials compared SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline) with placebo in children and adolescents with unipolar major depression (n >3000); SSRIs were superior to placebo and most of the benefit accrued within the first four weeks of treatment [21]. Although the study found no advantage for one SSRI over the other SSRIs, the paucity of trials limited the statistical power to detect a difference.

Fluoxetine — Fluoxetine is efficacious for treating children and adolescents with unipolar major depression [22-27]. A meta-analysis of patient level data from four randomized trials (708 youths with major depression) lasting six weeks found that response occurred in more patients who received fluoxetine than placebo (30 versus 6 percent) [3]. Other meta-analyses have also demonstrated the efficacy of fluoxetine [5,15,18]. In addition, fluoxetine is effective for continuation treatment [13,26]. (See 'Continuation and maintenance treatment' above.)

However, fluoxetine can cause side effects in depressed youth. A meta-analysis of two randomized trials (440 patients) found that adverse events occurred in more patients who received fluoxetine than placebo (risk ratio 1.2, 95% CI 1.1-1.4) [5]. One trial found that abdominal pain, diarrhea, influenza, insomnia, sedation, sinusitis, or vomiting were among the most common complaints in patients who received fluoxetine during 12 weeks of treatment, and the incidence of each adverse event was at least two times greater among patients who received fluoxetine than placebo [24]. Nevertheless, the frequency of these adverse events in patients receiving fluoxetine was low, ranging from two to six percent of patients. Additional information about side effects is discussed elsewhere in this topic. (See 'Adverse side effects' below.)

Other specific SSRIs — Sertraline is modestly efficacious for treating children and adolescents with depressive disorders, based upon randomized trials, and escitalopram and citalopram may also be effective. By contrast, evidence for the efficacy of fluvoxamine is lacking, and randomized trials with paroxetine have found no benefit [5].

- **Sertraline** – Sertraline appears to be efficacious for pediatric unipolar major depression. A pooled analysis of two similar, 10 week randomized trials compared sertraline (mean dose

131 mg per day) with placebo in 364 patients [28]. Response (reduction of baseline symptoms ≥40 percent) occurred in more patients who received sertraline than placebo (69 versus 59 percent). However, discontinuation of treatment due to side effects occurred in more patients treated with sertraline than placebo (9 versus 3 percent); adverse effects associated with sertraline included agitation, anorexia, diarrhea, and vomiting.

- **Escitalopram** – The benefit of escitalopram for children and adolescents with depressive disorders is modest, based upon two randomized trials:

  - An eight-week trial (n = 261 youth 6 to 17 years old) found that improvement of symptoms with escitalopram (mean dose 12 mg per day) and placebo was comparable [29]. However, a subgroup analysis in adolescents (age 12 to 17 years; n = 157) found that improvement of depressive symptoms was greater with escitalopram than placebo, consistent with results from one meta-analysis [15] discussed elsewhere in this topic. (See 'Second-generation antidepressants' above.)

  - Another-eight week trial compared escitalopram (mean dose 13 mg per day) with placebo in 311 patients and found that improvement was greater with escitalopram [30].

  - A meta-analysis of the two trials (572 patients) found that there was a trend for a greater rate of response or remission with escitalopram than placebo (risk ratio 1.19, 95% CI 0.97-1.45) [5].

- **Citalopram** – Citalopram may be beneficial for children and adolescents with depressive disorders, but the results across randomized trials are inconsistent:

  - An eight-week trial compared citalopram (mean dose 24 mg per day) with placebo in 174 patients [31]. Complete or nearly complete resolution of symptoms occurred in more patients who received citalopram than placebo (36 versus 24 percent), and discontinuation of treatment due to side effects in both groups was 6 percent.

    A 12-week trial (n = 233) found that the rate of remission with citalopram (mean dose 26 mg per day) and placebo was comparable (33 and 36 percent of patients) [32]. However, treatment was contaminated in that psychotherapy was allowed outside of the study protocol and administered to 69 percent of the patients. Among patients who did not receive psychotherapy (n = 65), remission occurred in more patients treated with citalopram than placebo (45 versus 19 percent).

A meta-analysis of the two trials (407 patients) found that remission with citalopram and placebo was comparable (risk ratio 1.2, 95% CI 0.7-1.9); heterogeneity across studies was moderate to large [5].

- In a third trial, adolescents who did not respond to initial treatment with an SSRI were assigned to switch to a different SSRI or venlafaxine [6]. Among those who switched to citalopram (n = 34) or fluoxetine (n = 84), response was comparable for the two groups (56 and 49 percent).

The US Food and Drug Administration issued warnings that citalopram causes dose-dependent QT interval prolongation that can lead to arrhythmias, and thus recommends that the maximum dose should not exceed 40 mg per day [33,34]. We generally get an electrocardiogram for patients who are taking 20 or 30 mg per day and are considering a dose increase to 40 mg per day. Additional information about the cardiac effects of SSRIs is discussed separately. (See 'Cardiac events' below and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Cardiac'.)

- **Fluvoxamine** – Although randomized trials have demonstrated the efficacy and safety of fluvoxamine for treating pediatric anxiety disorders [35,36], there are no high-quality studies in patients with depressive disorders

- **Paroxetine** – Paroxetine does not appear to help children and adolescents with depressive disorders. A meta-analysis of four randomized trials (704 patients) found that response or remission with paroxetine and placebo was comparable (risk ratio 1.1, 95% CI 0.9-1.4) [5].

Possible explanations for the lack of proven efficacy of some specific SSRIs for pediatric depressive disorders include the following [5,37,38]:

- The studies were performed quickly in response to the United States Food and Drug Administration's promise of exclusivity to manufacturers who conducted clinical trials of medications in children and adolescents. This may have contributed to suboptimal study design with smaller samples and shorter duration. Support for this hypothesis includes a finding that studies with more study sites had higher placebo response rates, suggesting that trials conducted quickly with a large number of sites may not have carefully screened for clinically significantly depressed patients, and thus enrolled youth with less severe illness [15].

  Increasing placebo response rates in pediatric patients with unipolar major depression decreases the ability to detect a statistically significant difference between active treatment and placebo [17,39-42]. Other factors associated with higher placebo effects

include study sites with relatively low enrollment numbers, as well as studies that include a large number of clinic visits, which provide repeated contact with solicitous research assistants and other support staff. In addition, placebo response appears to be affected by the disorder studied, and is higher in pediatric major depression than in anxiety disorders and obsessive-compulsive disorder [39].

- The controlled trials were not preceded by studies that established the most appropriate dose; there is evidence that metabolism of some SSRIs occurs more quickly in pediatric patients than adults [43].

- There may be greater heterogeneity in response among children and adolescents than in adults, perhaps due to varying rates of maturation in the neural networks involved in depressive disorders.

Adverse side effects — The SSRIs are generally well tolerated with minimal adverse effects (table 3 and table 1) that tend to be dose dependent. Most side effects subside over one to two weeks or with dose reduction [8]. The most common adverse effects include:

- Abdominal pain
- Agitation, jitteriness, or akathisia (restlessness and inability to sit still)
- Diarrhea
- Headache
- Nausea
- Sleep changes

Additional information about SSRI side effects is discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Side effects'.)

The risk of patients with bipolar disorder switching from major depression (table 4) to hypomania (table 5) or mania (table 6) due to treatment with antidepressants is discussed separately. (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants", section on 'Risk of switching to mania'.)

SSRIs may inhibit hepatic cytochrome P450 enzymes that metabolize other medications, thereby causing drug-drug interactions. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Drug-drug interactions'.)

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

Observational studies have found associations between SSRIs and other adverse effects; however, in many instances, the low quality of the evidence leads us to suggest that clinicians should not change their practice with regard to prescribing SSRIs. As an example, a retrospective national registry study found that use of SSRIs among individuals aged 15 to 24 years was associated with convictions for violent criminal behavior [44]. Problems with the study include confounds (eg, symptom severity or alcohol abuse); reverse causality (ie, individuals may have been more likely to receive SSRIs when they were at greater risk of committing violent crimes); and the finding that low doses, but not moderate or higher doses, were associated with violent crime. The authors concluded that their study did not warrant changes in clinical practice.

Low-quality studies have also examined the association between exposure to SSRIs and side effects, such as decreased bone density and bleeding, including upper gastrointestinal bleeding, intraoperative bleeding, and stroke. (See "Drugs that affect bone metabolism", section on 'Antidepressants' and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Bleeding'.)

Activation — Antidepressant-related behavioral activation is characterized by symptoms of disinhibition, restlessness, impulsivity, hyperactivity, irritability and insomnia [45]. The symptoms tend to occur together and frequently emerge early in treatment or following an increase in dose. The risk of activation appears to be greater in children than adolescents, as well as patients with rapidly increasing serum concentrations or relatively high concentrations. Symptoms resolve if the dose is decreased or the antidepressant is stopped. There appears to be a slight chance of recurrence with exposure to another antidepressant.

Cardiac events — Citalopram and escitalopram may be associated with adverse cardiac events in pediatric patients, but these rarely occur. A retrospective study of insurance claims data (n >100,000 patients, age <18 years) examined the risk of ventricular arrhythmia, cardiac arrest, and sudden death within 12 months of starting an SSRI [46]. Analyses were adjusted for propensity to receive a specific SSRI and factors such as age, sex, psychiatric and general medical diagnoses, and other medications. Forty cardiac events occurred, and the estimated risk was greater with citalopram (adjusted hazard ratio 3.5, 95% CI 1.1-11.5) and escitalopram (adjusted hazard ratio 3.3, 95% CI 1.1-10.1) than fluoxetine. By contrast, the risk with paroxetine or sertraline was comparable to that of fluoxetine.

Additional information about SSRIs and cardiac side effects is discussed separately in the context of adults. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Cardiac'.)

Serotonin syndrome — Serotonin syndrome is a potentially lethal condition caused by overstimulation of central and peripheral serotonin receptors. Clinical features include anxiety, agitation, delirium, diaphoresis, tachycardia, hypertension, hyperthermia, gastrointestinal distress, tremor, muscle rigidity, myoclonus, and hyperreflexia. It typically results from an interaction between multiple medications that increase serotonergic neurotransmission (table 7). However, the syndrome can occur after initiating or increasing a single serotonergic drug. It is not known whether SSRIs differ in their likelihood to cause this syndrome. The epidemiology, clinical features, diagnosis, treatment, and prevention of serotonin syndrome are discussed separately. (See "Serotonin syndrome (serotonin toxicity)".)

Suicidality — There is a potential for increased suicidal ideation and behavior in pediatric patients who initiate treatment with antidepressants or with dose increases or decreases. (See "Effect of antidepressants on suicide risk in children and adolescents".)

Discontinuation (withdrawal) syndrome — Abrupt discontinuation of SSRIs can cause withdrawal symptoms. (See "Pediatric unipolar depression and pharmacotherapy: General principles", section on 'Discontinuing pharmacotherapy'.)

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

The serotonin-norepinephrine reuptake inhibitors (SNRIs) include venlafaxine, desvenlafaxine (the active, major metabolite of venlafaxine), duloxetine, milnacipran, and levomilnacipran. The pharmacology, administration, and side effects of SNRIs in the context of treating adults are discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

Indications and efficacy — Although there is limited evidence from randomized studies to support the use of SNRIs as initial treatment of depressive disorders in children and adolescents, these medications appear to help patients who do not respond to initial treatment with a selective serotonin reuptake inhibitor (SSRI) or to a second trial with an alternate SSRI [47]. (See 'Second-line' above.)

Venlafaxine — Venlafaxine may possibly provide a small benefit for the initial treatment of youth with unipolar major depression [48]. A meta-analysis of two randomized trials (n = 334 children and adolescents with unipolar major depression, treated for eight weeks) compared venlafaxine extended release with placebo, and found that there was a trend for a greater rate of a modest response (reduction of baseline symptoms ≥35 percent) in patients treated with venlafaxine (risk ratio 1.2, 95% CI 1.0-1.4) [5].

In addition, venlafaxine appears to be useful for depressed, pediatric patients who are unresponsive to initial treatment with SSRIs. The Treatment of Resistant Depression in Adolescents (TORDIA) trial enrolled 334 adolescents with unipolar major depression who did not respond to initial treatment with an SSRI, and randomly assigned them to switch to venlafaxine (150 to 225 mg per day), a different SSRI (citalopram, fluoxetine, or paroxetine 20 to 40 mg per day), venlafaxine plus cognitive-behavioral therapy (CBT), or a different SSRI plus CBT [6]. The study lasted 12 weeks, and found that the response (reduction of baseline symptoms ≥50 percent) in patients who received venlafaxine and patients who received a different SSRI was similar (48 and 47 percent). However, venlafaxine caused greater increases in diastolic blood pressure and pulse, and more skin problems such as itching and rash. In addition, follow-up 48 weeks after study intake found that patients who received SSRIs had a more rapid decline in self-reported depressive symptoms, including suicidal ideation, than patients treated with venlafaxine [49].

Desvenlafaxine — Randomized trials indicate that desvenlafaxine is not efficacious for pediatric depression:

- In one trial, children and adolescents with unipolar major depression (n = 341) were randomly assigned to eight weeks of treatment with lower dose desvenlafaxine (20, 30, or 35 mg/day based upon baseline weight), higher dose desvenlafaxine (25, 35, or 50 mg/day), or placebo [50]. Improvement was comparable for the three groups.

- In another trial, children and adolescents with unipolar major depression (n = 337) were randomly assigned to eight weeks of treatment with desvenlafaxine (25, 35, or 50 mg/day based upon baseline weight), fluoxetine (20 mg/day), or placebo [51]. Response was comparable in patients who received desvenlafaxine or placebo (69 and 63 percent), whereas response occurred in more patients who received fluoxetine than placebo (78 versus 63 percent).

Duloxetine — Two randomized trials in children and adolescents with unipolar major depression found that the benefit of duloxetine and placebo was comparable [52,53]. However, the trials also found that fluoxetine was not superior to placebo; given that multiple randomized trials have demonstrated that fluoxetine is efficacious for youth with major depression (see 'Fluoxetine' above), the two trials investigating duloxetine are failed, uninformative trials. Both trials were conducted by the same group of investigators, and the acute phase of treatment lasted 10 weeks:

- One trial randomly assigned youth with major depression (n = 463) to duloxetine 30 mg/day, duloxetine 60 mg/day, fluoxetine 20 mg/day, or placebo [52]. Response (reduction

of baseline symptoms ≥50 percent) in each of the four groups was comparable (roughly 65 percent of patients).

- The second trial randomly assigned youth with major depression (n = 337) to duloxetine (flexible dose ranging from 60 to 120 mg/day), fluoxetine (flexible dose ranging from 20 to 40 mg/day), or placebo [53]. Response in each group was comparable (approximately 65 percent of patients).

Case reports suggest that duloxetine may possibly be useful for comorbid depression and pain in pediatric patients [54,55].

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants include amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine. Although tricyclics are efficacious for adults with depression [56,57], studies in children and adolescents often fail to demonstrate any benefit [14,58,59].

Indications — Tricyclics are rarely indicated for depressed youth because of a frequent lack of efficacy, an unfavorable side effect profile, high lethality in overdose, and the availability of selective serotonin reuptake inhibitors (SSRIs). However, it is reasonable to administer tricyclics in patients who do not respond to multiple trials of SSRIs, serotonin-norepinephrine reuptake inhibitors, and other antidepressants [47].

Efficacy — For pediatric patients with depressive disorders, the benefit of tricyclics is modest at best and may be limited to adolescents:

- In a meta-analysis of nine randomized trials (454 children and adolescents) that compared tricyclics with placebo, recovery/response was comparable (relative risk 1.1, 95% CI 0.9-1.3) [60]. In addition, tricyclics caused more adverse effects, including dry mouth, orthostatic hypotension, tremor, and vertigo.

  However, a second analysis (13 trials, 533 patients) examined reduction of depression rating scale scores and found a clinically small advantage favoring tricyclics (amitriptyline, desipramine, imipramine, or nortriptyline) over placebo; heterogeneity was moderate [60]. Subgroup analyses found that in adolescents (aged 13 to 18 years), tricyclics provided a clinically moderate benefit; by contrast, improvement of symptoms in children (aged 6 to 12 years) was comparable for tricyclics and placebo.

- A meta-analysis of 14 randomized trials (660 patients with depressive disorders, age ≤20 years) compared tricyclics with placebo, and found that there was a trend for a greater rate of response (reduction of baseline symptoms ≥50 percent) in patients treated with tricyclics (relative risk 1.15, 95% CI 0.98-1.34) [14]. Antidepressants provided one more response than placebo for every 15 patients treated with each regimen.

Tricyclics are less efficacious than SSRIs. (See 'SSRIs as a class' above.)

Adverse effects — Tricyclic side effects in children and adolescents include dry mouth (which may lead to dental caries), orthostatic hypotension, tremor, and vertigo [60]. Tricyclics may also affect heart rate, blood pressure, and electrocardiogram parameters (eg, tachycardia, postural hypotension, hypertension, increased PR interval, QRS duration, and corrected QT interval [QTc]). The long-term clinical significance of these cardiac changes is not known [58]. Additional information about the adverse effects of tricyclics is discussed separately in the context of adults. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Side effects'.)

Overdose — Tricyclics are highly lethal in overdose. The toxicity is usually due to prolongation of the QT interval, leading to arrhythmias. Overdose of cyclic antidepressants can also cause anticholinergic toxicity and seizures. (See "Tricyclic antidepressant poisoning".)

We recommend that parents or caregivers assume responsibility for storing and administering tricyclics because of the risk of lethality in overdose, particularly for young patients and those at risk for suicide [8,61]. This is especially important during the acute phase of therapy and the first two to four months of remission.

OTHER ANTIDEPRESSANTS

- **Bupropion** – Evidence for the effectiveness of bupropion in pediatric patients with depression includes an eight week observational study in 24 adolescents with attention deficit hyperactivity disorder plus either unipolar major depression or persistent depressive disorder (dysthymia); depressive symptoms were much improved in 88 percent [62]. The study used the sustained release formulation of bupropion at doses up to 3 mg/kg twice per day, with each dose ≤150 mg; however, many clinicians prescribe 100 to 200 mg twice per day [63]. We typically prefer the extended release formulation of bupropion (150 to 450 mg once per day), which appears to have a more favorable pharmacokinetic profile (lower but more sustained serum concentrations) compared with the sustained release formulation [64]. In addition, improvement of depression with

bupropion may be associated with higher serum concentrations of bupropion and its metabolites [65]. Seizures may occur with bupropion, especially in patients with eating disorders. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Side effects'.)

- **Vilazodone** – Two randomized trials indicate that vilazodone is not efficacious for pediatric unipolar major depression:
  - In an eight-week trial, adolescents aged 12 to 17 years old (n = 529) were randomized to fixed-dosed vilazodone (15 mg or 30 mg/day) or placebo; improvement for all three groups was comparable [66].
  - In another eight-week trial, 473 youth aged 7 to 17 years old were randomly assigned to flexibly dosed vilazodone (15 to 30 mg/day), fluoxetine (20 mg/day) or placebo. Improvement in all three groups was comparable [67].
- **Mirtazapine** – We generally avoid mirtazapine, based upon a pooled analysis of two trials that found mirtazapine (15 to 45 mg/day) provided no advantage over placebo [5]. Each trial lasted eight weeks and included youth (total n = 250) aged 8 to 18 years, who were diagnosed with unipolar major depression.

ADJUNCTIVE AGENTS

Several drugs are available as augmentation for depressed children and adolescents with a partial response to antidepressants, but it is not known if adjunctive drugs are beneficial. Augmentation permits treatment to continue without interruption, thus avoiding a period of time with untreated symptoms and/or loss of a partial response. Agents that have been considered as add-on therapy include buspirone, lithium, second-generation antipsychotics, stimulants, and thyroid hormone, as well as bupropion [47,68].

The use of adjunctive lithium, second-generation antipsychotics, thyroid hormone, and bupropion for depressed adults is discussed separately.

- (See "Unipolar depression in adults: Treatment with lithium", section on 'Add-on lithium for treatment-resistant depression'.)
- (See "Unipolar depression in adults: Treatment with second-generation antipsychotics".)
- (See "Unipolar depression in adults: Augmentation of antidepressants with thyroid hormone".)

- (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Initial approach'.)

TREATMENT OPTIONS WITH LITTLE OR NO BENEFIT

Omega-3 fatty acids — We typically do not use omega-3 fatty acids (n-3 polyunsaturated fatty acids) for acute pediatric depression, because there are no high-quality studies that have established that these medications are efficacious:

- A 16-week trial randomly assigned 28 children (aged 6 to 12 years) with unipolar major depression to receive omega-3 fatty acids (approximately 400 mg of eicosapentaenoic acid and 200 mg docosahexaenoic acid) or placebo [69]. Among the 20 children who completed at least one month of the study, improvement was greater with omega-3 fatty acids than placebo. In addition, there were no clinically important side effects. However, these results are not compelling, due to the small sample size as well as the analysis, which included only study completers rather than all patients who were randomized.

- Different meta-analyses of randomized trials in adults have found conflicting results regarding the benefit of omega-3 fatty acids compared with placebo. Heterogeneity across studies is typically substantial and publication bias may account for the benefits observed in some meta-analyses. (See "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'Omega-3 fatty acids'.)

St. John's wort — We do not suggest St. John's wort (*Hypericum perforatum*) for treating pediatric depressive disorders. Studies of St. John's wort in adults with mild to moderate depressive disorders have yielded inconsistent results, and no high-quality studies have been performed in children and adolescents. In addition, pharmacotherapy is not usually recommended for children and adolescents with mild depression. The efficacy of St. John's wort for depressed adults is discussed separately. (See "Clinical use of St. John's wort", section on 'Depression'.)

Additional information about St. John's wort is available at the website of the National Center for Complementary and Alternative Medicine, a branch of the United States National Institutes of Health.

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

Additional sources of information about unipolar major depression and treatment that is intended for patients and families is discussed separately. (See "Overview of prevention and treatment for pediatric depression", section on 'Education and resources'.)

SUMMARY AND RECOMMENDATIONS

- **Indications for and education about pharmacotherapy** – Pharmacotherapy is reserved for children and adolescents who meet criteria for a depressive disorder such as moderate to severe major depression (table 2), persistent depressive disorder (dysthymia) (table 8), or depressive symptoms with functional impairment, and who can be monitored by clinicians and families. Prior to starting antidepressants, it is incumbent upon clinicians to educate patients and families about depression, and discuss the

benefits and side effects of medications (table 9), the potential for increased suicidal ideation and behavior (table 10), other safety risks (eg, cardiac events), and the risks of untreated depression. (See "Pediatric unipolar depression and pharmacotherapy: General principles", section on 'Prescribing pharmacotherapy' and "Effect of antidepressants on suicide risk in children and adolescents" and 'Adverse side effects' above.)

- **First-line pharmacotherapy** – For children and adolescents with moderate to severe depressive disorders who are treated with pharmacotherapy, we suggest fluoxetine as first-line treatment, rather than other antidepressants (**Grade 2B**). (See 'First-line' above and 'Fluoxetine' above.)

- **Second-line pharmacotherapy** – For depressed pediatric patients who do not respond to initial treatment with fluoxetine, we suggest switching to sertraline, rather than other antidepressants (**Grade 2B**). However, reasonable alternatives include escitalopram, citalopram, or venlafaxine. We typically do not use paroxetine for pediatric depression because of its lack of demonstrated efficacy. (See 'Second-line' above and 'Other specific SSRIs' above and 'Indications and efficacy' above.)

- **Third-line pharmacotherapy** – Antidepressant options for depressed youth who do not respond to or tolerate selective serotonin reuptake inhibitors or venlafaxine include bupropion and duloxetine; tricyclic antidepressants are rarely used. (See 'Third-line' above and 'Tricyclic antidepressants' above.)

- **Continuation and maintenance pharmacotherapy** – For children and adolescents who are treated acutely with antidepressants and remit, we recommend that the same regimen be continued for at least six months, rather than discontinuing pharmacotherapy (**Grade 1A**). (See 'Continuation and maintenance treatment' above.)

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