Overview of prevention and treatment for pediatric depression

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INTRODUCTION

Pediatric depression typically presents in primary care and is undertreated [1,2]. Multiple studies in the United States, including a nationally representative surveys [3,4] and retrospective studies of an administrative claims database [2] and medical records [5], indicate that roughly 40 percent of children and adolescents with depressive disorders are not treated.

Among children and adolescents with depression who receive standard treatment, psychotherapy alone is used most often [2,5]. The second most frequently used treatment is medication monotherapy and the least used is psychotherapy plus an antidepressant.

This topic provides an overview of treating pediatric depression. Pharmacotherapy and psychotherapy for juvenile depression, as well as the assessment, diagnosis, and differential diagnosis of depression, are discussed separately.

- (See "Pediatric unipolar depression and pharmacotherapy: General principles".)
- (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication".)
- (See "Pediatric unipolar depression: Psychotherapy".)
- (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis".)

DEFINITION OF UNIPOLAR MAJOR DEPRESSION

Unipolar major depression (major depressive disorder) is diagnosed in patients who have suffered at least one major depressive episode (table 1) and have no history of mania (table 2) or hypomania (table 3) [6]. A major depressive episode is a period lasting at least two weeks, with five or more of the following symptoms: depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide. In addition, the symptoms must cause clinically significant distress or impairment in functioning, and the syndrome is not due to the physiologic effects of a substance (eg, drug abuse or medications) or another medical condition (eg, hypothyroidism). (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Unipolar major depression'.)

Severity — The severity (intensity) of unipolar major depression is often classified as either mild to moderate or severe.

Mild to moderate major depression is characterized by clinical features such as:

- No suicidal or homicidal ideation or behavior, or ideation that does not pose an imminent risk (eg, thoughts that family members would be better off if the patient was dead; or fleeting thoughts of killing oneself, with nonexistent or vague plans to commit suicide and no intent).
- No psychotic features (eg, delusions or hallucinations).
- Little to no aggressiveness.
- Intact judgement such that the patient or others are not at imminent risk of being harmed.

Mild to moderate major depression is indicated by a score <20 points on the self-report Patient Health Questionnaire – Nine Item (PHQ-9) (table 4) [7,8]. Patients with mild to moderate depression can generally be treated in an outpatient or partial (day) hospital program setting.

Severe unipolar major depression is characterized by seven to nine depressive symptoms that occur nearly every day, as indicated by a score ≥20 points on the PHQ-9. Severely ill patients often report suicidal ideation and behavior, typically demonstrate obvious impairment of functioning, are more likely to develop complications such as psychotic features, and are typically referred to a psychiatrist for management and inpatient hospitalization.

In addition, the PHQ-9 classifies patients as moderately severe if their score is 15 to 19. Patients with moderately severe major depression require urgent attention and often require treatment in either a partial hospital program or on an inpatient unit.

PREVENTION

Administering psychotherapy to children and adolescents in targeted populations can prevent onset of depressive disorders [9]. However, the benefits are small and do not appear to last beyond one year.

Targeted (selected) populations — Targeted treatment with psychotherapy to prevent either new or recurrent onset of depressive syndromes includes children and adolescents who are at high risk for the disorder by virtue of factors that include subsyndromal depressive symptoms, death of a parent, family conflict, or family history of depression [9]. We generally do not administer psychotherapy to prevent depressive disorders in at-risk youth, unless the individual has suicidal ideation or behavior, a comorbid psychiatric disorder, functional impairment, has previously had a depressive syndrome, or requests treatment. Nevertheless, it is reasonable to provide psychotherapy even in the absence of these five exceptions, or to monitor at-risk youth regularly (eg, once per month). (See 'Monitoring' below.)

Evidence regarding the use of psychotherapy to prevent depressive disorders includes a systematic review that performed a meta-analysis of 22 randomized trials, which compared psychotherapy with control conditions in children and adolescents (n >3900) who did not meet criteria for a depression diagnosis [9]. The youth were at risk for developing depressive syndromes due to the presence of subthreshold, mild to moderate depressive symptoms. Active treatment consisted of cognitive-behavioral therapy or interpersonal psychotherapy, and control conditions consisted of usual care or no treatment. Most of the trials were conducted in school settings and delivered either group or individual therapy, usually on a weekly basis for 8 to 12 sessions. Diagnosis of a depressive disorder for up to 12 months after randomization was less likely with psychotherapy than control conditions; however, the clinical effect was small and did not persist beyond one year, and none of the trials controlled for psychotherapy's nonspecific effects, such as attention.

In addition, the systematic review performed a second meta-analysis, which aggregated four trials (n >400 at-risk youth) that were not included in the first meta-analysis, and compared psychotherapy with control conditions consisting of an attention placebo (eg, psychoeducation about general mental and/or physical health) [9]. Self-reported depressive symptoms post intervention were comparable for the two groups.

Universal (unselected) populations — We do not suggest universal prevention for depressive disorders in children and adolescents. Universal prevention involves administering psychotherapy to the population regardless of risk for the disorder, and is not effective. In a meta-analysis of 10 randomized trials that compared either cognitive behavioral therapy or interpersonal psychotherapy with control conditions in children and adolescents (n >2000), the incidence of depressive disorders was comparable for the two groups [9].

GENERAL PRINCIPLES OF TREATING YOUTH WITH MAJOR DEPRESSION

Patient safety and treatment setting — The first step in acute phase treatment addresses potential safety concerns. Every depressed child and adolescent must be evaluated for suicide risk and if risk is identified, safety must be assured by choosing the right setting. (See "Suicidal ideation and behavior in children and adolescents: Evaluation and management".)

Treatment of pediatric depression may occur in a variety of settings: outpatient, partial hospital, inpatient, or residential [10]. Treatment should be provided in the least restrictive setting that is safe and effective for a given patient. The setting depends upon the severity of illness (including safety status), level of parental support, and motivation for treatment.

Treatment plan — Treatment planning should be collaborative with patients and their families [11]; successful treatment typically requires parental involvement and cooperation [10]. Clinicians (eg, pediatricians, psychiatrists, or psychologists) who are treating youth with major depression and are formulating a treatment plan should engage the parents to weigh the risks and benefits of the various interventions (eg, psychotherapy and/or pharmacotherapy) in deciding upon a treatment regimen. Involving the school may also help, depending upon the severity of symptoms and impairment in the school setting.

The plan specifies the choice of therapy and frequency of sessions based upon the severity of depressive symptoms, the age and developmental status of the patient, the degree of current exposure to negative life events, and comorbidity (eg, anxiety and substance use disorders) [10]. Many guidelines suggest a minimum of eight weeks of treatment for an acute episode of major depression [12]. Multiple sessions per week may be needed during the acute treatment phase. In addition, the plan should include interventions directed at problems in the patient's environment.

The plan also addresses the use of medication. (See "Pediatric unipolar depression and pharmacotherapy: General principles".)

Education and resources — An important component of treating depression in youths is education of patients and family members about the signs and symptoms of depression, treatment options and their benefits and risks, prognosis, and the ways in which the illness has affected their personal interactions [10-17]. With education, nonadherence with treatment may decrease, and patients and family members may view depression as an illness, which can reduce feelings of stigmatization and provide relief. Psychosocial difficulties may then be easier to address. Education may also help family members identify their own depressive symptoms and need for treatment [10,13,14].

Education addresses the:

- Signs and symptoms of depression (table 1), using language that is developmentally appropriate for the patient's level of understanding. (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis".)
- Clinical course of depression, including the likelihood of relapse and recurrence (see 'Clinical outcomes' below). Knowing the clinical features of depression can help patients and families recognize relapse early in its course.
- Impact of depression upon family and peer relationships, school attendance, and academic functioning. (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Functional impairment'.)
- Use of pharmacotherapy. (See "Pediatric unipolar depression and pharmacotherapy: General principles", section on 'Education'.)
- Use of psychotherapy. (See "Pediatric unipolar depression: Psychotherapy", section on 'General principles'.)
- Role of parents and teachers in treatment.
- Patient's safety and plans for limiting access to means for self-harm (eg, dangerous medications and weapons), particularly when there are concerns about suicidal or homicidal ideation, plans, and intent [18,19]. (See "Suicidal ideation and behavior in children and adolescents: Evaluation and management".)

Additional information for parents and adolescents about depression in adolescents is discussed elsewhere in this topic. (See 'Information for patients' below.)

Resources for clinicians, patients, and families regarding treatment of depression in children and adolescents include the following:

- American Academy of Child and Adolescent Psychiatry
- United States Food and Drug Administration
- The Guidelines for Adolescent Depression in Primary Care (GLAD-PC) Toolkit
- American Psychiatric Association
- American Psychological Association
- National Alliance on Mental Illness
- National Institute of Mental Health
- Mental Health America
- Resources for integrated health care (see 'Collaborative care' below)

Collaborative care — Collaborative (integrated) care involves pediatric primary care clinicians and mental (behavioral) health clinicians working together in the primary care setting to diagnose and treat depressive disorders in children and adolescents [20-29]. Patients are treated by a team that usually includes a primary care clinician, a case manager who provides support and outreach to patients, and a mental health specialist (eg, psychiatrist) who provides consultation and supervision. Other elements include a structured treatment plan that involves pharmacotherapy, psychotherapy, or both; scheduled follow-up visits; communication among the members of the treatment team; and measurement based care. Collaborative care is used for treating pediatric patients with mild to moderate episodes of unipolar major depression, as well as severe episodes and/or treatment-resistant episodes, and is used for patients managed by pediatricians or family medicine clinicians who lack experience with major depression. Instituting collaborative care to integrate the general medical and mental health of patients is endorsed by the American Academy of Child and Adolescent Psychiatry and the American Academy of Pediatrics. Measurement based care is discussed elsewhere in this topic. (See 'Monitoring' below.)

Multiple collaborative care programs, resources, and guidelines are available. As an example, the clinical practice guideline, Guidelines for Adolescent Depression in Primary Care, incorporates consultation and coordination of care with mental health specialists as one of its major tenets [11,30]. This guideline provides a toolkit that includes rating scales to aid in the assessment and diagnosis of pediatric depression, information on various treatment options, an algorithm/flowchart for management of depression, and educational materials. Videoconferencing and web based approaches may aid collaborative care [31].

Major depression is often identified in the primary care setting, and primary care clinicians manage the majority of depressed patients rather than referring patients to specialists such as psychiatrists or psychologists [11,20,32-39]. However, many primary care providers think that their training, support, or reimbursement for managing depressed youths is insufficient [36],

and that time constraints interfere with gathering an adequate psychiatric history [12]. These problems may result in inadequate treatment.

Given that suicide is associated with undertreated pediatric depression [40-43], primary care clinicians and mental health clinicians (eg, child psychiatrists, psychologists, and clinical social workers) are encouraged to collaborate to surmount barriers that prevent appropriate care. This may include brief consultations with mental health clinicians about individual patients, or identifying a mental health clinician who is willing to see more severely ill patients on relatively short notice [12].

Resources for integrated health care include the following:

- Integrated Primary Care; AAP Children's Mental Health in Primary Care, E-Newsletter.
- Hogg Foundation for Mental Health Integrative Care Initiative; Connecting Body & Mind: A Resource Guide to Integrated Health Care in Texas & the US – This report describes integrated health care and identifies resources to assist with developing and implementing integrated care systems. The online version is updated regularly with new information.
- A Resource Guide for Physicians: Integrating Child and Adolescent Mental Health into Primary Care; published by Texas Medical Association.
- The Massachusetts Child Psychiatry Access Program (MCPAP) provides primary care clinicians with timely access to child psychiatry consultation, and includes regional coordinators who identify appointment availability to psychiatrists and mental health practitioners. Many pediatric clinicians in Massachusetts have joined this program.

Evidence for the efficacy of integrated health care includes a meta-analysis of five randomized trials that compared collaborative care with usual care in children and adolescents (n >1000) with depression or behavior problems [44]. Improvement was greater with collaborative care and the clinical benefit was moderate to large. However, heterogeneity across studies was large. In addition, one randomized trial indicates that collaborative care for adolescents with major depression is cost effective [45]. Indirect evidence for the benefit of collaborative care includes numerous studies in adults who were treated for major depression in primary care settings. (See "Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments", section on 'Collaborative care'.)

Indications for referral — Although pediatric major depression is often treated successfully by primary care clinicians, referral to a psychiatrist is sometimes necessary [12]. Indications for

referral include [30,46,47]:

- Uncertainty about the diagnosis of major depression.
- Discomfort managing pediatric depression.
- Current agitation, suicidal or homicidal behavior, history of suicide attempt, or inability of the family to monitor the safety of the child or adolescent. (See "Suicidal ideation and behavior in children and adolescents: Evaluation and management".)
- Psychotic features (eg, delusions or hallucinations). (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis" and "Unipolar major depression with psychotic features: Acute treatment".)
- Bipolar depression. (See "Pediatric bipolar disorder: Clinical manifestations and course of illness" and "Pediatric bipolar disorder: Assessment and diagnosis".)
- Acute comorbid disorders such as conduct disorder or eating disorders, or when other comorbid disorders (eg attention deficit hyperactivity disorder, anxiety disorders, or substance use disorders) are not amenable to treatment in primary care settings or not responding to treatment.
- Recurrent or chronic (eg, ≥2 years) depression.
- Severe functional impairment or psychosocial stressors (eg, a high level of family discord).
- Lack of response to the initial course of treatment, despite using therapeutic doses for a sufficient length of time. (See 'Treatment-resistant depression' below.)
- Administration of psychotherapy (eg, cognitive-behavioral therapy or interpersonal therapy) (see "Pediatric unipolar depression: Psychotherapy"). Psychotherapy should be administered by properly trained clinicians; these can include psychiatrists, psychologists, social workers, and nurses.

After a referral is initiated, we suggest that primary care clinicians continue to monitor patients while they wait for the referral appointment. Primary care clinicians and psychiatrists (or other mental health clinicians who are administering psychotherapy) should communicate about the specific responsibilities for ongoing patient management [12].

Monitoring — We suggest that clinicians (eg, pediatricians, psychiatrists, or psychologists) who are treating patients for depression regularly monitor outcomes with a brief scale completed by patients (when feasible) and their parents to track progress and inform treatment adjustments

[12]. Limited evidence in adults suggests that monitoring depressive symptoms with a standardized scale may improve treatment outcomes. However, there is no evidence that using such scales improves outcomes in pediatric depression. (See "Pediatric unipolar depression and pharmacotherapy: General principles", section on 'Monitoring' and "Using scales to monitor symptoms and treat depression (measurement based care)", section on 'Evidence of efficacy'.)

We recommend using the Short Mood and Feelings Questionnaire to monitor outcomes for treatment of depression; this instrument has separate forms that are completed by the patient and the parent (table 5 and table 6) [48-51]. The questionnaire is validated for both children and adolescents, is brief and easy to interpret, and is in the public domain. A total score ≥8 on the patient form is considered clinically significant. The instrument lacks a question about suicidal ideation; therefore, clinicians should ask about this. Clinicians may be familiar with other available scales (table 7), and it is reasonable to use them as an alternative to the Short Mood and Feelings Questionnaire.

The most widely used and studied scale among adults is the self-report Patient Health Questionnaire – Nine Item (PHQ-9). The PHQ-9 has also been used in adolescents [7]. In addition, there is a modified form of the PHQ-9 specifically for adolescents (PHQ-9: Modified for Teens) (table 4) [8].

Although the Children's Depression Rating Scale – Revised is used most widely in studies of pediatric depression, this scale is typically not feasible for standard clinical care because it is administered by clinicians.

Clinical outcomes — Clinical outcomes in depressive disorders are classified as follows [10,52-54]:

- Response – Significant reduction (eg, ≥50 percent) of depressive symptoms during acute treatment. Response often coincides with the onset of remission. We suggest monitoring clinical improvement with standardized rating scales as well as measures of overall psychosocial functioning (table 7). (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

- Remission – Remission represents a period of time with minimal or no symptoms (eg, depression rating scale scores and psychosocial functioning indices within normal limits, (table 7)); the duration of this time period varies among different studies (eg, two to eight consecutive months).

- Relapse – Recrudescence of the presenting depressive episode during remission.

- Recovery – An asymptomatic period with onset at the end of remission (there is no established cutoff that separates the end of remission from the beginning of recovery).

- Recurrence – The emergence of unipolar major depression following recovery (a new episode).

Additional information about the terms used to describe the clinical course of mood disorders is discussed separately in the context of adults. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Continuation and maintenance treatment'.)

ACUTE TREATMENT

The goal of acute treatment is remission of symptoms and return to baseline functioning [12]. However, remission often occurs in fewer than half of patients [55], whereas response (eg, reduction of baseline symptoms ≥50 percent) occurs in up to 70 to 80 percent [56,57]. Remission or response typically occurs within 6 to 12 weeks, and treatment trials rarely last more than 12 weeks.

Choice of therapy — The three treatment options that are generally used for pediatric depression include:

- Pharmacotherapy (see "Pediatric unipolar depression and pharmacotherapy: Choosing a medication" and "Pediatric unipolar depression and pharmacotherapy: General principles")

- Psychotherapy (see "Pediatric unipolar depression: Psychotherapy")

- Combination therapy (pharmacotherapy plus psychotherapy)

Initial treatment — Choosing initial therapy for children and adolescents with acute depression depends upon illness severity and duration; the presence of agitation, psychosis, suicidal and homicidal ideation and behavior, as well as comorbidity (eg, anxiety and substance use disorders); the patient's age and functioning (eg, family conflict and academic problems); the number of previous depressive episodes; and response to and adherence with prior treatment [10]. Other factors to consider include adverse effects, availability of treatment options, patient and family preference (including their assessment regarding the balance of risks and benefits of therapy), clinician preference and familiarity with treatment options, and cost.

For children and adolescents with moderate to severe (eg, suicidal behavior) unipolar major depression, we suggest combination therapy with pharmacotherapy and psychotherapy as initial treatment. Randomized trials suggest that combination therapy may provide a modest advantage over pharmacotherapy alone and psychotherapy alone (see 'Combination therapy' below), and the use of combination therapy is consistent with practice guidelines [10,58-60]. We typically use selective serotonin reuptake inhibitors (SSRIs; eg, fluoxetine), and cognitive-behavioral therapy (CBT), because they have been widely studied, especially in adolescents. Reasonable alternatives include sertraline or escitalopram (for adolescents) and interpersonal psychotherapy. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication", section on 'Efficacy' and "Pediatric unipolar depression: Psychotherapy", section on 'Efficacy'.)

Antidepressant monotherapy is often not considered sufficient in light of the adverse psychosocial context in which depression frequently occurs. With few exceptions, the environmental problems associated with unipolar major depression remain after the patient's mood has stabilized. Combination treatment increases the chance of improving adaptive behaviors and coping skills, family and peer relationships, and self-esteem, as well as reducing the risk of relapse [10].

However, pharmacotherapy alone is a reasonable alternative for pediatric patients with moderate to severe depression when psychotherapy is declined or is not available, provided that the patient is regularly monitored (eg, every week, or every other week with a telephone call in between, until improvement occurs) [56]. In addition, pharmacotherapy alone is indicated for patients with severe symptoms (eg, psychotic features) that preclude psychotherapy, and depression that does not respond to an adequate trial of psychotherapy alone [10].

Unipolar major depression with psychotic features requires treatment with an antidepressant plus an antipsychotic. In addition, patients should be monitored closely for mania because the risk of bipolar disorder is higher in patients with psychotic depression.

Choosing a medication and the general principles for administering pharmacotherapy are discussed separately, as is the possible association between antidepressants and suicidal thoughts or behaviors. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication" and "Pediatric unipolar depression and pharmacotherapy: General principles" and "Effect of antidepressants on suicide risk in children and adolescents".)

For patients with mild episodes of major depression, we suggest psychotherapy alone (eg, cognitive-behavioral therapy) as initial treatment [12]. (See "Pediatric unipolar depression:

Psychotherapy".) However, among youth who do not respond after six to eight weeks of treatment, antidepressants should be added.

Treatment-resistant depression — If the child or adolescent does not respond to treatment using therapeutic doses within 6 to 12 weeks, we reevaluate the diagnosis of major depression, especially to rule out bipolar disorder, and assess the patient for comorbid illnesses (eg, substance use disorders), stressors (bullying, abuse, or family conflicts), side effects, or nonadherence, which may impede improvement. If the diagnosis of major depression is confirmed and potential factors for nonresponse are ruled out, our approach is as follows. For children and adolescents with moderate to severe unipolar major depression who do not respond to initial treatment with pharmacotherapy plus psychotherapy, we suggest switching antidepressants from one SSRI to another and continuing psychotherapy, based upon clinical experience.

For children and adolescents with moderate to severe unipolar major depression who do not respond to initial treatment with pharmacotherapy alone, we suggest switching antidepressants from one SSRI to another and adding CBT, rather than switching medications alone. However, changing antidepressants and not adding psychotherapy is a reasonable alternative if psychotherapy is declined or is not available.

Evidence for the efficacy of switching antidepressants and adding psychotherapy in depressed adolescents who do not respond to antidepressant monotherapy includes a randomized trial (the Treatment of Resistant Depression in Adolescents [TORDIA] study) that enrolled patients (n = 334) with major depression who did not respond to eight weeks of treatment with an SSRI [61]. Patients were assigned to one of four treatments: an alternative SSRI (citalopram, fluoxetine, or paroxetine), the serotonin-norepinephrine reuptake inhibitor venlafaxine, an alternative SSRI plus CBT, or venlafaxine plus CBT. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients treated with a different medication (either a different SSRI or venlafaxine) plus CBT, compared with patients who received a medication switch alone (55 versus 41 percent). Although the response rates with both medication switch strategies were similar, participants experienced fewer side effects when treated with an SSRI than when treated with venlafaxine.

Additional information about treatment-resistant depression is discussed in the context of adults. (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

Evidence of efficacy

Combination therapy — Pharmacotherapy plus psychotherapy appears to be efficacious for pediatric depression. As an example, a 12 week randomized trial (Treatment for Adolescents

with Depression Study [TADS]) compared fluoxetine (10 to 40 mg per day) plus CBT (15 sessions, each lasting 50 to 60 minutes) with pill placebo in 219 adolescents with unipolar major depression [57]. Response (defined as much or very much improved) occurred in more patients who received combination therapy than placebo (71 versus 35 percent).

In addition, short term treatment (eg, 12 weeks) with combination therapy may be superior to pharmacotherapy alone and psychotherapy alone. However, the benefits of these three options during longer-term (eg, 36 weeks) treatment generally appear to be comparable.

Compared with pharmacotherapy alone — For children and adolescents with depressive disorders, combination therapy (pharmacotherapy plus psychotherapy) may provide a modest advantage over pharmacotherapy alone in resolving depressive symptoms:

- A meta-analysis of four randomized trials (850 adolescents) compared pharmacotherapy (SSRIs or venlafaxine) plus CBT with pharmacotherapy alone [62]. At the 12-week assessment, improvement of depression and the incidence of suicidal ideation were each comparable. However, functioning was better in patients who received combination therapy.

- A meta-analysis of three trials compared SSRIs plus CBT with SSRIs alone in 419 adolescent patients who were treated for 6 or 12 weeks, and found that there was a trend for remission to occur in more patients who received combination therapy than SSRI monotherapy (odds ratio 1.50, 95% CI 0.99-2.27) [63].

Combination therapy may also provide advantages over pharmacotherapy during treatment that lasts longer than 12 weeks. As an example, a 36-week randomized trial compared fluoxetine plus CBT with fluoxetine alone in 216 adolescents with unipolar major depression [56]. Although response with combination therapy and fluoxetine monotherapy was comparable, clinically significant suicidal ideation occurred in fewer patients who received combination therapy than fluoxetine alone (3 versus 14 percent). Additional information about antidepressants and risk of suicide is discussed separately. (See "Effect of antidepressants on suicide risk in children and adolescents".)

Compared with psychotherapy alone — Combination therapy appears to be superior to psychotherapy alone for short term treatment of adolescents with unipolar major depression. A 12-week randomized trial compared fluoxetine plus CBT with CBT alone in 218 adolescents with unipolar major depression [55-57,64-71]. Remission occurred in more patients who received combination therapy than CBT alone (37 versus 16 percent) [55]. In addition, improvement of suicidal ideation was greater with fluoxetine plus CBT [57].

However, the advantage of combination therapy over psychotherapy alone during longer term treatment appears to dissipate. As an example, a 36-week randomized trial compared fluoxetine plus CBT with CBT alone in 218 adolescents with unipolar major depression [56]. Response was comparable with combination therapy and CBT alone (86 and 81 percent of patients).

Pharmacotherapy — Medications that have been used as initial treatment for children and adolescents with major depression include SSRIs, venlafaxine, and tricyclic antidepressants. Randomized trials have shown that SSRIs (eg, fluoxetine), are superior to placebo; by contrast, the benefits of venlafaxine are modest at best. Tricyclics are not used as initial treatment due to limited benefits, as well as substantial problems with safety and adverse effects. The efficacy of pharmacotherapy is discussed separately. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication".)

The use of antidepressants in children and adolescents is associated with a slightly increased risk of suicidal thoughts and behaviors. (See "Effect of antidepressants on suicide risk in children and adolescents".)

Compared with psychotherapy — For adolescents with unipolar major depression, short term treatment with pharmacotherapy alone may be superior to psychotherapy alone. As an example, a 12-week randomized trial compared fluoxetine with CBT in 220 adolescents with unipolar major depression, and found that response (defined as much or very much improved) occurred in more patients who received fluoxetine than CBT (61 versus 43 percent) [57].

However, the benefits of pharmacotherapy alone and psychotherapy alone during longer term treatment appear to be similar. In a 36-week observational follow-up of an acute randomized trial that compared fluoxetine alone with CBT alone in 220 adolescents with unipolar major depression, response with fluoxetine and with CBT was identical (81 percent of patients) [56].

Psychotherapy — Randomized trials have shown that CBT and interpersonal psychotherapy are better than control treatments for youth with major depression. However, other forms of psychotherapy, such as dialectical behavior therapy, family therapy, psychodynamic psychotherapy, supportive therapy, and other psychosocial interventions may also be beneficial [72]. A qualitative review of 42 randomized trials found that treatment effects for psychotherapy are often modest, and that fewer trials have been conducted in children than adolescents [73].

Psychotherapy may help patients and their families to [10,74]:

- Understand themselves and the nature of depression
- Change problematic behaviors
- Cope with depressive symptoms

- Manage relationships and life stressors associated with depression
- Improve social skills
- Increase self-confidence
- Prevent onset of depressive syndromes
- Adhere to treatment

The efficacy of psychotherapy for pediatric depression as well as an overview of psychotherapy is discussed separately. (See "Pediatric unipolar depression: Psychotherapy" and "Overview of psychotherapies".)

Electroconvulsive therapy — Observational studies suggest that electroconvulsive therapy (ECT) can effectively treat adolescents with severe major depression that has not responded to other treatments [75]. ECT is used with the caregivers' consent and adolescent's assent. In addition, the need for ECT is typically based upon a consensus of multiple child and adolescent psychiatrists, and government and hospital guidelines must be followed. Following a positive response, continuation and maintenance ECT may be indicated [76]. The use of ECT for severe, intractable depression is consistent with practice guidelines [77].

Additional information about ECT is discussed separately in the context of adults. (See "Overview of electroconvulsive therapy (ECT) for adults" and "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)" and "Medical evaluation for electroconvulsive therapy" and "Technique for performing electroconvulsive therapy (ECT) in adults".)

Adjunctive exercise — We suggest physical exercise as adjunctive treatment for patients with unipolar major depression, based upon multiple trials [78]. As an example, a meta-analysis of 17 randomized trials plus 4 nonrandomized studies compared aerobic exercise with control conditions in children and adolescents (n >2400) [79]. The studies included clinical and nonclinical samples from different countries, and the mean duration was 22 weeks. Exercise spanned a wide range of activities, and in most studies was prescribed as monotherapy and involved supervised, school-based interventions. The frequency of exercise was two to five days/week, and the mean duration of each session was 50 minutes. Control conditions included usual care or no treatment. Reduction of depressive symptoms was modestly greater with exercise than control conditions (effect size -0.29), with the benefit greater in adolescents and youth with a depression diagnosis. However, heterogeneity across studies was moderate to large, and after a mean follow-up of 21 weeks, improvement of depressive symptoms in the two groups was comparable.

Additional information about exercise is discussed separately, including the benefits of exercise for depression in adults and the general health benefits and risks of exercise for adolescents and adults. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Exercise' and "Physical activity and strength training in children and adolescents: An overview" and "The benefits and risks of aerobic exercise".)

Comorbidity — Comorbid psychiatric disorders are common in pediatric depression and should be treated [10]. Management is based upon the principle that clinicians initially treat the disorder (ie, the depressive disorder or the comorbid disorder) that causes the greatest distress or impairment. In addition, if a comorbid disorder (eg, substance use disorder or anorexia nervosa) reduces the likelihood of recovery from depression, then the comorbidity should be addressed first. Treating the comorbidity may improve the depressive symptoms (eg, initially treating attention deficit hyperactivity disorder may improve the depressive syndrome). Also, some comorbid disorders (eg, anxiety disorders) respond to the same treatments that are used for depression.

Comorbidity may indicate the need for referral to mental health clinicians. (See 'Indications for referral' above.)

Prognosis — Approximately 60 percent of children and adolescents with unipolar major depression respond to initial treatment [10]. However, response is not the same as remission; the threshold for response is relatively low, compared with remission. In addition, youth who achieve a symptomatic response may still suffer functional impairment.

Baseline predictors of nonresponse include severe (intense) depressive symptoms such as suicidal ideation with a plan and intent, suicidal or nonsuicidal self-injurious behavior, longer duration of illness, hopelessness, poorer functioning, comorbid psychiatric disorders (eg, anxiety disorders, substance use disorders, or obsessive-compulsive disorder), younger age, history of abuse, disappointing life events, family psychopathology, and family conflicts [70,80-87].

The long-term prognosis may not be related to the specific acute-phase treatment that is administered. An observational study followed adolescents with unipolar major depression (n = 196) for up to five years after onset of acute, randomly assigned treatment with fluoxetine alone, CBT alone, or fluoxetine plus CBT [81]. Almost all participants (96 percent) recovered, and among those who recovered, relapse occurred in 47 percent. Neither recovery nor recurrence (following recovery) was associated with any specific treatment. In addition, most patients achieved developmental milestones (enrolled in college or obtained employment), and on average, global functioning improved [88].

CONTINUATION TREATMENT

We suggest that all patients who respond to acute therapy receive continuation treatment to prevent relapses [10]. Practice guidelines indicate that the acute phase psychosocial or pharmacologic treatments that achieved remission should generally be used for continuation therapy, unless the treatment is contraindicated (eg, intolerable drug side effects). However, for patients who remit with pharmacotherapy alone, it can be useful to add psychotherapy to prevent relapses (see 'Sequential treatment' below). During continuation treatment, patients are typically seen every two to four weeks, depending upon their clinical status (including comorbidities), functioning, support systems, stressors, motivation for treatment, and comorbid psychiatric or general medical disorders [10,89].

Given the high rate of depressive relapses and recurrences in children and adolescents (40 to 60 percent), continuation therapy is recommended for all patients for at least 6 months after complete remission of depressive symptoms (ie, return to baseline mood), and preferably 12 months [12,90]. Patients who had difficulty achieving remission, have a history of recurrent depression, or present with ongoing risk factors (eg, comorbidity, suicidality, stressors, or family history of depression) should receive continuation therapy for at least 12 months. However, if the depressive episode was subsyndromal or mild, and occurred in the context of no prior episodes of depression or major risk factors, an extended continuation phase is probably not warranted.

Evidence for the efficacy of continuation treatment is discussed separately. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication", section on 'Continuation and maintenance treatment' and "Pediatric unipolar depression: Psychotherapy", section on 'Maintenance phase and prevention'.)

Sequential treatment — Patients with unipolar major depression who respond to acute phase pharmacotherapy may add psychotherapy (eg, CBT) for continuation treatment; this strategy is called sequential treatment [91]. Adding psychotherapy may be indicated for poor adherence, residual symptoms, or impaired functioning, as well as delaying or preventing relapse.

Evidence for the efficacy of sequential treatment includes randomized continuation/maintenance trials:

- In one trial, 46 children and adolescents (age 11 to 18 years) with acute major depression who responded (reduction of baseline symptoms ≥50 percent) to open label fluoxetine were randomly assigned to six months of fluoxetine plus CBT (8 to 11 sessions that included a family component) or fluoxetine alone [92]. Relapse occurred in fewer patients

who received pharmacotherapy plus CBT than pharmacotherapy alone (15 versus 37 percent). However, global functioning was comparable for the two groups.

- A larger trial replicated the first study of fluoxetine plus CBT for preventing depressive relapse. The larger trial included youths (age 8 to 17 years) with acute major depression who responded to open label fluoxetine (n = 144) and were then randomly assigned to fluoxetine plus CBT or fluoxetine alone for an additional six months [93,94]. CBT was administered over 8 to 11 sessions, each generally lasting one hour; the first two sessions included a family component. Patients were followed for up to 78 weeks after randomization; during follow-up, time to remission of residual symptoms did not differ between the two groups [94]. However, the estimated proportion of patients who relapsed by week 78 was smaller with CBT plus fluoxetine than fluoxetine alone (36 versus 62 percent), and the mean time to relapse was longer with CBT plus fluoxetine by approximately three months.

Additional information about sequential treatment of major depression is discussed separately in the context of adults. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Sequential treatment'.)

Discontinuing treatment — If the child or adolescent has had only a single, uncomplicated episode of depression (eg, no suicidality or psychosis), discontinuation (rather than maintenance treatment) is indicated once the continuation phase is complete. Discontinuing treatment should be decided collaboratively with patients and families. To avoid withdrawal side effects, the dose of most medicines needs to be slowly tapered (eg, approximately 25 to 50 percent per week) under the supervision of a physician.

Education about recurrence of depression is an important element of terminating treatment. Patients and families should be taught to recognize and monitor prodromal signs of recurrence (table 1), and have a plan in place to prevent full blown depressive episodes if prodromal symptoms occur. In addition, the role of primary care clinicians in monitoring patients for depressive symptoms cannot be overemphasized.

Additional information about discontinuing pharmacotherapy is discussed separately. (See "Pediatric unipolar depression and pharmacotherapy: General principles", section on 'Discontinuing pharmacotherapy'.)

MAINTENANCE TREATMENT

After depressive symptoms have resolved and patients have remained euthymic for a period of approximately 6 to 12 months (continuation phase), clinicians need to decide whether maintenance treatment is indicated to prevent recurrences. We suggest maintenance treatment for patients with risk factors associated with increased risk of recurrence, youth with recurrent episodes of major depression (eg, three or more episodes), as well as patients whose acute depressive episode preceding recovery was severe. Severity includes the intensity of symptoms, duration of the episode, and the occurrence of psychosis, suicidality, and functional impairment. Risk factors for recurrence are discussed separately. (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Recurrence'.)

Maintenance therapy typically consists of treatments that achieved remission of the acute episode and were used in continuation treatment (unless intolerable side effects intervene). However, children and adolescents who recovered with pharmacotherapy can be offered add-on psychotherapy to help them cope with the psychosocial sequelae of depression, and prevent recurrence of depression and/or development or exacerbation of comorbid psychiatric disorders [10,89].

Euthymic patients receiving maintenance treatment for depression are typically seen every one to three months, depending upon clinical status. Patients who decompensate will need to be seen more frequently, consistent with monitoring for acute treatment. (See "Pediatric unipolar depression and pharmacotherapy: General principles", section on 'Frequency'.)

The duration of maintenance treatment lasts from one year to indefinitely. For children and adolescents with two or three lifetime episodes of unipolar major depression, we recommend maintenance treatment for one to three years, based upon studies in adults. We suggest even longer maintenance therapy for patients with more than one episode accompanied by psychosis (eg, delusions or hallucinations), moderate to severe suicidal ideation and/or behavior (eg, suicidal ideation with a plan), moderate to severe functional impairment, or treatment resistance.

The efficacy of maintenance pharmacotherapy is discussed separately. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication", section on 'Continuation and maintenance treatment' and "Pediatric unipolar depression: Psychotherapy", section on 'Maintenance phase and prevention'.)

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 'Education and resources' above.)

SUMMARY AND RECOMMENDATIONS

- **Definition of unipolar major depression** – Unipolar major depression (major depressive disorder) is characterized by a history of one or more major depressive episodes (table 1) in the absence of manic (table 2) and hypomanic (table 3) episodes. (See 'Definition of unipolar major depression' above and "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis".)

- **Prevention** – We generally do not administer psychotherapy to prevent depressive syndromes in children and adolescents who are at risk of suffering a depressive disorder due to subsyndromal symptoms, unless the youth has suicidal ideation or behavior, a comorbid psychiatric disorder, functional impairment, has previously had a depressive syndrome, or requests treatment. Nevertheless, it is reasonable to provide psychotherapy even in the absence of these exceptions, or to monitor at-risk youth regularly. (See 'Prevention' above.)

- **Assess suicide risk** – Depressed children and adolescents must be evaluated for suicide risk. (See "Suicidal ideation and behavior in children and adolescents: Evaluation and management".)

- **Indications for referral** – Indications for referral to a mental health specialist include current agitation, suicidal or homicidal ideation or behavior, history of suicide attempt, inability of the family to monitor the child's or adolescent's safety, psychosis, bipolar depression, comorbidity, recurrent or chronic depressive episodes, severe functional impairment, administration of psychotherapy, and treatment-resistant depression. (See 'Indications for referral' above.)

- **Standard treatment options** – Standard treatment options for pediatric depression include psychotherapy, pharmacotherapy, or a combination of the two. (See 'Choice of therapy' above.)

- **Initial treatment** – For children and adolescents with acute moderate to severe unipolar major depression, we suggest pharmacotherapy plus psychotherapy as initial treatment rather than pharmacotherapy alone or psychotherapy alone (**Grade 2B**). We typically choose a selective serotonin reuptake inhibitor (eg, fluoxetine) plus cognitive-behavioral therapy (CBT). However, antidepressant monotherapy is a reasonable alternative if psychotherapy is declined or not available. In addition, psychotherapy alone is a reasonable alternative for mild depressive disorders. The choice of therapy involves educating patients and families about treatment options. Adjunctive exercise may also benefit patients. (See 'Initial treatment' above and 'Evidence of efficacy' above and 'Education and resources' above and "Pediatric unipolar depression and pharmacotherapy: Choosing a medication" and "Pediatric unipolar depression: Psychotherapy".)

- **Treatment-resistant depression** – For children and adolescents with moderate to severe unipolar major depression who do not respond to initial treatment with pharmacotherapy plus psychotherapy, we suggest switching antidepressants from one selective serotonin

reuptake inhibitor to another and continuing psychotherapy, rather than making other changes to the treatment regimen (**Grade 2C**). For child and adolescent patients with moderate to severe unipolar major depression who fail initial treatment with antidepressant monotherapy, we suggest switching antidepressants and adding CBT, rather than switching antidepressants alone (**Grade 2B**). However, switching antidepressants alone is a reasonable alternative if CBT is declined or not available. (See 'Treatment-resistant depression' above.)

- **Medication side effects** – Pharmacotherapy may be associated with adverse events, including an increased risk of suicidal thoughts or behaviors. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication" and "Effect of antidepressants on suicide risk in children and adolescents".)

- **Continuation and maintenance treatment** – For children and adolescents who are treated acutely with antidepressants and remit, we recommend that the same regimen be continued for at least 6 to 12 months, rather than discontinuing pharmacotherapy (**Grade 1A**). For patients treated acutely with psychotherapy alone or psychotherapy plus pharmacotherapy, we typically continue the same regimen for at least 6 to 12 months after remission. Further maintenance treatment may be warranted based upon the patient's risk profile for recurrence. (See 'Continuation treatment' above and 'Maintenance treatment' above and "Pediatric unipolar depression and pharmacotherapy: Choosing a medication", section on 'Continuation and maintenance treatment' and "Pediatric unipolar depression: Psychotherapy", section on 'Maintenance phase and prevention'.)

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