Pediatric unipolar depression and pharmacotherapy: General principles

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INTRODUCTION

There are several general principles for prescribing pharmacotherapy to children and adolescents with unipolar depression. Following these principles may improve outcomes [1-3].

This topic reviews the general principles of administering pharmacotherapy to pediatric patients with depressive disorders. Choosing a drug and the efficacy of antidepressants in depressed youth is discussed separately, as are psychosocial treatments for adolescent depression, an overview of treating pediatric depression, and the effect of antidepressant medications on suicide risk in children and adolescents.

- (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication".)
- (See "Pediatric unipolar depression: Psychotherapy".)
- (See "Overview of prevention and treatment for pediatric depression".)
- (See "Effect of antidepressants on suicide risk in children and adolescents".)

PRESCRIBING PHARMACOTHERAPY

Indications — Pharmacotherapy for depression is indicated for children and adolescents with moderate to severe:

- Major depression (table 1) according to the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition (DSM-5) [4] or the World Health Organization's International Classification of Diseases-10th Revision (ICD-10) [5].
- Persistent depressive disorder (dysthymia) (table 2).
- Depressive symptoms with functional impairment.

Other indications for medications include depression with coexisting diagnoses amenable to antidepressants, as well as nonresponse to psychotherapy. Medications are generally not used for patients who have subsyndromal depressive symptoms [6].

Approach to the patient — Consider the following points when initiating pharmacotherapy for depressed children and adolescents (table 3):

- The diagnosis of a unipolar major depression should be confirmed.
- Pharmacotherapy is not an emergency medical treatment for depressed children and adolescents. For depressed patients, there is time for clinicians, patients, and families to discuss the use of medications and for patients and families to review the information to make informed decisions. Although suicidal behavior is a medical emergency, the emergent administration of antidepressants has no role in the acute management of suicidal youth because antidepressants generally do not take effect for at least two to four weeks. (See "Suicidal ideation and behavior in children and adolescents: Evaluation and management".)
- Frequent face-to-face contact (eg, once every week or two weeks) at the beginning of treatment fosters a trusting, supportive relationship.
- Antidepressants should be started only if clinicians and families can monitor patients. (See 'Monitoring' below.)
- Clinicians can help motivate patients and families to accept pharmacotherapy by explaining its benefits and risks, and the risks of no treatment [1].

Education — Before pharmacotherapy is initiated for pediatric depression, clinicians, patients, and families should discuss the medication's benefits, safety risks, and potential side effects; the lag in onset of therapeutic effects; and criteria for discontinuation (table 4 and table 5 and table 6). Education is part of obtaining assent from patients and informed consent from the parents or guardians.

Education about pharmacotherapy should be developmentally appropriate for the patient's level of understanding. In addition, education involves the families as partners of the treatment team and helps them understand the symptoms, causes, and treatment of depression; identify and manage dysphoria in the patient; address psychosocial deficits; and learn the importance of adherence with treatment [1]. The clinical features and diagnosis of depression are discussed separately. (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis".)

Discussion about the safety of antidepressants should include the United States Food and Drug Administration boxed warning in medication package inserts regarding suicidal ideation and behavior (table 7). The warning requires clinicians to discuss its content before prescribing the medication [6,7]. One of the driving forces behind this warning was that parents have the right to know about potential side effects, and a sense that clinicians were not properly monitoring the use of these medications. (See "Effect of antidepressants on suicide risk in children and adolescents", section on 'FDA black box warning'.)

Patients and families should also be educated about the high risk of morbidity and mortality from untreated depression. Following the advent of boxed warnings about antidepressants and suicidal ideation and behavior, studies of antidepressants in pediatric patients have concluded that the benefits of antidepressants under ordinary clinical circumstances outweigh the potential risk of suicidal ideation and behavior [8]. The adverse effects of untreated depression include the risk of suicide. (See "Suicidal behavior in children and adolescents: Epidemiology and risk factors".)

Patient and family education about aspects of depression that are not specifically related to pharmacotherapy are discussed elsewhere in this topic and in other topics. (See 'Information for patients' below and "Overview of prevention and treatment for pediatric depression", section on 'Education and resources'.)

Pretreatment evaluation — The initial assessment of depressed pediatric patients who are candidates for pharmacotherapy includes the following elements:

- Psychiatric history
- Mental status examination
- General medical history
- Physical examination
- Focused laboratory tests based upon findings from the history and physical examination

The psychiatric history should address baseline depressive symptoms, including suicidality, homicidality, psychosis, anxiety (particularly panic attacks), irritability, restlessness, agitation,

and impulsivity. Clinicians should confirm the diagnosis of unipolar major depression (table 1) or persistent depressive disorder (dysthymia) (table 2) by ensuring that the diagnostic criteria (including functional impairment) are met and that other psychiatric disorders (eg, bipolar disorder or psychotic prodrome) are excluded [4,5]. In addition, patients often have significant symptoms of depression with functional impairment that warrant pharmacotherapy, but fail to meet the full criteria for major depression. The term "Other specified depressive disorder" is used to describe this condition. (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Diagnosing depressive disorders'.)

Confirming the diagnosis of unipolar depressive disorders includes ruling out bipolar disorder by checking for a past history of mania (table 8) and hypomania (table 9), as well as a family history of bipolar disorder. Episodes of major depression usually precede the onset of manic and hypomanic episodes in bipolar disorder; thus, youth who initially present with a depressive syndrome may actually have bipolar disorder. Patients with known bipolar disorder should not receive antidepressant monotherapy. (See "Pediatric bipolar disorder: Clinical manifestations and course of illness", section on 'Major depression' and "Pediatric bipolar disorder: Assessment and diagnosis", section on 'Diagnosis'.)

In addition, the evaluation should address comorbidity such as substance use disorders. (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Comorbidity'.)

Further assessment depends upon the choice of antidepressant. For pediatric patients who are candidates for a selective serotonin reuptake inhibitor (SSRI), no pretreatment laboratory evaluation is necessary other than a urine pregnancy test in postpubertal females who are not using reliable contraception. The effects of SSRIs in pregnancy are discussed separately. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors", section on 'Selective serotonin reuptake inhibitors'.)

Tricyclics — Although tricyclics are not recommended for treatment of pediatric depression, there is some evidence that clomipramine is efficacious in older adolescents. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication", section on 'Choice of medication for acute treatment'.)

Clinicians using tricyclics should obtain the patient's cardiac history as well as a family (first-degree relative) cardiac history before administering tricyclics to children and adolescents. For

patients with a personal history of cardiac disease or a family history of premature (<40 years of age) cardiac problems, a pediatric cardiology consult is warranted before starting tricyclics [9].

In youth who are candidates for treatment with tricyclics, the pretreatment physical examination and laboratory tests include weight, blood pressure, pulse, and a baseline electrocardiogram (ECG) [9]. Tricyclics should not be initiated unless these parameters are within the normal limits for the child's age, sex, and height. Additional baseline tests include a pregnancy test for postpubertal females who are not using reliable contraception.

Additional information about the baseline cardiac evaluation that is performed prior to initiating tricyclics and the effects of tricyclics in pregnancy are discussed separately. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Cardiac evaluation' and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors", section on 'Tricyclic antidepressants'.)

Dose — For adolescents, SSRIs are generally started at approximately one-half the usual adult dose (table 10) for the first week of treatment. For children, lower doses are used when prescribing fluoxetine. By contrast, doses of citalopram, escitalopram, and sertraline are similar for children and adolescents because younger children metabolize these drugs more quickly than fluoxetine. For both children and adolescents, doses are titrated up, depending upon response and tolerability:

- Fluoxetine – For adolescents, fluoxetine is started at 10 mg per day for one week and then increased to a target dose of 20 mg per day. After three weeks, if response is insufficient and the drug is tolerated, the dose is increased to 40 mg per day for the remainder of the drug trial. However, if a partial response occurs within four weeks of prescribing 40 mg per day, the dose is increased to 60 mg per day.

  For children, we start at 5 mg per day for one week and then titrate up to a target dose of 10 mg per day. After three weeks, if response is inadequate, we increase the dose to 20 mg per day for the remainder of the drug trial.

- Citalopram – Citalopram is started at 10 mg per day for one week and then increased to a target dose of 20 mg per day. After three weeks, if response is insufficient and the drug is tolerated, the dose is increased to 40 mg per day for the remainder of the drug trial. However, if a partial response occurs within four weeks of prescribing 40 mg per day, we discuss with the patient and family both the possibility of raising the dose further, as well as concerns that doses above 40 mg per day can cause QT interval prolongation. If the patient and family wish to continue citalopram, we obtain an electrocardiogram (ECG) at

40 mg per day, prior to increasing the dose, and if the ECG is normal, we increase the dose to 60 mg per day. One week after increasing the dose to 60 mg, we obtain a second ECG.

- Escitalopram – Escitalopram is started at 5 mg per day for one week and then increased to a target dose of 10 mg per day. After three weeks, if response is insufficient and the drug is tolerated, the dose is increased to 20 mg per day for the remainder of the drug trial. However, if a partial response occurs within four weeks of prescribing 20 mg per day, we discuss with the patient and family both the possibility of raising the dose further, as well as concerns that doses above 20 mg per day can cause QT interval prolongation. If the patient and family wish to continue escitalopram, we obtain an ECG at 20 mg per day, prior to increasing the dose, and if the ECG is normal, we increase the dose to 30 mg per day. One week after increasing the dose to 30 mg per day, we obtain a second ECG.

- Sertraline – Sertraline is started at 25 mg per day for one week and then increased to a target dose of 50 mg per day. After three weeks, if response is insufficient and the drug is tolerated, the dose is increased to 100 mg per day for the remainder of the drug trial. However, if a partial response occurs within four weeks of prescribing 100 mg per day, the dose may be increased by 25 to 50 mg per day every several (eg, three) weeks to a maximum dose of 200 mg per day.

We typically do not use paroxetine for pediatric depression because of its lack of demonstrated efficacy [10,11]. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication", section on 'Other specific SSRIs'.)

Symptoms typically begin to improve within two to four weeks after the target dose is achieved [1,12].

Although 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), and found no advantage for the maximum dose of the SSRI that was used, none of the studies were fixed-dose trials (which is a preferred method for studying dose effects) [12]. In addition, studies in treatment-resistant pediatric depression suggest that higher doses of SSRIs may be superior to continued low doses [13,14].

Dose dependent QT interval prolongation with citalopram and escitalopram is discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Cardiac'.)

Duration of an adequate trial — An adequate antidepressant trial in children and adolescents lasts 6 to 12 weeks, which includes the time to titrate from the starting dose to the minimum

therapeutic dose, as well as 4 to 6 weeks at the minimum therapeutic dose [8,15,16]. For depressed patients who improve but do not remit at the minimum therapeutic dose, a dose increase within the therapeutic range is indicated, provided the drug is tolerated. If improvement is insufficient after 4 weeks at the maximum therapeutic dose, switching medications is indicated [17]. Evidence supporting this approach includes a meta-analysis of 13 randomized trials that compared SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline) with placebo in pediatric unipolar major depression (n >3000) [12]. Approximately 70 percent of the benefit occurred within the first two weeks of treatment, and minimal treatment gains were observed after four weeks of treatment.

Monitoring — Clinicians prescribing pharmacotherapy for depressed patients should assess symptoms, side effects (table 4 and table 5 and table 6), functioning, adherence, and satisfaction with treatment [16].

Pediatric patients with depressive disorders who are treated with antidepressants must be monitored by clinicians and families for the following adverse responses, particularly during the initial few months of therapy and when doses are increased or decreased [6,17-20]:

- Worsening depressive symptoms (eg, suicidal ideation and behavior, anxiety and panic attacks, or insomnia)
- Agitation
- Irritability or hostility
- Impulsivity
- Akathisia (ie, restlessness and inability to sit down)
- Hypomania (table 9) or mania (table 8)

The family should be educated about possible indicators of worsening depression and suicidality, and should notify clinicians if these symptoms occur because it may be necessary to adjust the dose, switch to a different medication, or discontinue the medication.

We encourage clinicians to provide measurement based care, that is, monitor progress by serially measuring the severity of symptoms with a standardized scale. The most widely used and studied scale among adults is the self-report Patient Health Questionnaire – Nine Item (PHQ-9) (table 11), and other studies indicate that the questionnaire can be used in adolescents as well [21]. In addition, the Mood and Feelings Questionnaire can be used [22-24]. The Mood and Feelings Questionnaire has a separate form that is completed by the patient and

the parent or caregiver; the questionnaire is validated for both children and adolescents and is in the public domain. However, there is no evidence that using such scales improves outcomes in pediatric depression. Additional information about measurement based care is discussed separately in the context of adults. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

Frequency — For outpatients who are treated with antidepressants, we typically contact families weekly for the first four weeks at the onset of pharmacotherapy and when medications are switched. Contact can be in person or by phone but should include several in-person appointments within the first eight weeks of starting medication and as clinically necessary.

The frequency of follow-up at other times is individualized, and can range from once every two weeks to once every three months. The schedule is based upon the severity of the depressive syndrome, level of social support, and the presence of comorbidity, adverse effects, and stressors (eg, break-up with girlfriend, death of a close relative, or poor school performance).

Tricyclics — Tricyclics are rarely used to treat pediatric depression. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication", section on 'Choice of medication for acute treatment'.)

For pediatric patients treated with tricyclics, blood pressure, pulse, and an ECG should be repeated after the therapeutic dose is achieved, when the dose is changed, if the patient receives medications that can interact with tricyclics, after discontinuation of tricyclics, or if clinicians think the tricyclic serum concentration has changed [9]. If cardiac parameters are outside the normal limits for age, sex, and height during therapy with tricyclics (particularly patients who are hypotensive or tachycardic), patients should have their dose decreased and testing repeated (in two weeks for nortriptyline and one week for all other tricyclics). In addition, consultation with a cardiologist is generally warranted.

Treatment-emergent suicidality — Patients treated with antidepressants who suffer suicidal behavior or sudden or severe suicidal ideation should be referred for emergency assessment to determine whether hospitalization is required. In addition, we suggest that clinicians adjust the dose, or switch to a different SSRI or a drug from a different antidepressant class, consistent with guidelines from the American Academy of Child and Adolescent Psychiatry (table 4) [20].

DISCONTINUING PHARMACOTHERAPY

Pharmacotherapy for pediatric depression generally lasts for at least 6 to 12 months after remission. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication",

section on 'Continuation and maintenance treatment'.)

For patients who decide to stop antidepressants, prescribing clinicians should supervise discontinuation of treatment. It is preferable to stop pharmacotherapy when psychosocial stress is reduced and the consequences of recurrences are reduced (eg, summer vacation) [7].

Antidepressants should generally be tapered before discontinuation. A taper of approximately 25 to 50 percent per week provides a gradual decrease that allows the body time to adjust to the lower dose. As an example, sertraline 200 mg per day can be decreased to 150 mg per day for week one, 100 mg per day for week two, 50 mg per day for week three, and 25 mg per day for week four, after which the medication is stopped.

Abrupt discontinuation of selective serotonin reuptake inhibitors can cause a discontinuation (withdrawal) syndrome marked by:

- Anxiety
- Chills
- Dizziness
- Fatigue
- Myalgias
- Nausea

Discontinuation symptoms may occur after just six to eight weeks of therapy. However, the half-life of fluoxetine is long enough such that abrupt discontinuation generally does not cause problems [25,26].

Discontinuation of antidepressants is discussed further in the context of adults. (See "Discontinuing antidepressant medications in adults".)

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

- Pharmacotherapy should be reserved for children and adolescents who meet criteria for moderate to severe major depression (table 1), persistent depressive disorder (dysthymia) (table 2), or depressive symptoms with functional impairment, as well as nonresponse to psychotherapy. (See 'Indications' above.)
- Pharmacotherapy is not an emergency medical treatment for depressed children and adolescents. Although suicidal behavior is a medical emergency, the emergent administration of antidepressants has no role in the acute management of suicidal youth. (See 'Approach to the patient' above and "Suicidal ideation and behavior in children and adolescents: Evaluation and management".)
- Prior to starting antidepressants, clinicians should educate patients and families about depression, including its symptoms and available treatments. Clinicians should also discuss the benefits and side effects of pharmacotherapy (table 4 and table 5 and table 6), the United States Food and Drug Administration boxed warning about suicidal

ideation and behavior (table 7) and other safety risks, as well as the risks of untreated depression. (See 'Education' above and "Effect of antidepressants on suicide risk in children and adolescents".)

- The initial assessment of depressed pediatric patients who are candidates for pharmacotherapy includes a psychiatric and general medical history, mental status and physical examination, and focused laboratory tests based upon findings from the history and physical examination. (See 'Pretreatment evaluation' above.)

- For children and adolescents, selective serotonin reuptake inhibitors (SSRIs) are generally started at approximately one-half the usual adult dose (table 10) for the first week of treatment. (See 'Dose' above.)

- An adequate antidepressant trial in children and adolescents lasts 6 to 12 weeks, which includes the time to titrate from the starting dose to the minimum therapeutic dose, as well as 4 to 6 weeks at the minimum therapeutic dose. (See 'Duration of an adequate trial' above.)

- Clinicians and families should monitor patients who are treated with pharmacotherapy by assessing symptoms, including suicidal and homicidal ideation and behavior, anxiety and panic attacks, agitation, irritability or hostility, impulsivity, akathisia (ie, restlessness and inability to sit down), and insomnia. Patients should also be monitored for hypomania (table 9) or mania (table 8), as well as medication side effects (table 5 and table 4) and adherence, psychosocial functioning, and satisfaction with treatment. (See 'Monitoring' above.)

- If patients treated with antidepressants suffer suicidal behavior or sudden or severe suicidal ideation, we generally adjust the dose, or switch to a different SSRI or a drug from a different antidepressant class. (See 'Treatment-emergent suicidality' above.)

- Before discontinuing antidepressants, the dose is generally tapered by 25 to 50 percent per week to avoid discontinuation symptoms. However, it is reasonable to discontinue fluoxetine abruptly. (See 'Discontinuing pharmacotherapy' above.)

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