



## TREATING PEDIATRIC DEPRESSION IN PRIMARY CARE: COPING WITH THE PATIENTS' BLUE MOOD AND THE FDA'S BLACK BOX

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Identifying and treating depression in young patients can save lives, but the current climate leaves physicians fearful and confused about how best to proceed.<sup>1</sup> The United States Food and Drug Administration (FDA) "Black Box Warnings" about antidepressants have reduced the frequency with which physicians prescribe these medications.<sup>2</sup> Although most psychotropic prescriptions written for children, including the antidepressants, are written by pediatricians,<sup>3</sup> these physicians often lack access to alternative interventions, such as cognitive behavioral therapy (CBT). Emerging research and FDA recommendations can be integrated to provide reasonable guidelines for pediatricians to evaluate and manage their patients with depression. Pediatricians' comfort level in accurately diagnosing and treating depressed patients is shaped by appropriate training and experience during their residency, continuing education, access to mental health resources and adequate time for patient counseling/education and for monitoring their patients for potential adverse side effects.<sup>4</sup>

### CHARACTERISTICS OF PEDIATRIC DEPRESSION

The symptoms of depression change with development.<sup>5</sup> Depressed preschoolers often exhibit irritability, apathy, and regression. School-age children may display sad or irritable mood, crying spells, and lack of pleasure. These depressed children are more likely to complain of somatic symptoms, such as headaches, than older children.<sup>6</sup> In contrast to depressed adults who frequently complain of sad mood, depressed adolescents often are intensely mood reactive, irritable and sensitive to criticism. Comorbid dysthymia, substance abuse, and conduct and anxiety disorders are also common in adolescents.<sup>7</sup>

Psychosis may occur in a substantial number (25%) of very depressed youth, usually as a single voice criticizing them.<sup>8</sup> This pattern contrasts with preadolescents, where hallucinations ("saw a scary man in my closet" after viewing frightening movie) are not necessarily associated with significant psychopathology. Disconcerting to clinicians is the depressed patient who progresses to a more disabling bipolar disorder. Switching from depression to mania may occur in children and adolescents who present with depressive symp-

tomms, particularly those with sudden onset depression, hypersomnia, and psychomotor retardation, and warrants consideration in every case. Escalating lability throughout the day and emotional tantrums lasting hours suggest pediatric mania.<sup>9</sup> The highest rates of manic switching occur in children ages 10 to 14, and no antidepressant appears uniquely "safe" or substantially less likely to precipitate mania in juveniles.<sup>10</sup> Discerning the risk for unmasking bipolar disorder with an antidepressant remains difficult, given the diagnostic controversy about developmentally appropriate criteria for juvenile bipolar disorder.<sup>11</sup> Severe tantrums (lasting hours), family history of antidepressant-induced hypomania/mania and, perhaps most importantly, a family history of bipolar disorder all increase the risk of underlying mania, even if patients present initially with depressive symptoms.

Frequently there are coexisting conditions that may influence the onset, treatment response and recurrence of depression. Comorbid disruptive disorder and substance abuse are more likely to be associated with suicidal behavior.<sup>12</sup> Coexisting anxiety often precedes depression and learning cognitive strategies can prevent relapse.<sup>13</sup> Undetected learning disorders can present as apathy and difficulty concentrating. Chronic medical illness can increase the risk of depression. Depressed adolescents with comorbid attention deficit disorder may be less responsive to treatment, so underlying conditions may require attention to improve the depression as well.<sup>14</sup>

### TREATMENT OF PEDIATRIC DEPRESSION

Psychotherapy is a standard initial treatment for juvenile depression, and pediatricians often refer patients for counseling. CBT has been the most studied psychotherapy for pediatric depression, demonstrating benefit in pediatric patients with Major Depressive Disorder, both alone and in combination with antidepressant medications.<sup>15</sup>

Although pediatricians are unlikely to provide formal CBT to their patients, CBT techniques can be incorporated, and often alleviate depressive/suicidal and anxiety symptoms. Identifying available mental health clinicians who can provide CBT is useful for young depressed patients. CBT encourages patients to increase self-awareness and challenge ideas that perpetuate depressive thoughts. Pediatricians frequently give advice to children and families about how to address these negative statements; CBT techniques useful in all clinical encounters are provided in Table I (available at [www.](http://www.)

jpeds.com). Clinicians can encourage patients to chart their mood to detect trends, increase exercise and pleasurable activities (natural antidepressants), and to expand their problem-solving repertoire to “fix” problems or mistakes rather than replay failures.

For those youth with a moderate to severe mood disorder, and experiencing substantial impairment in multiple domains (family, school, peers), patients and their family may consider a medication trial. Multisite, randomized, placebo-controlled trials have shown significant efficacy of selective serotonin reuptake inhibitors (SSRIs, including sertraline, fluvoxamine, and fluoxetine) for treating obsessive-compulsive disorder with a significant difference between drug and placebo.<sup>16</sup> The available evidence for the use of antidepressants for major depression has been more modest.

Of the fifteen published randomized, double-blind, placebo-controlled trials using SSRIs to treat pediatric depression, four were considered positive by the FDA.<sup>17</sup> The first large study of fluoxetine (Prozac) was published in 1997.<sup>18</sup> In this 8-week study of 96 patients aged 7-17, 56% responded to fluoxetine, compared to 33% treated with a placebo. More recent multi-site adolescent depression trials with paroxetine, sertraline, and escitalopram have yielded similar response rates, but were compromised by high placebo rates. In addition, inclusion/exclusion criteria (excluding children with comorbid psychiatric conditions common in clinic patients with depression), short study duration (typically 6 to 12 weeks), and the limitations of measurement tools (adult scales often failed to show benefit in these trials despite clinician perceptions of improvement, such as in the paroxetine trial) compromise the applicability of these data to clinical practice.<sup>19</sup> Larger study samples and longer trials are needed to better determine efficacy and effectiveness of antidepressants in pediatric populations. Despite limitations in the data, antidepressants are often an appropriate and helpful part of the treatment plan for pediatric depression. Current antidepressant treatment guidelines are summarized in Table II (available at [www.jpeds.com](http://www.jpeds.com)).

## MONITORING OF ANTIDEPRESSANTS IN PEDIATRIC PATIENTS

The FDA black box warning suggested vigilant monitoring of patients started on antidepressants based on a statistically significant increase in suicidality following analysis of 4,000 children in drug trials, although there were no completed suicides in any of these trials.<sup>1</sup> FDA recommendations<sup>20</sup> for monitoring pediatric patients receiving antidepressants were derived from the TADS (Treatment of Adolescent Depression Study) protocol. The FDA recommended that patients placed on antidepressants, should be seen weekly for medication monitoring for 4 weeks, then every other week for the second month, then every 3 months or more frequently, as clinically indicated. Increased visits were recommended based on clinical circumstances, such as patient deterioration after an initial positive response to an antidepressant.

These recommendations may pose some problems. Some patients and families may resist this frequency of visits or have difficulty adhering to these recommendations. More-

over, these recommendations can inadvertently provide a false sense of security, as weekly visits do not, by themselves, ensure patient safety. The message for all clinicians treating patients with antidepressants remains, “If the patient feels like hurting self or anyone else, becomes more agitated, has increased impulsivity, decreased sleep or uncharacteristic aggression after beginning an antidepressant, contact the prescribing clinician immediately.” Patients need to know how to reach the physician quickly should suicidality or untoward effects occur following initiation of an antidepressant.

Given heightened concerns about antidepressant-related suicidality, clinicians should also provide information about possible behavioral changes occurring during antidepressant treatment. Adverse responses to starting antidepressant medication are summarized in Table III (available at [www.jpeds.com](http://www.jpeds.com)).

Walkup et al<sup>21</sup> suggest patients may become activated (agitation, anxiety, and insomnia) 4 to 6 weeks after an antidepressant is started. This reaction may be dose-related and appears more often in younger patients. This drug-related side effect does not necessarily mean the patient has bipolar disorder. Dose reductions or switching to a different antidepressant, even in the same class, may be effective for treating activated patients. Apathy that develops during antidepressant treatment can be confused with worsening depression. The apathy sometimes is relieved with a dose change or augmentation with another low dose antidepressant from a different antidepressant class. Adolescents may be less inclined to report sexual dysfunction while taking antidepressants, so clinicians may need to inquire directly about sexual functioning to sustain adherence to treatment.<sup>22</sup>

The consensus about the duration of medication treatment is to make changes slowly and to consider the magnitude of ongoing functional impairment. It appears preferable to continue a dose at which the patient improved for 9 to 12 months before tapering.<sup>23</sup> Usually children and adolescents are most susceptible to relapse (approximately 40%) between 6 months to one year after discontinuing medication treatment.<sup>24</sup>

Antidepressants are appropriately initiated in pediatric patients to reduce the morbidity and mortality of depression (including substance abuse, homicide, suicide, early pregnancy), to alleviate suffering, and to minimize the impact of depression on the child's development. Pediatricians must continue to weigh the potential benefits and risks of treatments in each child's unique situation, as decisions are made with the patient and family about continuation, tapering, or switching antidepressants.

Avoidance in treating depressed youth may reverse the significant 30% reduction in rates of completed suicide that has coincided with the availability of SSRIs since the early 1990s. Rather, careful assessment of children and adolescents with depression, coupled with tailored, individualized treatment which may include medications and therapy, is clinically appropriate and may be life saving.

*References are available at [www.jpeds.com](http://www.jpeds.com).*

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**Table I. Cognitive behavioral techniques for primary care encounters**

<b>CBT technique</b>	<b>Patient examples</b>	<b>Application with clinician responses</b>
1. Evaluate the evidence for a conclusion	"I'm no good at sports."	"What happened when you played this sport? Did any good things occur? Which other do you play better?"
2. Challenge negative cognitions	"I can't go to school—people will make fun of me."	"What do students do when you arrive? Which students are glad to see you?"
3. Identify automatic thoughts	"I'm no fun. No one wants to be around/play with me."	"What makes you no fun? What happened that you thought this? What evidence leads you to reach such conclusions?"
4. Examine other perspectives	"I don't know what to do."	"How would Spiderman/your best friend/someone you admire react to this? What did your friend/classmate/parent think about your situation?"
5. Provide competing responses	"I'm afraid I'll start crying in class."	"If you start to feel sad, what can you do before you start to cry? How can you read something that makes you laugh, doodle?"
6. Cultivate positive self-talk	"I do badly at everything I try."	"I'm just going to get my paper out—now, I'm just going to try to write my name up here."
7. Practice and reinforce positive skills	"I'm too tired to do anything."	Plan for your friend to come over as you finish your homework in case you need to review or some help.

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**Table II. Use of antidepressants in children and adolescents**

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## Evaluation

1. Consider antidepressant for patients with moderate to severe depression, or recurrent depressive episodes
2. Consider antidepressant for patients who have family members with positive response to SSRI antidepressant (and screen if family members had negative response/side effects to SSRIs)
3. Screen for potential bipolar disorder (See [Table III](#) for indications of manic switching following treatment)
  - Family history of bipolar disorder, pressured speech, lack of sleep, impulsivity, patient initially presents suddenly very depressed out of the blue, excessive sleeping, very slowed down
4. Review potential risk for increased agitation, suicidal ideation, and clarify importance of contacting physician if any thoughts of harm to self or others emerge
5. Review SSRI Discontinuation syndrome (See [Table III](#)) if medication is stopped abruptly (dizziness, paresthesias, nausea, increased irritability)
6. Have patient and family sign consent (can obtain form from [www.aacap.org](http://www.aacap.org))

## Follow-Up

1. If not feasible to meet weekly, ensure patient and family know how to contact physician if any thoughts of harm to self or others emerge, or if patient becomes more agitated
  2. Review symptoms AND provide side effect scale (download free from [www.schoolpsychiatry.org](http://www.schoolpsychiatry.org)) and rating scales
  3. Create reasonable expectations (time line of medication response can take four to six weeks, if taken consistently).
  4. Establish realistic outcome measures with patient (medication will improve sadness, ruminations, but will not make patient "mind" better, or no longer argue about curfew/bedtime)
  5. Counsel adolescent about risks of substance use, especially alcohol, when depressed and on medication
  6. Consider safety issues in the home (availability of dangerous medications, weapons) and provide phone number to access emergency psychiatric services
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**Table III. Monitoring and addressing adverse responses to starting antidepressants**

	<b>Suicidality</b>	<b>Akathisia**</b>	<b>Manic switching***</b>	<b>Discontinuation syndrome</b>	<b>Serotonergic syndrome*</b>	<b>Apathy</b>
Symptoms	Thoughts or acts of self-harm	Inner restlessness; sense of being "driven": pacing or movements usually bilateral, symmetrical, often specific muscle groups	Silliness, giggling, angry outbursts, lack of sleep	Fear, dizziness, lethargy, parasthesias, nausea, vivid dreams, insomnia, increased irritability or depression	Confusion, restlessness, agitation, fever, hyperthermia, diaphoresis, hypertonia/clonus (usually symmetrical), tremor, shivering, hyper-reflexia	Disinterest, confusion, lack of enjoyment in previously enjoyed activities; NOT depressed
Incidence	2%	5-25%	2-70% in bipolar depression, but 1-10% in unipolar depression (TCA > SSRI)	4-18%; shorter half-life antidepressants > longer half-life agents	Rare (<1%)	
When most commonly occurs	1-4 weeks	2-6 weeks	2-4 weeks, or within weeks of dose increases	Within 1-7 days of stopping, decreasing antidepressant	When multiple serotonergic medications are added or combined	24-78 weeks
Response	Discontinue, monitor resolution of suicidality, consider alternative antidepressant	Consider switch to alternative agent; if very positive response for depression, consider propranolol, or <4 weeks augmentation with clonazepam	Discontinue antidepressant; consider mood stabilizers if impairing mania (vs. milder hypomanic symptoms); after manic symptoms resolve, if prominent depression, consider alternative antidepressants, but titrate slowly and attempt low doses	Resume antidepressant and titrate down slowly; consider switching/ adding long half-life antidepressant (fluoxetine) to allow more gradual taper	Hospital management of hyperthermia, benzodiazepines for seizures or muscle hyperactivity; serotonin antagonists such as cyproheptadine 4-8 mg up to qid	Consider augmentation with additional antidepressant, but at low dose (e.g., bupropion SR 100 mg qam)

\*Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med* 2005;352:1112-20.

\*\*Hanse L. A critical review of akathisia, and its possible association with suicidal behavior. *Hum Psychopharm Clin Exp* 2001; 16:495-505.

\*\*\*Martin A, Young C, Leckman JF, Mukonoweshuro C, Rosenheck R, Leslie D. Age effects on antidepressant-induced manic conversion. *Arch Pediatr Adolesc Med* 2004;158:773-780.

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