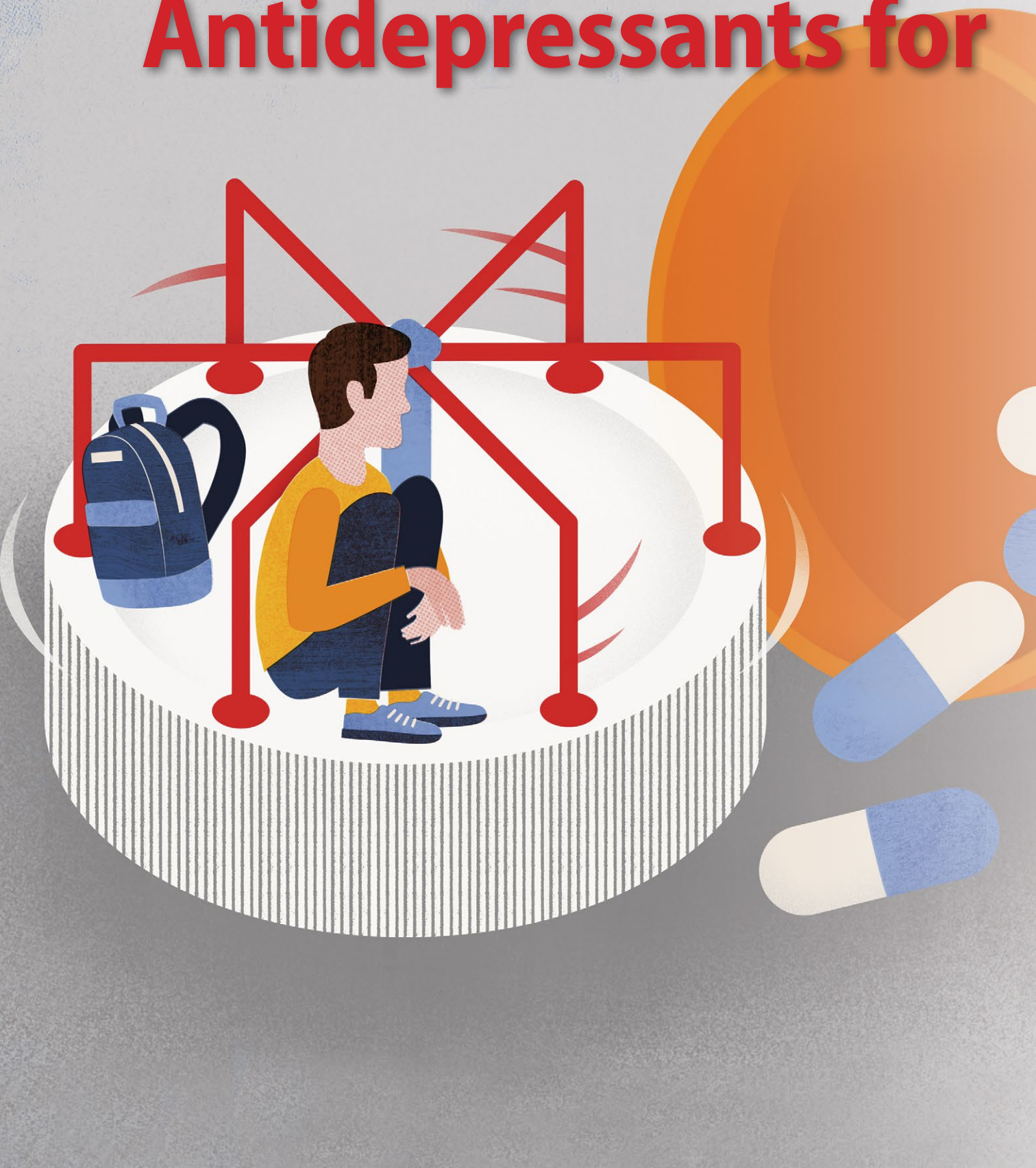
Antidepressants for



pediatric patients

Optimal prescribing depends on a thorough understanding of these agents' efficacy and safety

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Disclosures
Dr. Bloch receives grant or research support from Biohaven Pharmaceuticals, Janssen Pharmaceuticals, Neurocrine Biosciences, and Therapix Biosciences. Dr. Dwyer received support from T32- MH018268 during the preparation of this manuscript.

Major depressive disorder (MDD) is a significant pediatric health problem, with a lifetime prevalence as high as 20% by the end of adolescence.[1-3] Major depressive disorder in adolescence is associated with significant morbidity, including poor social functioning, school difficulties, early pregnancy, and increased risk of physical illness and substance abuse.[4-6] It is also linked with significant mortality, with increased risk for suicide, which is now the second leading cause of death in individuals age 10 to 24 years.[1,7,8]

As their name suggests, antidepressants comprise a group of medications that are used to treat MDD; they are also, however, first-line agents for generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) in adults. Anxiety disorders (including GAD and other anxiety diagnoses) and PTSD are also common in childhood and adolescence with a combined lifetime prevalence ranging from 15% to 30%.[9,10] These disorders are also associated with increased risk of suicide.[11] For all of these disorders, depending on the severity of presentation and the preference of the patient, treatments are often a combination of psychotherapy and psychopharmacology.

Clinicians face several challenges when considering antidepressants for pediatric patients. Pediatricians and psychiatrists need to understand whether these medications work in children and adolescents, and whether there are unique developmental safety and tolerability issues. The evidence base in child psychiatry is considerably smaller compared with that of adult psychiatry. From this more limited evidence base also came the controversial "black-box" warning regarding a risk of emergent suicidality when starting antidepressants that accompanies all antidepressants for pediatric, but not adult, patients. This warning has had major effects on clinical encounters with children experiencing depression, including altering clinician prescribing behavior.[12]

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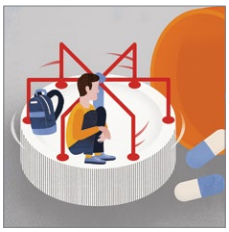

Antidepressants for pediatric patients

Clinical Point

There is strong evidence that SSRIs are effective for treating pediatric anxiety disorders and OCD

Table 1

Characteristics of commonly used antidepressants[a]

	Pediatric			Adult	
	Starting dose (mg/d)	Typical dose range (mg/d)	FDA indications	Starting dose (mg/d)	Typical dose range (mg/d)
Selective serotonin reuptake inhibitors					
Citalopram	10 to 20	20 to 40	—	20	40
Escitalopram	5 to 10	10 to 40	MDD	10	20 to 40
Fluoxetine	10 to 20	20 to 80	MDD, OCD	20	20 to 80
Fluvoxamine	25 to 50	50 to 300	OCD	100 to 300	100 to 300
Paroxetine	10 to 20	20 to 60	—	10 to 20	40 to 60
Sertraline	25 to 50	100 to 200	OCD	50	150 to 250
Serotonin-norepinephrine reuptake inhibitors					
Venlafaxine	37.5	150 to 225	—	37.5 to 75	75 to 375
Duloxetine	30	40 to 60	GAD	20 to 60	20 to 80
Desvenlafaxine	25	25 to 100	—	50	50 to 400
Atypical antidepressants					
Bupropion	100	150 to 300	—	100 to 150	150 to 300
Mirtazapine	7.5 to 15	15 to 45	—	15	15 to 45
Vilazodone	Not studied		—	10	10 to 40
Vortioxetine	5	5 to 20	—	10	10 to 80
Tricyclic antidepressants					
Clomipramine	25	50 to 200	OCD	25	100 to 250
Desipramine	25 to 50	50 to 200	—	100 to 200	150 to 300
Nortriptyline	30 to 50	30 to 150	—	100	75 to 150
Imipramine	10	50 to 150	Enuresis	25 to 75	150 to 300

[a]All information in this Table is based on the FDA-approved prescribing information for each medication.

GAD: generalized anxiety disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PD: panic disorder; PTSD: posttraumatic stress disorder; SAD: social anxiety disorder

In this article, we review the current evidence for antidepressant efficacy, tolerability, and safety in pediatric patients. We also suggest ways in which clinicians might choose, start, and stop antidepressants in children, as well as how to talk with parents about benefits, risks, and the black-box warning.

Do antidepressants work in children?

Selective serotonin reuptake inhibitors. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used class of antidepressants in both children and adults.[13] While only a few SSRIs are FDA-approved for pediatric indications, the lack of FDA approval is typically related to a lack of sufficient testing in randomized controlled trials (RCTs) for specific pediatric indications, rather than to demonstrable differences in efficacy between antidepressant agents. Since there is currently no data to suggest inferiority of one agent compared to another in children or adults,[14,15] efficacy data will be discussed here as applied to the class of SSRIs, generalizing from RCTs conducted on individual drugs. ***Table 1*** lists FDA indications and dosing information for individual antidepressants.

There is strong evidence that SSRIs are effective for treating pediatric anxiety disorders (eg, social anxiety disorder and GAD)[16] and OCD,[17] with numbers needed to treat (NNT) between 3 and 5. For both of these disorders, SSRIs combined with cognitive-behavioral therapy (CBT) have the

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	FDA indications	Half-life
	MDD	20 hours
	MDD, GAD	27 to 32 hours
	MDD, OCD, PD	4 to 6 days
	OCD	16 hours
	MDD, OCD, PTSD, GAD, SAD, PD	21 hours
	MDD, OCD, PTSD, SAD, PD	26 hours
	MDD, GAD, SAD, PD	10 hours
	MDD, GAD	12.5 hours
	MDD	11 hours
	MDD	21 hours
	MDD	20 to 40 hours
	MDD	25 hours
	MDD	66 hours
	OCD	32 hours
	MDD	12 to 27 hours
	MDD	18 to 44 hours
	MDD	11 to 25 hours

highest likelihood of improving symptoms or achieving remission.[17,18]

Selective serotonin reuptake inhibitors are also effective for treating pediatric MDD; however, the literature is more complex for this disorder compared to GAD and OCD as there are considerable differences in effect sizes between National Institute of Mental Health (NIMH)–funded studies and industry-sponsored trials.[13] The major NIMH-sponsored adolescent depression trial, TADS (Treatment for Adolescents and Depression Study), showed that SSRIs (fluoxetine in this case) were quite effective, with an NNT of 4 over the acute phase (12 weeks).[19] Ultimately, approximately 80% of adolescents improved over 9 months. Many industry-sponsored trials for MDD in pediatric patients had large placebo response rates (approximately 60%), which resulted in smaller between-group differences, and estimates of an NNT closer to 12,[13] which has muddied the waters in meta-analyses that include all trials.[20] Improvement in depressive symptoms also appears to be bolstered by concomitant CBT in MDD,[19] but not as robustly as in GAD and OCD. While the full benefit of SSRIs for depression may take as long as 8 weeks, a meta-analysis of depression studies of pediatric patients suggests that significant benefits from placebo are observed as early as 2 weeks, and that further treatment gains are minimal after 4 weeks.[15] Thus, we recommend at least a 4- to 6-week trial at therapeutic dosing before deeming a medication a treatment failure.

Posttraumatic stress disorder is a fourth disorder in which SSRIs are a first-line treatment in adults. The data for using SSRIs to treat pediatric patients with PTSD is scant, with only a few RCTs, and no large NIMH-funded trials. Randomized controlled trials have not demonstrated significant differences between SSRIs and placebo[21,22] and thus the current first-line recommendation in pediatric PTSD remains trauma-focused therapy, with good evidence for trauma-focused CBT.[23] Practically speaking, there can be considerable overlap of PTSD, depression, and anxiety symptoms in children,[23] and children with a history of trauma who also have comorbid MDD may benefit from medication if their symptoms persist despite an adequate trial of psychotherapy.

Taken together, the current evidence suggests that SSRIs are often effective in pediatric GAD, OCD, and MDD, with low NNTs (ranging from 3 to 5 based on NIMH-funded trials) for all of these disorders; there is not yet sufficient evidence of efficacy in pediatric patients with PTSD.

Fluoxetine has been studied more intensively than other SSRIs (for example, it was the antidepressant used in the TADS trial), and thus has the largest evidence base. For this reason, fluoxetine is often considered the first of the first-line options. Additionally, fluoxetine has a longer half-life than other antidepressants, which may make it more effective in situations where

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Fluoxetine has been studied more intensively than other SSRIs and is often considered the first of the first-line options

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In general, adverse effect profiles are worse for SNRIs compared to SSRIs

Table 2

Summary of clinical guidance for antidepressants for pediatric patients and adults

	MDD	Anxiety	OCD
Medications with FDA-approval in children	Fluoxetine, escitalopram	Duloxetine (GAD)	Fluoxetine, fluvoxamine, sertraline
Medications with demonstrated efficacy in adults	SSRIs (not fluvoxamine), SNRIs, atypical antidepressants, TCAs (not clomipramine)	SSRIs, venlafaxine, duloxetine	SSRIs (not citalopram or escitalopram), clomipramine
Time course of response in children and adults	Logarithmic pattern of response compared with placebo. Greatest incremental benefits seen early in treatment, but may take time for it to reach a clinically significant degree		
Time course of adverse effects	Adverse effects typically occur within days to a week of starting medications or dose increase. Many patients may spontaneously remit with continued treatment for 1 to 2 weeks. If adverse effects do not remit at that point, they are unlikely to improve spontaneously (unless attributable to underlying condition)		
Minimal recommended duration of treatment to determine efficacy in children and adults	4 to 6 weeks	6 to 8 weeks	8 to 12 weeks
Monitoring guidelines for initiation of antidepressants in children	Weekly for the first month, biweekly for the next month, then monthly		
Dose-response relationship for SSRIs in adults	Higher likelihood of response at higher doses within therapeutic range		
Dose-response relationship for SSRIs in children	No evidence of greater response at higher doses within recommended therapeutic range. Minimal fixed-dose trial data		

GAD: generalized anxiety disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

patients are likely to miss doses, and results in a lower risk of withdrawal symptoms when stopped due to "self-tapering."

SNRIs and atypical antidepressants. Other antidepressants commonly used in pediatric patients but with far less evidence of efficacy include serotonin-norepinephrine reuptake inhibitors (SNRIs) and the atypical antidepressants bupropion and mirtazapine. The SNRI duloxetine is FDA-approved for treating GAD in children age 7 to 17, but there are no other pediatric indications for duloxetine, or for the other SNRIs.

In general, adverse effect profiles are worse for SNRIs compared to SSRIs, further limiting their utility. While there are no pediatric studies demonstrating SNRI efficacy for neuropathic pain, good data exists in adults.[24] Thus, an SNRI could be a reasonable option if a pediatric patient has failed prior adequate SSRI trials and also has comorbid neuropathic pain.

Neither bupropion nor mirtazapine have undergone rigorous testing in pediatric patients, and therefore these agents should generally be considered only once other first-line treatments have failed. Bupropion has been evaluated for attention-deficit/hyperactivity disorder (ADHD)[25] and for adolescent smoking cessation.[26] However, the evidence is weak, and bupropion is not considered a first-line option for children and adolescents.

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Tricyclic antidepressants. Randomized controlled trials have demonstrated that tricyclic antidepressants (TCAs) are efficacious for treating several pediatric conditions; however, their significant side effect profile, their monitoring requirements, as well as their lethality in overdose has left them replaced by SSRIs in most cases. That said, they can be appropriate in refractory ADHD (desipramine[27,28]) and refractory OCD (clomipramine is FDA-approved for this indication[29]); they are considered a third-line treatment for enuresis.[30]

Why did my patient stop the medication?

Common adverse effects. Although the greatest benefit of antidepressant medications compared with placebo is achieved relatively early on in treatment, it generally takes time for these benefits to accrue and become clinically apparent.[15,31] By contrast, most adverse effects of antidepressants present and are at their most severe early in treatment. The combination of early adverse effects and delayed efficacy leads many patients, families, and clinicians to discontinue medications before they have an adequate chance to work. Thus, it is imperative to provide psychoeducation before starting a medication about the typical time-course of improvement and adverse effects (***Table 2, page 30***).

Adverse effects of SSRIs often appear or worsen transiently during initiation of a medication, during a dose increase,[32] or, theoretically, with the addition of a medication that interferes with SSRI metabolism (eg, cimetidine inhibition of cytochrome P450 2D6).[33] If families are prepared for this phenomenon and the therapeutic alliance is adequate, adverse effects can be tolerated to allow for a full medication trial. Common adverse effects of SSRIs include sleep problems (insomnia/sedation), gastrointestinal upset, sexual dysfunction, dry mouth, and hyperhidrosis. Although SSRIs differ somewhat in the frequency of these effects, as a class, they are more similar than different. Adequate psychoeducation is especially imperative in the treatment of OCD and anxiety disorders, where there is limited evidence of efficacy for any non-serotonergic antidepressants.

Serotonin-norepinephrine reuptake inhibitors are not considered first-line medications because of the reduced evidence base compared to SSRIs and their enhanced adverse effect profiles. Because SNRIs partially share a mechanism of action with SSRIs, they also share portions of the adverse effects profile. However, SNRIs have the additional adverse effect of hypertension, which is related to their noradrenergic activity. Thus, it is reasonable to obtain a baseline blood pressure before initiating an SNRI, as well as periodically after initiation and during dose increases, particularly if the patient has other risk factors for hypertension.[34]

Although TCAs have efficacy in some pediatric disorders,[27-29,35] their adverse effect profile limits their use. Tricyclic antidepressants are highly anticholinergic (causing dizziness secondary to orthostatic hypotension, dry mouth, and urinary retention) and antihistaminergic (causing sedation and weight gain). Additionally, TCAs lower the seizure threshold and have adverse cardiac effects relating to their anti-alpha-1 adrenergic activity, resulting in dose-dependent increases in the QTc and cardiac toxicity in overdose that could lead to arrhythmia and death. These medications have their place, but their use requires careful informed consent, clear treatment goals, and baseline and periodic cardiac monitoring (via electrocardiogram).

Serious adverse effects. Clinicians may be hesitant to prescribe antidepressants for pediatric patients because of the potential for more serious adverse effects, including severe behavioral activation syndromes, serotonin syndrome, and emergent suicidality. However, current FDA-approved antidepressants arguably have one of the most positive risk/benefit profiles of any orally-administered medication approved for pediatric patients. Having a strong understanding of the evidence is critical to evaluating when it is appropriate to prescribe an antidepressant, how to properly monitor the patient, and how to obtain accurate informed consent.

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Most adverse effects of antidepressants present and are at their most severe early in treatment

Pediatric behavioral activation syndrome. Many clinicians report that children receiving antidepressants experience a pediatric behavioral activation syndrome, which exists along a spectrum from mild activation, increased energy, insomnia, or irritability up through more severe presentations of agitation, hyperactivity, or possibly mania. A recent meta-analysis suggested a positive association between antidepressant use and activation events on the milder end of this spectrum in pediatric patients with non-OCD anxiety disorders,[16] and it is thought that compared with adolescents, younger children are more susceptible to activation adverse effects.[36] The likelihood of activation events has been associated with higher antidepressant plasma levels,[37] suggesting that dose or individual differences in metabolism may play a role. At the severe end of the spectrum, the risk of induction of mania in pediatric patients with depression or anxiety is relatively rare (<2%) and not statistically different from placebo in RCTs of pediatric participants.[38] Meta-analyses of larger randomized, placebo-controlled trials of adults do not support the idea that SSRIs and other second-generation antidepressants carry an increased risk of mania compared with placebo.[39,40] Children or adolescents with bona fide bipolar disorder (ie, patients who have had observed mania that meets all DSM-5 criteria) should be treated with a mood-stabilizing agent or antipsychotic if prescribed an antidepressant.[41] These clear-cut cases are, however, relatively rare, and more often clinicians are confronted with ambiguous cases that include a family history of bipolar disorder along with "softer" symptoms of irritability, intrusiveness, or aggression. In these children, SSRIs may be appropriate for depressive, OCD, or anxiety symptoms, and should be strongly considered before prescribing antipsychotics or mood stabilizers, as long as initiated with proper monitoring.

Serotonin syndrome is a life-threatening condition caused by excess synaptic serotonin. It is characterized by confusion, sweating, diarrhea, hypertension, hyperthermia, and tachycardia. At its most severe, serotonin syndrome can result in seizures, arrhythmias, and death. The risk of serotonin syndrome is very low when using an SSRI as monotherapy. Risk increases with polypharmacy, particularly unexamined polypharmacy when multiple serotonergic agents are inadvertently on board. Commonly used serotonergic agents include other antidepressants, migraine medications (eg, triptans), some pain medications, and the cough suppressant dextromethorphan.

The easiest way to mitigate the risk of serotonin syndrome is to use an interaction index computer program, which can help ensure that the interacting agents are not prescribed without first discussing the risks and benefits. It is important to teach adolescents that certain recreational drugs are highly serotonergic and can cause serious interactions with antidepressants. For example, recreational use of dextromethorphan or 3,4-methylenedioxymethamphetamine (MDMA; commonly known as "ecstasy") has been associated with serotonin syndrome in adolescents taking antidepressant medications.[42,43]

Suicidality. The black-box warning regarding a risk of emergent suicidality when starting antidepressant treatment in children is controversial.[44] The prospect that a medication intended to ameliorate depression might instead risk increasing suicidal thinking is alarming to parents and clinicians alike. To appropriately weigh and discuss the risks and benefits with families, it is important to understand the data upon which the warning is based.

In 2004, the FDA commissioned a review of 23 antidepressant trials, both published and unpublished, pooling studies across multiple indications (MDD, OCD, anxiety, and ADHD) and multiple antidepressant classes. This meta-analysis, which included nearly 4,400 pediatric patients, found a small but statistically significant increase in spontaneously-reported suicidal thoughts or actions, with a risk difference of 1% (95% confidence interval [CI], 1% to 2%).[45] These data suggest that if one treats 100 pediatric patients, 1 to 2 of them may experience short-term increases in suicidal thinking or behavior.[45] There were no differences in suicidal thinking when assessed systematically (ie, when all subjects reported symptoms

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Compared with adolescents, younger children are more susceptible to activation adverse effects

Antidepressants for pediatric patients

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Current guidelines suggest seeing children weekly for the first month after medication initiation

of suicidal ideation on structured rating scales), and there were no completed suicides.[45] A subsequent analysis that included 27 pediatric trials suggested an even lower, although still significant, risk difference (<1%), yielding a number needed to harm (NNH) of 143.[46] Thus, with low NNT for efficacy (3 to 6) and relatively high NNH for emergent suicidal thoughts or behaviors (100 to 143), for many patients the benefits will outweigh the risks.

Figure 1, ***Figure 2***, and ***Figure 3*** (see this article at MDedge.com/psychiatry) are Cates plots that depict the absolute benefits of antidepressants compared with the risk of suicidality for pediatric patients with MDD, OCD, and anxiety disorders. Recent meta-analyses have suggested that the increased risk of suicidality in antidepressant trials is specific to studies that included children and adolescents, and is not observed in adult studies. A meta-analysis of 70 trials involving 18,526 participants suggested that the odds ratio of suicidality in trials of children and adolescents was 2.39 (95% CI, 1.31 to 4.33) compared with 0.81 (95% CI, 0.51 to 1.28) in adults.[47] Additionally, a network meta-analysis exclusively focusing on pediatric antidepressant trials in MDD reported significantly higher suicidality-related adverse events in venlafaxine trials compared with placebo, duloxetine, and several SSRIs (fluoxetine, paroxetine, and escitalopram).[20] These data should be interpreted with caution as differences in suicidality detected between agents is quite possibly related to differences in the method of assessment between trials, as opposed to actual differences in risk between agents.

Epidemiologic data further support the use of antidepressants in pediatric patients, showing that antidepressant use is associated with decreased teen suicide attempts and completions,[48] and the decline in prescriptions that occurred following the black-box warning was accompanied by a 14% increase in teen suicides.[49] Multiple hypotheses have been proposed to explain the pediatric clinical trial findings. One idea is that potential adverse effects of activation, or the intended effects of restoring the motivation, energy, and social engagement that is often impaired in depression, increases the likelihood of thinking about suicide or acting on thoughts. Another theory is that reporting of suicidality may be increased, rather than increased de novo suicidality itself. Antidepressants are effective for treating pediatric anxiety disorders, including social anxiety disorder,[16] which could result in more willingness to report. Also, the manner in which adverse effects are generally ascertained in trials might have led to increased spontaneous reporting. In many trials, investigators ask whether participants have any adverse effects in general, and inquire about specific adverse effects only if the family answers affirmatively. Thus, the increased rate of other adverse effects associated with antidepressants (sleep problems, gastrointestinal upset, dry mouth, etc.) might trigger a specific question regarding suicidal ideation, which the child or family then may be more likely to report. Alternatively, any type of psychiatric treatment could increase an individual's propensity to report; in adolescent psychotherapy trials, non-medicated participants have reported emergent suicidality at similar frequencies as those described in drug trials.[50] Regardless of the mechanism, the possibility of treatment-emergent suicidality is a low-frequency but serious event that necessitates careful monitoring when starting medication. Current guidelines suggest seeing children weekly for the first month after medication initiation, every 2 weeks for the following month, and monthly thereafter.[51]

How long should the antidepressant be continued?

Many patients are concerned about how long they may be taking medication, and whether they will be taking an antidepressant "forever." A treatment course can be broken into an acute phase, wherein remission is achieved and maintained for 6 to 8 weeks. This is followed by a continuation phase, with the goal of relapse prevention, lasting 16 to 20 weeks. The length of the last phase—the maintenance phase—depends both on the child's history, the underlying therapeutic indication, the adverse effect burden experienced, and the family's

preferences/values. In general, for a first depressive episode, after treating for 1 year, a trial of discontinuation can be attempted with close monitoring. For a second depressive episode, we recommend 2 years of remission on antidepressant therapy before attempting discontinuation. In patients who have had 3 depressive episodes, or have had episodes of high severity, we recommend continuing antidepressant treatment indefinitely. Although much less well studied, the risk of relapse following SSRI discontinuation appears much more significant in OCD, whereas anxiety disorders and MDD have a relatively comparable risk.[52]

In general, stopping an antidepressant should be done carefully and slowly. The speed with which a specific antidepressant can be stopped is largely related to its half-life. Agents with very long half-lives, such as fluoxetine (half-life of 5 days for the parent compound and 9 days for active metabolite), can often be stopped altogether, being "auto-tapered" by the long half-life. One might still consider a taper if the patient were taking high doses. Medications with shorter half-lives must be more carefully tapered to avoid discontinuation syndromes. Discontinuation syndromes are characterized by flu-like symptoms (nausea, myalgias, fatigue, dizziness) and worsening mood. Medications with short half-lives (eg, paroxetine and venlafaxine) have the highest potential for this syndrome in children,[53] and thus are used less frequently.

What to do when first-line treatments fail

When a child does not experience sufficient improvement from first-line treatments, it is crucial to determine whether they have experienced an adequate dosing, duration, and quality of medication and psychotherapy.

Adequate psychotherapy? To determine whether children are receiving adequate CBT, ask:

1. if the child receives homework from psychotherapy
2. if the parents are included in treatment
3. if therapy has involved identifying thought patterns that may be contributing to the child's illness, and
4. if the therapist has ever exposed the child to a challenge likely to produce anxiety or distress in a supervised environment and has developed an exposure hierarchy (for conditions with primarily exposure-based therapies, such as OCD or anxiety disorders).

If a family is not receiving most of these elements in psychotherapy, this is a good indicator that they may not be receiving evidence-based CBT.

Adequate pharmacotherapy? Similarly, when determining the adequacy of previous pharmacotherapy, it is critical to determine whether the child received an adequate dose of medications (at least the FDA-recommended minimum dose) for an adequate duration of time at therapeutic dosing (at least 6 weeks for MDD, 8 weeks for anxiety disorders, and 8 to 12 weeks for pediatric patients with OCD), and that the child actually took the medication regularly during that period. Patient compliance can typically be tracked through checking refill requests or intervals through the patient's pharmacy. Ensuring proper delivery of first-line treatments is imperative because (1) the adverse effects associated with second-line treatments are often more substantial; (2) the cost in terms of time and money is considerably higher with second-line treatments, and; (3) the evidence regarding the benefits of these treatments is much less certain.

Inadequate dosing is a common reason for non-response in pediatric patients. Therapeutic dose ranges for common antidepressants are displayed in ***Table 1*** (***page 28***). Many clinicians underdose antidepressants for pediatric patients initially (and often throughout treatment) because they fear that the typical dose titration used in clinical trials will increase the risk of adverse effects compared with more conservative dosing. There is limited evidence to suggest that this underdosing strategy is likely to be successful; adverse effects attributable to these medications are modest, and most that

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Medications with short half-lives have the highest potential for discontinuation syndromes in children, and thus are used less frequently

are experienced early in treatment (eg, headache, increased anxiety or irritability, sleep problems, gastrointestinal upset) are self-limiting and may be coincidental rather than medication-induced. Furthermore, there is no evidence for efficacy of subtherapeutic dosing in children in the acute phase of treatment or for preventing relapse.[14] Thus, from an efficacy standpoint, a medication trial has not officially begun until the therapeutic dose range is reached.

Once dosing is within the therapeutic range, however, pediatric data differs from the adult literature. In most adult psychiatric conditions, higher doses of SSRIs within the therapeutic range are associated with an increased response rate.[14,54] In pediatrics, there are few fixed dose trials, and once within the recommended therapeutic range, minimal data supports an association between higher dosing and higher efficacy.[14] In general, pediatric guidelines are silent regarding optimal dosing of SSRIs within the recommended dose range, and higher antidepressant doses often result in a more significant adverse effect burden for children. One exception is pediatric OCD, where, similar to adults, the guidelines suggest that higher dosing of SSRIs often is required to induce a therapeutic response as compared to MDD and GAD.[31,55]

If a child does not respond to adequate first-line treatment (or has a treatment history that cannot be fully verified), repeating these first-line interventions carries little risk and can be quite effective. For example, 60% of adolescents with MDD who did not initially respond to an SSRI demonstrated a significant response when prescribed a second SSRI or venlafaxine (with or without CBT).[56]

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If a child does not respond to adequate first-line treatment, repeating first-line interventions carries little risk and can be quite effective

Related Resource

- Bonin L, Moreland CS. Overview of prevention and treatment for pediatric depression. https://www.uptodate.com/contents/overview-of-prevention-and-treatment-for-pediatric-depression. Last reviewed July 2019.

Drug Brand Names

Bupropion • Wellbutrin, Zyban
Cimetidine • Tagamet
Citalopram • Celexa
Clomipramine • Anafranil
Desipramine • Norpramin
Desvenlafaxine • Pristiq
Duloxetine • Cymbalta
Escitalopram • Lexapro
Fluoxetine • Prozac
Fluvoxamine • Luvox
Imipramine • Tofranil
Mirtazapine • Remeron
Nortriptyline • Pamelor
Paroxetine • Paxil
Sertraline • Zoloft
Venlafaxine • Effexor
Vilazodone • Viibryd
Vortioxetine • Trintellix

When pediatric patients continue to experience significantly distressing and/or debilitating symptoms (particularly in MDD) despite multiple trials of antidepressants and psychotherapy, practitioners should consider a careful referral to interventional psychiatry services, which can include the more intensive treatments of electroconvulsive therapy, repetitive transcranial magnetic stimulation, or ketamine (see ***Box 1*** of this article at MDedge.com/psychiatry). Given the substantial morbidity and mortality associated with adolescent depression, interventional psychiatry treatments are under-researched and underutilized clinically in pediatric populations.

Antidepressants in general, and SSRIs in particular, are the first-line pharmacotherapy for pediatric anxiety, OCD, and MDD. For PTSD, although they are a first-line treatment in adults, their efficacy has not been demonstrated in children and adolescents. Antidepressants are generally safe, well-tolerated, and effective, with low

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Bottom Line

Although the evidence base for prescribing antidepressants for children and adolescents is smaller compared to the adult literature, properly understanding and prescribing these agents, and explaining their risks and benefits to families, can make a major difference in patient compliance, satisfaction, and outcomes. Antidepressants (particularly selective serotonin reuptake inhibitors) are the first-line pharmacologic intervention for pediatric patients with anxiety disorders, obsessive-compulsive disorder, or major depressive disorder.

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NNTs (3 to 5 for anxiety and OCD; 4 to 12 in MDD, depending on whether industry trials are included). It is important that clinicians and families be educated about possible adverse effects and their time course in order to anticipate difficulties, ensure adequate informed consent, and monitor appropriately. The black-box warning regarding treatment-emergent suicidal thoughts or behaviors must be discussed (for suggested talking points, see ***Box 2*** of this article at MDedge.com/psychiatry). The NNH is large (100 to 143), and for many patients, the benefits will outweigh the risks. For pediatric patients who fail to respond to multiple adequate trials of antidepressants and psychotherapy, referrals for interventional psychiatry consultation should be considered.

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Clinical Point

Discuss the black-box warning regarding treatment-emergent suicidal thoughts or behaviors with families

Antidepressants for pediatric patients

Clinical Point

For pediatric patients, interventional psychiatry treatments are under-researched and underutilized

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WEB EXCLUSIVES

Visit this article at MDedge.com/psychiatry for more on antidepressants for pediatric patients:

- Cates plots: Risks vs benefits of antidepressants for pediatric anxiety disorders, MDD, and OCD
- How to talk to families
- Interventional treatments

Box 1

Interventional treatments

Continuing severe depression is associated with reduced educational attainment and quality of life, as well as increased risk of substance abuse and suicide,[1,2] which is the second leading cause of death in individuals age 10 to 24 years.[3] Given the substantial morbidity and mortality associated with adolescent depression, interventional psychiatry treatments are under-researched and underutilized in pediatric patients. Interventional antidepressants in adults include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and, most recently, ketamine.

Electroconvulsive therapy is the most effective therapy available for depression in adults, alleviating depressive symptoms in treatment-refractory patients and outperforming both pharmacotherapy[4] and rTMS.[5] Despite its track record of effectiveness and safety in adults, ECT continues to suffer considerable stigma.[4] Cognitive adverse effects and memory problems in adults are generally self-limited, and some aspects of cognition actually improve after ECT as depression lifts.[6] The combination of stigma and the concern about possible cognitive adverse effects during periods of brain development have likely impeded the rigorous testing of ECT in treatment-refractory pediatric patients. Several case series and other retrospective analyses suggest, however, that ECT has strong efficacy and limited adverse effects in adolescents who have severe depression or psychotic symptoms.[7-9] Despite these positive preliminary data in pediatric patients, and a large body of literature in adults, no controlled trials of ECT have been conducted in the pediatric population, and it remains a rarely used treatment in severe pediatric mental illness.

Repetitive transcranial magnetic stimulation is a technique in which magnetic stimulation is used to activate the left dorsolateral prefrontal cortex (DLPFC), a target thought to be important in the pathophysiology of MDD. Repetitive transcranial magnetic stimulation is FDA-approved to treat medication-refractory major depressive disorder (MDD) in adults, and has been shown to be effective as both a monotherapy[10] and an adjunctive treatment.[11] The estimated number needed to treat (NNT) for rTMS ranges from 6 to 8, which is quite effective, although less so than ECT (and probably initial pharmacotherapy).[5] Similar to ECT, however, there are no large randomized controlled trials (RCTs) in children or adolescents. Pilot RCTs[12] and open trials[13] suggest that DLPFC rTMS may be effective as an adjunctive treatment, speeding or augmenting response to a selective serotonin reuptake inhibitor in adolescents with MDD. Larger trials studying rTMS in pediatric patients are needed. While rTMS is generally well tolerated, disadvantages include the time-consuming schedule (the initial treatment is typically 5 days/week for several weeks) and local adverse effects of headache and scalp pain.

Ketamine, which traditionally is used as a dissociative anesthetic, is a rapidly emerging novel treatment in adult treatment-refractory MDD. It acts quickly (within hours to days) and cause significant improvement in difficult symptoms such as anhedonia[14] and suicidal ideation.[15] In adult studies, ketamine has a robust average effect size of >1.2, and an NNT ranging from 3 to 5 in medication-refractory patients.[16,17] Ketamine is a glutamatergic modulator, acting outside of the monoamine neurochemical systems traditionally targeted by standard antidepressants.[16] The efficacy of ketamine in treatment-refractory adults is impressive, but the effects of a single treatment are ephemeral, dissipating within 1 to 2 weeks, which has led to significant discussion surrounding optimal dosing strategies.[16] Although small RCTs in pediatric patients are currently underway, at this time, the only evidence for ketamine for pediatric MDD is based on case series/report data[18,19] which was positive.

For all of these interventional modalities, it is critical to refer children with treatment-refractory disorders to interventionists who have appropriate experience and monitoring capabilities.

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Box 2

Talking to families when starting antidepressants for pediatric patients

Efficacy

- Selective serotonin reuptake inhibitors are the most effective pharmacologic treatment we have for pediatric depression, OCD, and anxiety
- More than one-half of children who are prescribed SSRIs have a significant improvement, regardless of condition
- Based on current estimates, we need to treat 4 to 6 children with an SSRI to find one that will improve who would not improve with placebo
- The clinical benefits of SSRIs generally take a while to accrue; therefore, it is advisable to take the medication for at least 2 to 3 months before concluding that it is ineffective
- In addition to medication, evidence-based psychotherapies provide significant benefit for pediatric depression, OCD, and anxiety

Tolerability

- Most commonly prescribed pediatric antidepressants have been used safely in children for 2 to 3 decades. The safety profiles of SSRIs are among the best of any medications used for children and adolescents
- While many children get better when taking these medications, it's important that we also talk about potential adverse effects. Some children will experience sleep problems (either sleepier than usual or difficulty sleeping), changes in energy levels, headache, gastrointestinal upset, and dry mouth. These are most likely at the beginning of treatment, or when we increase the dose; they usually are time-limited and go away on their own
- Often adverse effects occur first and the benefits come later. Because it may take at least a few weeks to start to see the mood/anxiety benefits, it's important for us to talk about any adverse effects your child experiences and remember that they usually are short-lived

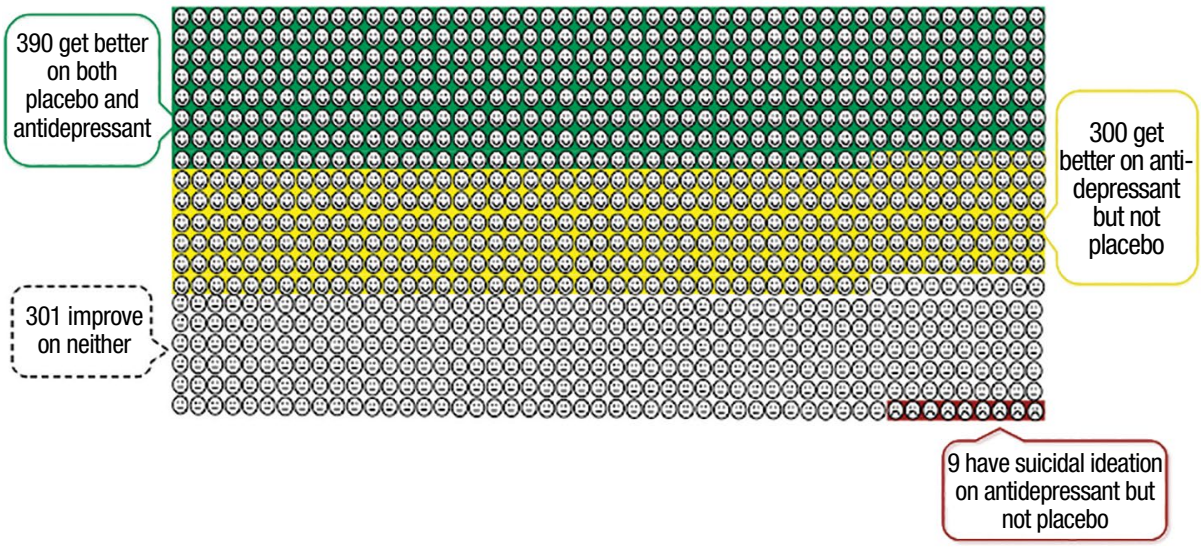
Suicidality

- The FDA placed a "black-box" warning on antidepressants after pediatric studies found a small but statistically significant increased risk of reporting suicidal thoughts or behaviors over the short-term compared with placebo
- The increased risk of spontaneously reporting suicidal ideation was quite small. Studies suggested that one would need to treat 100 to 140 children to see 1 child report suicidal ideation compared to placebo. Suicidal ideation is a common symptom in children with depression and anxiety
- Studies found no increased risk when suicidal ideation was systematically assessed using structured rating scales
- In the studies evaluated, there were no completed suicides by patients taking medication or placebo
- Population studies show that higher rates of antidepressant prescriptions are associated with lower rates of attempted and completed teen suicide, which underscores that in general, these medicines treat the underlying causes of suicidality
- No scientific consensus exists on whether these medications are truly associated with an increased risk of new-onset suicidal ideation, or if this association is due to other factors (eg, improvement in anxiety and depressive symptoms that make patients more comfortable to report suicidal ideation spontaneously)
- Regardless, the FDA recommends frequent monitoring of children for suicidal thoughts when these medications are started. This should be done anyway in children experiencing depression and anxiety, and it's why we will plan to have more frequent appointments as the medication is initiated

OCD: obsessive-compulsive disorder; SSRIs: selective serotonin reuptake inhibitors

Figure 1

Cates plot depicting the benefits of antidepressants vs risk of suicidal ideation for pediatric patients with anxiety disorders



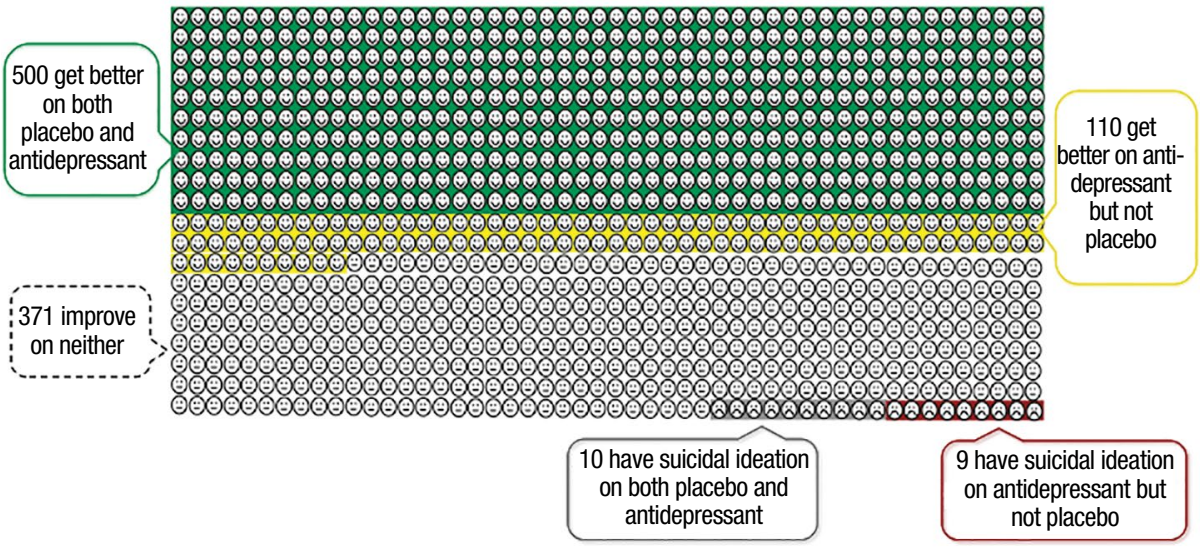
Green faces: Children who will respond to both placebo and antidepressant
Yellow faces: Children who respond to antidepressants but not placebo
White faces: Nonresponders to both medication and placebo
Red faces: Children who will experience suicidal ideation on medication but not placebo
Faces covered with an X: Children who will complete suicide on medication but not placebo

Note: There are no faces with Xs because there were no suicides in randomized controlled trials

Source: Based on data from reference 46

Figure 2

Cates plot depicting the benefits of antidepressants vs risk of suicidal ideation for pediatric patients with major depressive disorder



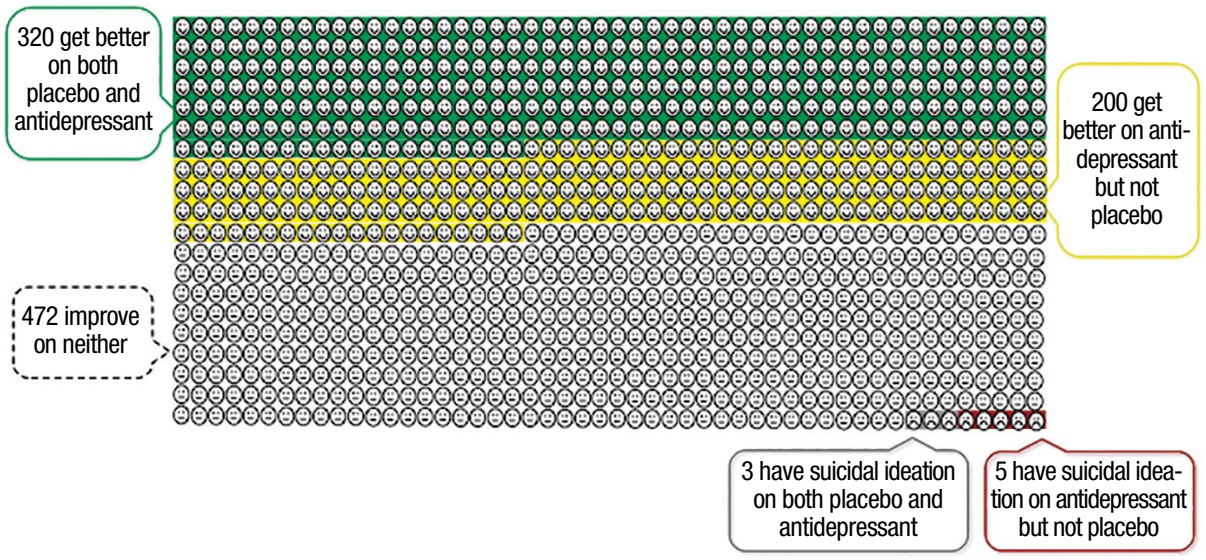
Green faces: Children who will respond to both placebo and antidepressant
Yellow faces: Children who respond to antidepressants but not placebo
White faces: Nonresponders to both medication and placebo
Gray faces: Children who will experience suicidal ideation on both medication and placebo
Red faces: Children who will experience suicidal ideation on medication but not placebo
Faces covered with an X: Children who will complete suicide on medication but not placebo

Note: There are no faces with Xs because there were no suicides in randomized controlled trials

Source: Based on data from reference 46

Figure 3

Cates plot depicting the benefits of antidepressants vs risk of suicidal ideation for pediatric patients with obsessive-compulsive disorder



Green faces: Children who will respond to both placebo and antidepressant
Yellow faces: Children who respond to antidepressants but not placebo
White faces: Nonresponders to both medication and placebo
Gray faces: Children who will experience suicidal ideation on both medication and placebo
Red faces: Children who will experience suicidal ideation on medication but not placebo
Faces covered with an X: Children who will complete suicide on medication but not placebo

Note: There are no faces with Xs because there were no suicides in randomized controlled trials

Source: Based on data from reference 46