Advances in Pharmacotherapy for Pediatric Anxiety Disorders

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KEYWORDS

- Selective serotonin reuptake inhibitor (SSRI)
- Serotonin and norepinephrine reuptake inhibitor (SNRI) • Benzodiazepine
- Buspirone • Guanfacine • Tricyclic antidepressant (TCA) • Anxiety disorders
- Generalized anxiety disorder (GAD)

KEY POINTS

- Selective serotonin reuptake inhibitors (SSRIs) are the first-line psychopharmacologic treatment for pediatric anxiety disorders.
- SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) differ in their tolerability.
- The risk of treatment-emergent suicidality does not differ between SSRIs, SNRIs, and placebo in pediatric patients with anxiety disorders.

Abbreviations	
GAD	Generalized anxiety disorder
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

INTRODUCTION

More than a dozen prospective randomized trials suggest that multiple medication classes are effective for youth with anxiety disorders. These trials focus on generalized anxiety disorder (GAD), social anxiety disorder, and separation anxiety disorder,

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referred to as the "pediatric anxiety triad." These disorders are highly comorbid and have a similar response to pharmacotherapy.[1–3] This review summarizes randomized controlled trials of SSRIs, SNRIs, benzodiazepines, and other agents (**Table 1**) and reviews their tolerability, the trajectory of response, and the role of pharmacotherapy in combination with psychotherapy for treating youth with anxiety disorders.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used medications for pediatric anxiety disorders.[4] As a class, SSRIs, relative to serotonin norepinephrine reuptake inhibitors (SNRIs), produce improvement early (by 2 weeks) (**Fig. 1**), and nearly half of the improvement seen by 12 weeks is evident by 4 weeks. Additionally, earlier improvement may occur in patients treated with higher SSRI doses.[5] A network meta-analysis of 22 randomized controlled trials of SSRIs and SNRIs along with tricyclic antidepressants (TCAs), benzodiazepines, 5-HT_{1A} agonist (buspirone), and α_2 agonist (guanfacine) in youth with anxiety disorders found that SSRIs were the most effective class of medications.[6]

Escitalopram

Escitalopram, the s-enantiomer of citalopram, is a highly serotonergically-specific SSRI[7,8] and has been evaluated in two prospective double-blind, placebo-controlled trials of youth with GAD. First, forced flexible titration of escitalopram to 15 to 20 mg in adolescents with GAD (n = 26) for 8 weeks was superior to placebo (n = 25). In this study, greater improvement was seen in slower CYP2C19 metabolizers. The discontinuation rate was similar for escitalopram and placebo, and bruising was the only adverse event more common in patients receiving escitalopram versus those receiving placebo. Activation (impulsivity, irritability, restlessness, insomnia, and so forth) was associated with higher plasma escitalopram concentrations but not the absolute dose.[9] In the second study of escitalopram, children and adolescents (age 7–17 years) with GAD were treated with flexibly dosed escitalopram (n = 138; 10–20 mg/d) or placebo (n = 137) for 8 weeks. The mean change from baseline to week eight on the Pediatric Anxiety Rating Scale (PARS) of severity for GAD score was significantly greater for escitalopram than for placebo. Escitalopram was relatively well tolerated, with treatment-emergent adverse events occurring in approximately 55% of patients receiving escitalopram and 40% of those receiving placebo. No evidence of QTc prolongation was observed in either study.[10]

Finally, 1 small open-label study of flexibly-dosed citalopram (10–40 mg/d, mean dose 35 $\pm$ 7 mg/d, n = 12) in children and adolescents aged 8 to 17 years (mean age 13.4 $\pm$ 3 years) with social anxiety disorder found that 83% of youth responded based on Clinical Global Impression Improvement (CGI-I) scale. Patients and parents also reported improved social anxiety symptoms, and citalopram was well tolerated.[10]

Fluoxetine

Birmaher and colleagues (2003) evaluated the efficacy and tolerability of fluoxetine in a fixed-dose, randomized, placebo-controlled trial of youth (age 7–17 years, N = 37) with GAD, separation anxiety disorder, and social anxiety disorder.[11] In this 12-week trial, fluoxetine was initiated at 10 mg and titrated to 20 mg daily at the end of the first week. Fluoxetine-treated patients had greater improvements on dimensional and global measures of anxiety and functioning than placebo, which was statistically significant by week nine. Fluoxetine was well tolerated[11] and a follow-up study

Table 1
Selected randomized controlled trials of pharmacologic interventions in pediatric anxiety disorders

Reference	Diagnoses	Age (y)	Duration (wk)	Treatment Modalities	N	Dose Range (mg/d)	Average Dose
Strawn et al,[10] 2023	GAD	7-17	8	Escitalopram Placebo	138 137	10-20	Flexibly dosed
Strawn et al,[9] 2020	GAD	12-17	8	Escitalopram Placebo	26 25	15-20	Fixed dose
Beidel et al,[13] 2007	SocAD	7-17	12	Fluoxetine Placebo SET-C	33 57 32	10-40	Fixed dose
Birmaher et al,[11] 2003	GAD SocAD SepAD	7-17	12	Fluoxetine Placebo	37 37	20	Fixed dose
Walkup et al,[1] 2008	GAD SocAD SepAD	7-17	12	Sertraline CBT Combination Placebo	133 139 140 76	25-200 25-200	146.0 ± 60.8 mg 133.7 ± 59.8 mg
Rynn et al,[16] 2001	GAD	5-17	9	Sertraline Placebo	11 11	50	Fixed dose
Walkup et al,[22] 2001 (RUPP)	GAD SocAD SepAD	6-17	8	Fluvoxamine Placebo	61 63	50-300 Max 250 in <12 yo Max 300 in adolescents	2.9 ± 1.3 mg/kg
Wagner et al,[24] 2004	SocAD	8-17	16	Paroxetine Placebo	163 156	10-50	24.8 mg for all patients, 21.7 mg for children, and 26.1 mg for adolescents
March et al,[26] 2007	SocAD	8-17	16	Venlafaxine ER Placebo	137 148	37.5-225	2.6-3 mg/kg

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Table 1
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Reference	Diagnoses	Age (y)	Duration (wk)	Treatment Modalities	N	Dose Range (mg/d)	Average Dose
Rynn et al,[25] 2007	GAD	6-17	8	Study 1:			Flexibly dosed based on weight
				Venlafaxine ER	76	37.5-225	
				Placebo	77		
				Study 2:			
				Venlafaxine ER	78	37.5-225	Flexibly dosed based on weight
				Placebo	82		
Strawn et al.,[27] 2015	GAD SocAD SepAD	7-17	10	Duloxetine Placebo	135 137	30-120	Flexibly dosed
Strawn et al,[37] 2017	GAD SocAD SepAD	6-17	12	Guanfacine Placebo	62 21	1-6	0.06-0.12 mg/kg for 50 kg, 3-6 mg for >50 kg
Strawn et al,[34] 2018	GAD	6-17	6	Study 1:			Flexibly dosed
				Buspirone	111	15-60	
				Placebo	111		
				Study 2:			Fixed dose
				Buspirone	221	15-60	
				Placebo	112		

Abbreviations: GAD, generalized anxiety disorder; SepAD, separation anxiety disorder; SET-C, Social Effectiveness Therapy for Children; SocAD, social anxiety disorder; ER, extended-release venlafaxine.

Adapted from Strawn, et al. Psychopharmacologic Treatments of Children and Adolescents with Anxiety Disorders. Child and Adolescent Psychiatric Clinics of North America. 2012;21(3):527-539.

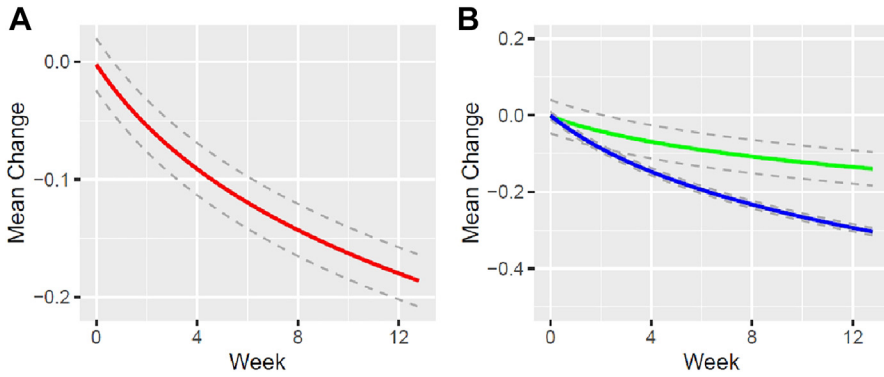

Fig. 1. Response trajectory in antidepressant-treated children and adolescents with DSM-5 anxiety disorders. Dotted *grey* lines represent the 95% credible interval. (*A*) Red line represents the overall standardized medication (SSRI and SNRI)-placebo mean difference over time with the best-fit model (logarithmic). (*B*) The blue line represents SSRI-placebo difference. Green line represents SNRI-placebo difference. (*Reproduced from* Strawn, et al. The impact of antidepressant dose class on treatment response in pediatric anxiety disorders: A meta-analysis. Journal of the American Academy of Child and Adolescent Psychiatry. 2018;57;4;235-244.)

suggested that fluoxetine may be effective as a maintenance treatment in children and adolescents with anxiety disorders.[12]

A double-blind, randomized trial compared Social Effectiveness Therapy for Children (SET-C), fluoxetine (forced titration 10–40 mg/d), and placebo in children and adolescents (age 7–17 years) with social anxiety disorder (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, DSM-IV criteria). Fifty-three percent of the SET-C group no longer met diagnostic criteria (compared to 21.2% of patients treated with fluoxetine and 3.1% of those treated with placebo) after 8 weeks of treatment. SET-C and fluoxetine were superior to placebo in all outcome measures and overall functioning.[13]

Two open-label studies have evaluated fluoxetine in youth with anxiety disorders. In the first study, youth with mixed anxiety disorders (overanxious disorder/GAD, or separation anxiety disorders) who failed to respond to psychotherapy were treated with flexibly-dosed fluoxetine for up to 10 months. Birmaher and colleagues (1994) observed moderate to marked improvements in 81% of patients, and fluoxetine was well tolerated.[14] Later, Fairbanks and colleagues (1997) evaluated 16 outpatients (age 9–18 years) who failed to respond to psychotherapy and were treated with flexibly-dosed fluoxetine (5 mg daily, titrated to a maximum of 40 mg in children and 80 mg daily in adolescents).[15] Clinical improvement occurred in all patients with separation anxiety disorder (n = 10), 8 of 10 with social anxiety disorder, 3 of 5 with panic disorder, and 1 of 7 with GAD, with a mean time to improvement of 5 weeks. Fluoxetine was well tolerated, with the most frequent side effects being drowsiness, sleep problems, anorexia, nausea, and abdominal pain. In this study, patients with only 1 anxiety disorder responded to lower doses of fluoxetine than those with multiple anxiety disorders (0.49 $\pm$ 0.14 mg/kg vs 0.80 $\pm$ 0.28 mg/kg).[15]

Sertraline

In a placebo-controlled trial of fixed-dose sertraline (50 mg/d), youth aged 5 to 17 years with GAD (n = 22) were treated for 9 weeks. Compared with placebo-treated youth,

Hamilton Anxiety Rating Scale (HAM-A) scores and global measures of improvement were greater in patients receiving sertraline than in those receiving placebo. No differences in side effects were observed between sertraline and placebo.[16]

A small study of flexibly-dosed sertraline (mean dose 123 ± 37 mg/d) evaluated 14 children and adolescents (age 10–17 years) with social anxiety disorder for 8 weeks. Based on CGI-I scores, 36% of patients were responders, and 29% were partial responders. Sertraline was well tolerated; the most common side effects reported were nausea, diarrhea, and headaches.[17]

In the Child/Adolescent Anxiety Multimodal Study, sertraline was compared to placebo, cognitive behavioral therapy (CBT), and their combination (sertraline + CBT) in 488 patients aged 7 to 17 years (mean age 11.8 years) over 12 weeks. Sertraline was superior to placebo, and the combination of sertraline + CBT was superior to both monotherapy and placebo. Specifically, improvement (CGI-I) scores for sertraline + CBT were greater (80.7%) than those for CBT (59.7%) or sertraline alone (54.9%). Rates of adverse events with sertraline were similar to those with placebo. However, those children who received CBT were less likely to report insomnia, fatigue, sedation, restlessness, or fidgeting than those who received sertraline.[1] Predictors of remission included younger age, nonminority status, lower baseline anxiety severity, absence of other internalizing disorders (eg, anxiety, depression), and absence of social phobia.[18] Additionally, in this study, response emerged relatively early,[19] sertraline was well tolerated,[20] and response was maintained for many youth over a 6-month follow-up period.[21]

Fluvoxamine

Fluvoxamine was evaluated in a double-blind, placebo-controlled trial in youth with anxiety disorders (N = 128). In this study, children were treated with fluvoxamine titrated to 300 mg daily (mean dose 2.9 ± 1.3 mg/kg). Global improvement and dimensional measures of anxiety were significantly better in patients receiving fluvoxamine than in those receiving placebo. In addition, fluvoxamine was well tolerated, with only abdominal discomfort and increased motor activity occurring more frequently than it does in those who received placebo.[22] In a 6-month, open-label extension study, 94% of fluvoxamine responders maintained response, and 71% of the fluvoxamine-treated patients who had not initially responded to fluvoxamine subsequently improved.[23]

Paroxetine

While paroxetine has been less frequently used, as it is associated with greater treatment emergent suicidality,[6] 1 large study evaluated its efficacy in pediatric anxiety disorders. In this multicenter, double-blind, placebo-controlled trial of paroxetine, Wagner and colleagues (2004) randomized 322 youth (aged 8–17 years) with social anxiety disorder.[24] They observed greater responses (by CGI-I score) in paroxetine-treated youth (n = 161) than in those receiving placebo (n = 156); response rates were 78% and 38.3%, respectively. Insomnia, decreased appetite, and vomiting were among the most common side effects, and four paroxetine-treated patients reported suicidal ideation compared to zero patients in the placebo group. Upon discontinuation, SSRI withdrawal symptoms, including nausea, dizziness, and vomiting, were experienced twice as frequently by patients treated with paroxetine compared to those who received placebo.[24]

SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS

In a meta-analysis of 22 randomized controlled trials of SNRIs and SSRIs, TCAs, benzodiazepines, 5-HT_{1A} agonist (buspirone), and α_2 agonist (guanfacine) found SNRIs as

a class to have a more frequent treatment response versus placebo but less so than SSRIs. Additionally, in this meta-analysis, SNRIs were the most tolerable class with statistically significantly less discontinuation due to adverse effects than other treatments.[6]

Venlafaxine

Extended-release venlafaxine (venlafaxine ER) has been evaluated in two 8-week, randomized placebo-controlled trials involving youth with GAD aged 6 to 17 years (N = 323). Venlafaxine ER was initiated at 37.5 mg daily and was titrated based on weight. In the pooled analysis, venlafaxine ER was superior to placebo in improving scores derived from the GAD section of the Columbia Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS). Improvements on the PARS, HAM-A, and Screen for Child Anxiety Related Disorders (SCARED) parent and child scores were also statistically significant compared to placebo in 1 study but failed to reach statistical significance in the second study. Relative to other SNRIs, venlafaxine may be less tolerable; venlafaxine was also associated with more asthenia, pain, anorexia, somnolence, and weight loss than those receiving placebo.[25]

Venlafaxine ER was also evaluated in children and adolescents (age 8–17 years, n = 293) with social anxiety disorder. In this study, venlafaxine ER was initiated at 37.5 mg daily and titrated to a maximum dose based on weight over 16 weeks (dose range 112.5–225 mg). Youth receiving venlafaxine ER had a greater reduction in their symptoms than those receiving placebo (response rates 56% vs 37%, respectively). Significant weight loss was noted in several patients treated with venlafaxine ER, and three patients receiving venlafaxine ER developed suicidal ideation compared to zero patients receiving placebo.[26]

DULOXETINE

A 10-week, randomized placebo-controlled trial of duloxetine in children and adolescents (age 7–17 years) with GAD found that duloxetine (30–120 mg daily) was superior to placebo in improving dimensional measures of anxiety (PARS severity for GAD), as well as measures of functioning, including the Children's Global Assessment Scale and response/remission based on Clinical Global Impression Severity scale score. Duloxetine was associated with weight loss and increased heart rate, and there were no differences in discontinuation rate or suicidality emergence between duloxetine and placebo.[27]

Atomoxetine

Atomoxetine was evaluated in a placebo-controlled trial of children and adolescents (age 8–17 years) with attention-deficit/hyperactivity disorder (ADHD) and comorbid anxiety (GAD, separation anxiety disorder, and/or social anxiety disorder). Atomoxetine was initiated at 0.8 mg/kg/d for 3 days and increased to the target dose of 1.2 mg/kg/d, with a maximum dose of 1.8 mg/kg/d; treatment was continued for 12 weeks. A last observation carried forward analysis of PARS scores revealed improvement with atomoxetine versus placebo (effect size = 0.5) along with significant improvements in ADHD symptoms. Atomoxetine was generally well tolerated[28]; however, it is noteworthy that this study did not use the CYP2D6 genotype to guide dosing, which is the current recommendation.

Benzodiazepines

Benzodiazepines, the positive allosteric modulators at gamma-aminobutyric acid-A (-$GABA_A$) receptors, vary in their affinity, time of onset, and duration of effect in adults

with anxiety disorders.[29] However, despite the common use of benzodiazepines for the treatment of anxiety disorders in adults, trials of this class of medication in youth with anxiety disorders have produced mixed results. One open-label trial of 12 adolescents with overanxious disorder (the DSM-III-R forerunner of GAD) treated with alprazolam (0.5–1.5 mg/d) for 4 weeks noted significant improvements in anxiety and insomnia. Alprazolam was generally well tolerated despite some sedation, agitation, headaches, and nausea.[30] However, double-blind trials have failed to identify drug-placebo differences. A double-blind, placebo-controlled trial of alprazolam in youth aged 8 to 16 years (N = 30) with overanxious disorder found no difference between alprazolam and placebo on CGI-I; however, the study was significantly underpowered. Alprazolam was well tolerated in this study but with some reports of fatigue and dry mouth. No withdrawal symptoms were identified.[31]

One study evaluated clonazepam (up to 2 mg/d) in children (age 7–13 years) with separation anxiety disorder (n = 14) and GAD (n = 5) using a crossover design. In this study, CGI-I was observed between youth receiving clonazepam and those receiving placebo and failed to show a significant difference. Side effects were more common in those receiving clonazepam (83%) than in those receiving placebo (58%) and included drowsiness, irritability, and oppositional behavior.[32]

In a meta-analysis of 22 randomized controlled trials that included three studies of benzodiazepines,[31–33] benzodiazepines were the least effective class, and early discontinuation was more likely, specifically with clonazepam.[6]

Buspirone

A 2018 analysis of two randomized controlled trials of buspirone, a $5HT_{1A}$ agonist, in youth aged 6 to 17 years with GAD found no significant differences in improvement between youth receiving buspirone and those receiving placebo using K-SADS as the primary outcome. In these studies, the discontinuation rate of buspirone was similar to that of SSRIs and SNRIs. Lightheadedness was the most common adverse event, consistent with adult studies.[34]

Additionally, an open-label trial of buspirone in youth with overanxious disorder found that over 6 weeks of treatment, flexibly dosed buspirone (15–30 mg/d) was associated with improvement in anxiety.[35] Subsequently, in 13 children and 12 adolescents with anxiety, Salazar and colleagues (2001) reported improvement in anxiety over 4 weeks of treatment.[36] In both open-label studies, buspirone was generally well tolerated although some patients experienced sedation, nausea, stomachaches, and headaches.

Guanfacine

In a pilot trial, flexibly dosed extended-release guanfacine (guanfacine ER) was compared to placebo in pediatric patients aged 6 to 17 years with GAD, separation anxiety disorder, and/or social anxiety disorder (N = 83). Guanfacine was safe and tolerable compared to placebo. Guanfacine ER did not differ from placebo in scores on the PARS although statistically significant improvements were noted on global measures of severity. The most common adverse effects reported were headache, somnolence/fatigue, abdominal pain, and dizziness, consistent with its known side effect profile from pediatric ADHD and tic disorder studies.[37] Of note, in this trial, the dosing of guanfacine was relatively low and significantly below a typical dose in youth with ADHD (ie, >0.08 mg/kg).[38]

Tricyclic Antidepressants

In recent years, TCAs have been less commonly used secondary to their side effect profiles, yet several older studies have evaluated youth with school refusal along

with comorbid separation and/or social anxiety disorders. First, 35 children (age 6–14 years) were treated with flexibly dosed imipramine (100–200 mg/d). Imipramine-treated patients improved more than those who received placebo.[39] However, subsequent trials of TCAs in youth with school refusal, overanxious disorder, and separation anxiety disorder have failed to find differences between imipramine or clomipramine and placebo.[33,40] Finally, Bernstein and colleagues (2000) compared combination treatments of imipramine + CBT to placebo + CBT in 63 adolescents (mean age: 13.9 ± 3.6 years) with major depressive disorder and an anxiety disorder.[41] In this study, school attendance and clinician-rated depression significantly improved in the patients who received imipramine + CBT compared with that in those who received placebo + CBT. However, neither clinician- nor self-report measure of anxiety significantly differed between groups.[41]

Combination of Pharmacotherapy and Psychotherapy

Psychotherapeutic treatment of youth with anxiety disorders is becoming more widely recognized as a part of the evidence-based, comprehensive treatment plan. Of the available studies of psychotherapy, most have evaluated the efficacy of CBT,[1,19,42–45] and several alternate forms of psychotherapy that are efficacious in other types of psychopathology in youth remain understudied in those with anxiety disorders (eg, interpersonal psychotherapy for adolescents, mentalization-based therapy). In general, synergistic effects of psychotherapy and psychopharmacologic interventions have been observed,[1,19,46] and current practice guidelines from the American Academy of Child & Adolescent Psychiatry recommend a multimodal treatment approach.[47]

Tolerability of Selective Serotonin Reuptake Inhibitors and Serotonin and Norepinephrine Reuptake Inhibitor

Two meta-analyses have examined the risks of specific adverse events in children and adolescents treated with SSRIs and SNRIs.[6,48] Strawn and colleagues' 2015 meta-analysis of SSRIs and SNRIs in youth found that discontinuation due to adverse effects was similar to relative risk estimates derived from recent network meta-analyses that focused primarily on efficacy and compared multiple medication classes (eg, SSRIs, SNRIs, TCAs, benzodiazepines, α_2 agonists).[48]

Across disorders, SSRIs are more likely to produce activation, abdominal pain, sedation/drowsiness, and adverse-effect-related discontinuation than placebo. SSRI tolerability is similar among pediatric patients with anxiety disorders and obsessive-compulsive disorder (OCD) as well as depressive disorders.[49] The relationship between SSRI dosing and exposure has received limited attention, and there are very few data concerning the discontinuation or tapering of SSRIs in children and adolescents. Several studies suggest that some SSRIs may have more adverse effects at higher doses (or in patients with greater exposure).[35] With very few exceptions, these studies do not consider variations in pharmacodynamic genes that may differentially affect side effect expression nor differences in pharmacokinetic genes that produce variation in metabolism and, thus, differences in exposure, even when patients are treated with the same dose.

Adverse Effects

Clinical trials of antidepressants in youth rarely examine the time course of side effects, yet clinicians know that some side effects emerge early and resolve quickly (eg, activation, gastrointestinal symptoms). In contrast, other side effects are tardive (eg, weight gain) or persistent (eg, sexual dysfunction). For acutely emerging side effects, such as gastrointestinal symptoms, dynamic physiologic relationships may

mitigate these effects. For example, nausea, which emerges early, may relate to acute increases in serotonergic tone, thus increasing gastrointestinal motility. The resolution of gastrointestinal side effects may relate to the desensitization of enteric serotonergic receptors.[49] Discussing the temporal course of the side effects and distinguishing between static and dynamic side effects are critical in clinical practice. Ensuring that patients are aware not only of the potential types of side effects (**Fig. 2**) but also about the tendency of some side effects to be transient is important and should be part of discussions with patients and their families prior to the initiation of pharmacotherapy. Understanding the transient nature of many side effects may improve adherence and mitigate anxiety related to treatment with antidepressant medications.

Pharmacogenetics

Several studies have evaluated the role of pharmacogenetics in pediatric patients with anxiety and related disorders. In general, for SSRIs metabolized by CYP2C19 (ie, sertraline and escitalopram/citalopram), slower metabolizers have greater medication exposure at a given dose than faster metabolizers,[9,50,51] and escitalopram-related adverse events are more likely in slower metabolizers.[52] However, for CYP2D6-metabolized SSRIs (ie, fluoxetine, paroxetine), the evidence is less clear. Regarding pharmacogenetic testing in child and adolescent psychiatry, we recommend considering pharmacogenetic test results for genes with high levels of evidence if they are available or testing if the clinician feels that results of evidence-based genes (eg, CYP2D6, CYP2C19, HLA-A, HLA-B) would inform medication dosing or selection. This recommendation concords with the International Society of Psychiatric Genetics, which supports CYP2C19 and CYP2D6 testing for patients having had inadequate

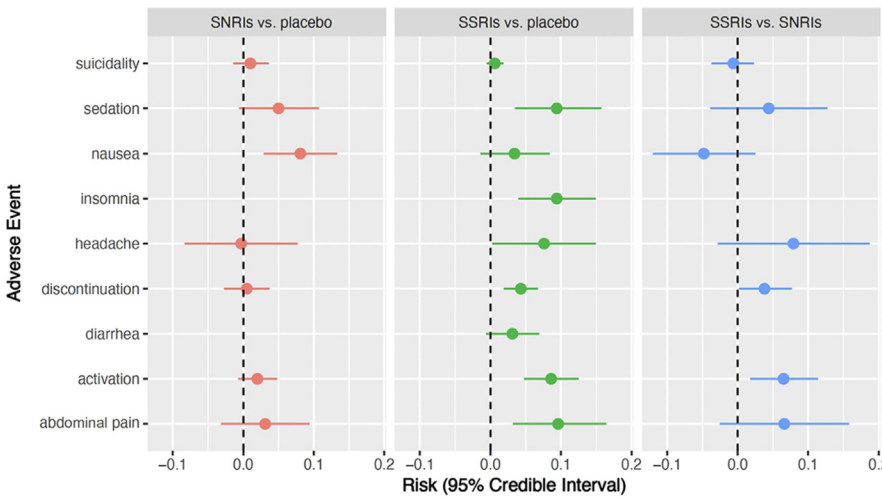

Fig. 2. Relative risk of antidepressant-related adverse effects (AEs), suicidality, and discontinuation secondary to adverse effects. The relative risk of each AE is shown in addition to the 95% credible interval. The large interval estimates for AE-related discontinuation and suicidality relate to the small number of occurrences relative to the number of patients leading to a skewed distribution when converting the estimated relative probabilities to the log odds scale, rather than an indication of large potential chances of those outcomes. (*Reproduced from* Mills and Strawn, Antidepressant tolerability in pediatric anxiety and obsessive compulsive disorders: A Bayesian hierarchical modeling meta-analysis. Journal of the American Academy of Child and Adolescent Psychiatry. 2020;59(11):1240-1251.)

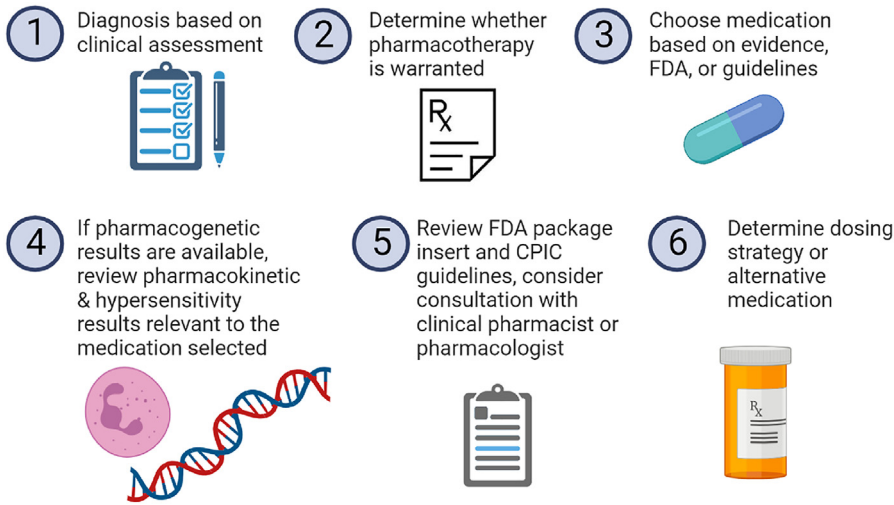

Fig. 3. Incorporation of pharmacogenetic testing into clinical practice. Graphic description of proposed pharmacogenetic testing approach for children and adolescents. CPIC, clinical pharmacogenetics implementation consortium. (Created with BioRender.com.)

responses to or adverse effects with antidepressants or antipsychotics.[53] Importantly, deciding whether to use a specific pharmacologic intervention should be based on thorough evaluation and available evidence from efficacy studies. Pharmacogenetic testing, when obtained, should influence dosing and alter the level of monitoring or choice of medication within the evidence-based class of medications for a given disorder (Fig. 3).[54,55]

SUMMARY

In children and adolescents with anxiety disorders, double-blind, placebo-controlled trials support the efficacy of the SSRIs and SNRIs, but there are mixed results for other medication classes. SSRIs are more effective than SNRIs for anxiety symptom improvement. Additionally, SSRI + CBT produce greater benefit than SSRI monotherapy across most internalizing disorders, including anxiety disorders.[19] SSRIs and SNRIs should be initiated after a discussion with patients and families regarding the risk of potential adverse effects. Initial doses should be low and titrated slowly to minimize these effects, particularly activation syndrome. Pharmacogenetic testing can be used as a guide for dosing and monitoring strategies for selected medications.[54]

CLINICS CARE POINTS

- SSRIs are the most effective pharmacotherapy for pediatric anxiety disorders and represent the first-line medication.
- In patients who have not responded to an initial SSRI, a trial of a second SSRI represents the next best step prior to a trial of an SNRI.
- Combining pharmacotherapy and psychotherapy consistently produces the best outcomes in youth with anxiety disorders.

DISCLOSURE

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