Pharmacotherapy for anxiety disorders in children and adolescents

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INTRODUCTION

Anxiety disorders are the most common psychiatric disorders diagnosed in childhood and adolescence [1,2]. Anxiety disorders that may begin in childhood include generalized anxiety disorder, social anxiety disorder, selective mutism, panic disorder, agoraphobia, separation anxiety disorder, and specific phobia.

Pediatric anxiety disorders are associated with increased difficulty in school performance and peer relationships [3-5]. When left untreated, anxiety disorders starting in childhood tend to persist into adulthood, and are frequently associated with depression [6], substance use disorder [7,8], occupational impairment [9], and suicidal behavior [10].

Pharmacotherapy for anxiety disorders in children will be discussed here. The epidemiology, pathogenesis, clinical manifestations, course, and diagnosis of anxiety disorders in children are discussed separately. Psychotherapy for anxiety disorders in children is also discussed separately. Obsessive-compulsive disorder and posttraumatic stress disorder in children and adolescents are also discussed separately.

- (See "Anxiety disorders in children and adolescents: Epidemiology, pathogenesis, clinical manifestations, and course".)
- (See "Overview of fears and phobias in children and adolescents".)
- (See "Psychotherapy for anxiety disorders in children and adolescents".)

- (See "Obsessive-compulsive disorder in children and adolescents: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)
- (See "Obsessive-compulsive disorder in children and adolescents: Treatment overview".)
- (See "Posttraumatic stress disorder in children and adolescents: Trauma-focused psychotherapy".)

ANTIDEPRESSANTS

For most children receiving medication treatment for an anxiety disorder, we suggest first-line treatment with a selective serotonin reuptake inhibitor (SSRI), rather than other treatments. Serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants have also shown efficacy in the treatment of pediatric anxiety disorders. Because they are associated with less easily tolerated side effects compared with SSRIs, these drugs are generally used second or third line.

SSRI/SNRI — Serotonin reuptake inhibitors (SRIs) used in the treatment of pediatric anxiety disorders include SSRIs, SNRIs, and clomipramine. (See 'Tricyclic antidepressants' below.)

Efficacy — SSRIs and SNRIs, as a class, are considered effective for pediatric anxiety disorders. A meta-analysis of 16 randomized trials on published between 1992 and 2008 found a number of SSRI and SNRI medications – fluoxetine, sertraline, fluvoxamine, paroxetine, and venlafaxine – to be superior to placebo in the treatment of pediatric anxiety [11,12]. Network meta-analysis showed that treatment response was more likely with SSRIs as compared with SNRIs [13]. The SNRI duloxetine and the SSRI escitalopram have US Food and Drug Administration (FDA) indication for the treatment of generalized anxiety disorder (GAD) in youth [14,15]. Some children experienced weight loss, increased cholesterol, and changes in vital signs while taking the medication class of SNRIs.

Generalized anxiety disorder — Two randomized trials by the same research team found that the SNRI venlafaxine and the SSRI sertraline reduced symptoms of GAD in children and adolescents diagnosed with the disorder:

- An eight-week randomized trial of 320 youths (age 6 to 17) with GAD found venlafaxine extended release (ER) to be superior to placebo in reduction of GAD symptoms and in the proportion of patients responding to treatment (69 versus 48 percent) [16].

- A nine-week trial randomly assigned 22 participants (age 5 to 17) with GAD to either sertraline or placebo. Treatment with sertraline led to greater symptom reduction compared with placebo according to the Hamilton Anxiety Rating Scale. Dizziness (64

versus 18 percent) and nausea (55 versus 5 percent) were more commonly experienced by participants taking sertraline compared with placebo; however, these differences were not statistically significant in this small sample [12].

- A 10-week randomized trial assigned 272 youth (age 7 to 17) with GAD to duloxetine or placebo. Duloxetine was associated with greater symptom reduction on the Pediatric Anxiety Rating Scale, remission and functional improvement compared with placebo. Duloxetine was also associated with weight loss and changes in pulse and blood pressure [14].

Social anxiety disorder — Randomized trials have found the SNRI venlafaxine and the SRIs fluoxetine and paroxetine reduced symptoms of social phobia in children and adolescents.

- A 16-week randomized trial of 322 participants (age 8 to 17) with social phobia compared treatment with paroxetine with placebo [17]. Paroxetine led to a higher response rate than placebo (78 versus 38 percent).

- A 16-week trial randomly assigned 293 youths with social anxiety disorder (age 8 to 17) to venlafaxine ER or placebo [18]. Venlafaxine led to a higher response rate compared with placebo (56 versus 37 percent).

- A 12-week clinical trial randomly assigned 122 individuals with social phobia (age 7 to 17) to fluoxetine, behavioral treatment or placebo [19]. At the end of the treatment period, the proportion of patients no longer meeting criteria for social phobia were much greater for behavioral treatment and fluoxetine compared with placebo (53 and 21.2 versus 3.1 percent).

Selective mutism — Very small randomized trials of an SSRI in children/adolescents with selective mutism (with and without co-occurring anxiety disorders) found no difference between groups treated with an SSRI versus placebo. A small but slightly larger uncontrolled trial had more promising results.

- A 12-week clinical trial randomly assigned 15 youths to either fluoxetine or placebo [20]. No differences between groups were found between groups based on clinician and teacher ratings; parent ratings found participants assigned to fluoxetine improved compared with those in the placebo group. Symptom reduction was seen both groups; however, participants remained highly symptomatic.

- A 16-week clinical trial of five children (age 5 to 11 years) with selective mutism showed no difference in symptom change between sertraline and placebo-treated groups [21].

- A nine-week, uncontrolled trial of fluoxetine in 21 youths age 5 to 14 with selective mutism along with a concurrent DSM-III-R anxiety disorder (separation anxiety disorder, overanxious disorder/GAD, avoidant disorder, or social phobia) found 76 percent of the sample to experience improved symptoms, with diminished anxiety and increased speech [22].

Panic disorder — Three uncontrolled trials with a total of 46 pediatric subjects with panic disorder treated with an SSRI experienced response rates between 75 and 90 percent [23-25].

Specific phobias — An uncontrolled trial tested fluoxetine in six youths (age 10 to 17) who met criteria for specific phobia and at least one additional anxiety disorder [26]. Three of six were rated as "improved" and two were rated as "much improved" after nine weeks of treatment [25].

Other — Three randomized trials compared SSRIs with placebo in a total of 706 youth with a mix of anxiety disorders (GAD, separation anxiety disorder, or social phobia). Response rates ranged from 54.9 to 76 percent of the mixed samples after 8 to 12 weeks of treatment [27-29]. A trial that reported results by disorder found improvement in response to an SSRI in subjects with social phobia and GAD compared with placebo, but not with separation anxiety disorder [29].

There have been no clinical trials of SRIs in children with agoraphobia or separation anxiety disorder alone.

Adverse effects — The risks associated with SRIs/SNRIs for pediatric anxiety should be carefully weighed against their potential benefits whenever the use of these medications is considered. Risks and benefits should be discussed with both the parents and child before initiating treatment. SSRIs have been associated with psychiatric adverse events, such as disinhibition, agitation, and worsening of anxiety symptoms. Physical side effects most commonly include headaches, gastric distress, and sleep disturbance [30]. Antidepressant medications are associated with an increased risk of suicidality in children, which we address below. (See 'Suicidality and antidepressants in children' below.)

Some children receiving SNRIs have been reported to experience weight gain, elevated cholesterol, and hypertension.

Administration — SRIs are generally started at the lowest available dose in children. After a week during which the patient is known to be taking the medication and tolerating it with minimal side effects, the dose can be increased incrementally to an initial therapeutic dose. If symptoms do not remit after six to eight weeks, the dose is increased incrementally and tested,

until the maximum dose is reached or side effects are not tolerable. Antidepressants often require dosages similar to those in adults, due to the fast metabolism seen in children. A table summarizes initial daily doses, therapeutic ranges, and suggested dose titration rates for SSRIs in anxiety disorders in children (table 1).

As an example, sertraline can be started at an initial dose of 12.5 to 25 mg/day for a minimum of seven days and titrated up to 50 mg/day in increments of 12.5 mg (child) or 25 to 50 mg (adolescent) per week. If an adequate clinical response is not seen after six to eight weeks of treatment, subsequent trials should be tried following dose increases of 12.5 mg/day for children and 25 to 50 mg/day for adolescents to a maximum of 200 mg/day.

When stopping an SRI, decrease the dose gradually to avoid discontinuation symptoms, eg, by 25 to 50 percent weekly. During the tapering period, the treating clinician should carefully monitor the child or adolescent for adverse events.

Following reports of associations between antidepressant use and suicidality in children, the FDA made recommendations regarding clinical monitoring and duration of the medications, below. (See 'Suicidality and antidepressants in children' below.)

Augmentation — Several medications including buspirone, benzodiazepines, stimulants, a second SSRI, atypical antipsychotics, and tricyclic antidepressants (TCAs) have been proposed for augmentation of SSRI/SNRI treatment of pediatric anxiety disorders; however, there is minimal to no evidence to support these strategies [31,32].

Evidence from clinical trials suggests that augmentation of pharmacotherapy with cognitive-behavioral therapy (CBT) may be effective in treating pediatric anxiety disorders, and the combination of SSRI medication and CBT may provide a greater treatment response than either treatment on its own. This combination treatment is recommended for youth with severe anxiety presentations. (See 'Combining medication and psychotherapy' below and "Psychotherapy for anxiety disorders in children and adolescents", section on 'Combining medication and psychotherapy'.)

Tricyclic antidepressants — TCAs are not generally recommended as first- or second-line treatment of anxiety disorders in children, because of the limited support from clinical trials and side effect profile that is typically less well-tolerated than SRIs/SNRIs.

Efficacy — Clinical trials have found mixed results on the efficacy of TCAs in pediatric anxiety disorders:

Separation anxiety disorder — A six-week clinical trial in 21 youths (age 6 to 15) with separation anxiety disorder compared imipramine with placebo, finding no difference in the response rate between the two groups (45 versus 44 percent) [33].

Mixed anxiety disorders — Clinical trials have found that imipramine reduced and clomipramine did not reduce symptoms in a sample of youth with mixed anxiety disorders (overanxious disorder [GAD in DSM-IV and DSM-5], separation anxiety disorder, or school refusal):

- A six-week, randomized trial compared imipramine with placebo in 35 youths (age 6 to 14) with separation anxiety disorder leading to school refusal [34]. Psychiatrist ratings found that participants who received imipramine had a marked decrease in symptoms compared with patients who received placebo (73 versus 32 percent on a global improvement scale). Children receiving imipramine were more likely to regularly attend school at post-treatment compared with children in the placebo group (81 versus 47 percent).

- A 12-week clinical trial comparing clomipramine with placebo in 51 youths (age 9 to 14) with overanxious disorder, separation anxiety disorder, or school refusal did not find a difference in response rates between the two groups [35].

Adverse effects — Anticholinergic effects are frequently observed in children and adolescents taking TCAs. Dry mouth and constipation have been found to be common in both children/adolescents and adults [36]. Blurred vision and urinary retention have been found less frequently in children and adolescents compared with adults. Irritability and anger outbursts were found to be common adverse effects of imipramine.

TCAs can lead to irregular or rapid heartbeat in some individuals. Prior to starting a TCA, children should receive a cardiac risk assessment consisting of a baseline electrocardiogram, vital signs, and baseline labs. Alternative medications should be used in patients with an elevated cardiac risk. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

Antidepressant medications are associated with an increased risk of suicidality in children, which we address below. (See 'Suicidality and antidepressants in children' below.)

Suicidality and antidepressants in children — There is an increased risk of suicidal thinking and behavior in children and adolescents taking antidepressant medications, a risk that should be weighed against the potential benefits of the medication. The FDA issued a “black box” warning in 2004, stating that children and adolescents taking antidepressant medication, including SSRIs and TCAs, are at increased risk for suicidal thinking or behavior [37].

Antidepressant risks and the evaluation/management of suicidality in children are discussed in more detail separately.

A meta-analysis of 39 medication trials conducted in children and adolescents treated with an SSRIs, SNRIs, nefazodone, venlafaxine, or mirtazapine for an anxiety disorder (including obsessive-compulsive disorder [OCD] under DSM-IV) showed a small increase in the risk of suicidal ideation and suicide attempts compared with those assigned to placebo (0.5 percent for OCD; 0.7 percent for anxiety disorders other than OCD) [38]. The number needed to harm was 200 for OCD and 143 for non-OCD anxiety disorders. There were no completed suicides reported in the trials studied. The meta-analysis indicated good efficacy for the antidepressants in the treatment of pediatric anxiety disorders, with a number-needed-to-treat of six for OCD and three for non-OCD anxiety disorders. Youth with OCD were 33 times more likely to benefit from antidepressant treatment than to experience a suicidal event. For youth with anxiety disorders other than OCD, treatment benefit was 47 times more likely than a suicidal event.

Another meta-analysis evaluated the suicidality of nine antidepressants in a total of 24 randomized controlled trials of children with pediatric anxiety disorders, depression, or attention deficit hyperactivity disorder. The risk ratio of suicidality across trials was 1.95, 95% CI, 1.28-2.98 [39]. Child suicidality and antidepressant drugs are discussed in greater detail separately, as is the evaluation and management of suicidality in children. (See "Suicidal ideation and behavior in children and adolescents: Evaluation and management" and "Effect of antidepressants on suicide risk in children and adolescents".)

The long-term effects of chronic antidepressant medication use in children and adolescents are not known [30].

In reporting on the association between antidepressants and suicide, the FDA recommended that the medications be started at low doses and increased gradually [30]. An example is provided above. (See 'Administration' above.)

The FDA additionally recommended close monitoring of patient's clinical status during the early weeks of antidepressant treatment and limiting the duration of their use. We agree with the recommendation that children prescribed an antidepressant medication should meet with the prescribing clinician:

- Weekly for the first four weeks
- Biweekly beginning the second month
- Monthly beginning the third month (ie, 12 weeks following the start of medication)

Patients should be seen more frequently than monthly maintenance visits if they experience an acute increase in symptoms or decline in functioning, if medications are being adjusted or changed, or if the patient is experiencing suicidal thoughts/behavior or consuming alcohol or illicit substances.

The FDA recommended a medication-free trial of patients who experience diminished anxiety once the reduction is maintained for more than a year. A time period when the child has lower stress (eg, school vacation) is recommended for the trial. The medication should be resumed if the patient experiences a relapse of symptoms after the medication has been stopped [30].

BENZODIAZEPINES

Benzodiazepines have a limited role in the treatment of pediatric anxiety disorders. They have a rapid onset of anxiolysis (minutes to hours) compared with antidepressants, which can take as long as several weeks. Benzodiazepines are, however, associated with significant adverse effects and their use in this population should be limited. (See 'SSRI/SNRI' above and "Psychotherapy for anxiety disorders in children and adolescents".)

Indications for benzodiazepine treatment in pediatric anxiety disorders are discussed below. (See 'Treatment selection' below.)

Efficacy — By clinical reports, benzodiazepines may to be effective in some cases of pediatric anxiety disorders.

Clinical trials of benzodiazepines for these disorders have been inadequate to assess efficacy. Trials, which had multiple limitations, reported no differences in symptom reduction between benzodiazepines and placebo in:

- 8- to 16-year-olds with overanxious disorder (renamed generalized anxiety disorder [GAD] in DSM-IV) [40]
- 7- to 13-year-olds with separation anxiety disorder with or without co-occurring anxiety disorders [41]
- 7- to 18-year-olds with GAD, separation anxiety disorder, or school refusal [42]

Larger trials are needed that assess higher dosages and longer treatment periods, and employ structured diagnosis and gradual tapering periods.

Clinical trials of benzodiazepines for anxiety disorders in adults provide indirect evidence for efficacy in children [43,44].

Adverse effects — Common adverse effects of benzodiazepines include drowsiness, irritability and oppositional behavior [45]. Benzodiazepines can be subject to misuse, addiction, and diversion. (See "Prescription drug misuse: Epidemiology, prevention, identification, and management".)

Administration — Benzodiazepines with longer half-lives are generally suggested, as is a gradual titration up from a low starting dose. As an example, clonazepam can be started at 0.25 mg/day to observe response. The dose can be increased to 0.5 mg/day if well-tolerated; further increases are based on response and tolerability

OTHER MEDICATIONS

A 2016 pilot study comparing guanfacine with placebo in 83 youth age 6 to 17 with generalized anxiety disorder (GAD), separation anxiety disorder, or social anxiety disorder found that guanfacine was associated with greater improvement than placebo according to the Clinical Global Impression of Improvement Scale, but not on other measures of anxiety. Guanfacine was well-tolerated in the study [46].

Buspirone was found to have no difference in primary outcomes compared with placebo in the treatment of pediatric GAD in two clinical trials with a total of 559 patients age 6 to 17 [47]. Nausea, headaches, and stomach aches were reported by youth treated with buspirone.

COMPARING MEDICATION AND PSYCHOTHERAPY

Clinical trials comparing serotonin reuptake inhibitor medication versus cognitive-behavioral therapy for pediatric anxiety disorders in children have yielded mixed results, which are described separately. (See "Psychotherapy for anxiety disorders in children and adolescents", section on 'Comparing medication and psychotherapy'.)

COMBINING MEDICATION AND PSYCHOTHERAPY

A clinical trial comparing cognitive-behavioral therapy to selective serotonin reuptake inhibitor treatment in pediatric anxiety disorders found that combined treatment was superior to either modality delivered individually; these results are described separately. (See "Psychotherapy for anxiety disorders in children and adolescents", section on 'Combining medication and psychotherapy'.)

TREATMENT SELECTION

Evidence from clinical trials on the treatment of pediatric anxiety disorders is, in general, inadequate to fully inform selection among treatment options, particularly for second- and third-line decisions. Some anxiety disorders (panic disorder, agoraphobia, specific phobias, and selective mutism) have not been subject to clinical trials in children. In many cases, available trials have had small samples. Head-to-head trials of efficacious drugs have not been performed. Our recommendations are thus informed by research evidence where available as well as by our clinical experience.

First-line treatment

Mild to moderate anxiety disorder — We recommend considering either cognitive-behavioral therapy (CBT) and medication treatment with a serotonin reuptake inhibitor (SRI) medication as first-line treatments of children with any anxiety disorder of mild to moderate severity. Both selective serotonin reuptake inhibitor (SSRI) medication and CBT have shown to be efficacious as stand-alone interventions for youth with mild to moderate anxiety. If assessable, monotherapy treatment with CBT is recommended for younger children with milder symptoms of anxiety. Clinical trials comparing CBT with SSRI treatment for a pediatric anxiety disorder are mixed, with the largest trial finding no difference in remission rates between groups and another finding CBT to be superior to sertraline. Selection between these modalities may also be influenced by availability of CBT and by child/parent preferences. (See 'Comparing medication and psychotherapy' above and "Psychotherapy for anxiety disorders in children and adolescents" and "Psychotherapy for anxiety disorders in children and adolescents", section on 'Comparing medication and psychotherapy'.)

Moderate to severe anxiety disorder — For children with a moderate to severe pediatric anxiety disorder, we suggest first-line treatment with a combination of CBT and an SRI. Combined CBT-SSRI treatment performed better than either modality individually in clinical trials of children with social phobia, generalized anxiety disorder, or separation anxiety disorder [48] as well as in a trial of school refusal [49]. (See 'SSRI/SNRI' above and 'Combining medication and psychotherapy' above and "Psychotherapy for anxiety disorders in children and adolescents" and "Psychotherapy for anxiety disorders in children and adolescents", section on 'Combining medication and psychotherapy'.)

Co-occurring anxiety disorder and major depression — A combination of CBT and SSRI medication may be beneficial for children with an anxiety disorder and comorbid major depression, although this treatment combination has not been tested directly in clinical trials.

Second-line treatment — For a patient with a pediatric anxiety disorder that does not respond to an adequate trial of CBT alone, we suggest the addition of SRI treatment rather than other medications. If the patient was treated initially with SRI only with some response next step to consider is the addition of CBT. SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been found to be efficacious in clinical trials of pediatric anxiety disorders. There are no head to head trials comparing medications for the disorders. SRIs are most extensively studied class and are generally better tolerated than the other antidepressants (see 'SSRI/SNRI' above and 'Tricyclic antidepressants' above). There is no clear evidence on the approach to switching to other SRIs or SNRIs.

Third-line treatment — For patients whose symptoms do not remit after a six- to eight-week trial on a maximum tolerated dose of a second SRI and at this point psychotherapy should be a part of treatment, SNRIs can be considered as another option.

SNRIs, are a reasonable option if two SSRI trials both lead to inadequate clinical responses.

SRIs are generally preferred to benzodiazepines for long-term treatment of a pediatric anxiety disorder, though benzodiazepines can be useful in these patients to treat disabling anxiety while waiting for an antidepressant to take effect, or to treat SSRI-induced jitteriness. (See 'Benzodiazepines' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Anxiety and trauma-related disorders in children".)

SUMMARY AND RECOMMENDATIONS

- **Introduction** – Anxiety disorders are the most common psychiatric disorders diagnosed in childhood and adolescence. Pediatric anxiety disorders are associated with increased difficulty in school performance and peer relationships. When left untreated, anxiety disorders starting in childhood tend to persist into adulthood, and are associated with depression, substance use disorders, suicidal behavior, and occupational impairment. (See 'Introduction' above.)

- **Mild to moderate anxiety disorder** – We suggest first line treatment of individuals with a mild to moderate anxiety disorder treatment with cognitive-behavioral therapy (CBT)

rather than medication (**Grade 2B**). Medication treatment a reasonable alternative if preferred by the patient and CBT is unavailable. (See 'Mild to moderate anxiety disorder' above.)

For individuals with a pediatric anxiety disorder that does not respond to an adequate trial of CBT, we suggest adding serotonin reuptake inhibitor (SRI) treatment rather than other medications (table 1) (**Grade 2C**). (See 'Second-line treatment' above.)

- **Moderate to severe anxiety disorder** – We suggest treatment of moderate severe anxiety disorder with a combination of CBT and an SRI rather than either modality as monotherapy or other treatments (**Grade 2B**). (See 'Moderate to severe anxiety disorder' above.)

- **Suicidality** – There is an increased risk of suicidal thinking and behavior in children and adolescents taking antidepressant medications. We weigh this risk against the potential benefits of the medication in all children and adolescents we treat with antidepressant medications. (See 'Suicidality and antidepressants in children' above.)

- **Subsequent treatment** – We suggest pharmacologic treatment with a second SRI rather than other medication strategies (eg, tricyclic antidepressants benzodiazepines) for individuals whose symptoms do not remit after a therapeutic trial of an SRI (**Grade 2C**). (See 'Third-line treatment' above.)

  Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a reasonable option if two prior trials of SRI lead to inadequate clinical responses. We monitor all children taking SNRIs for adverse effects such as weight gain, elevated cholesterol, and hypertension.

  Benzodiazepines have a limited role in the treatment of pediatric anxiety disorder. Longer-acting benzodiazepines can be useful in children with anxiety disorders to treat disabling anxiety while waiting for an antidepressant to take effect or to treat selective serotonin reuptake inhibitor-induced jitteriness. (See 'Benzodiazepines' above.)

- **Discontinuation** – We taper the dose of antidepressants by 25 to 50 percent weekly when stopping them to avoid discontinuation symptoms. During the tapering period, we monitor the individual carefully for adverse events. (See 'Adverse effects' above.)

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