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Dr. Strawn: Predictors of outcome and multimodal treatment for pediatric anxiety

An evidence-based approach to treating pediatric anxiety disorders

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Research supports SSRIs, other medications as part of a multimodal approach

Anxiety disorders are remarkably common among pediatric patients[1,2] and are associated with significant morbidity[3] and increased risk of suicidality in adolescents.[4,5] Effective diagnosis and treatment of pediatric anxiety disorders are critical for reducing psychosocial morbidity,[3,6] suicidality, and the risk of secondary mood disorders.[7]

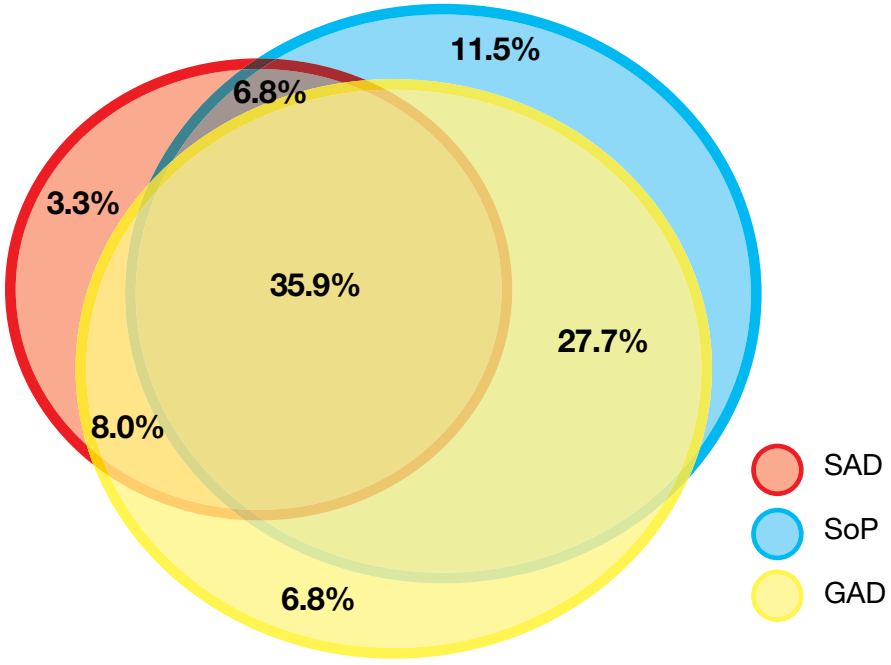
This article summarizes open-label studies and randomized controlled trials (RCTs) of selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors, atypical anxiolytics, and benzodiazepines in children and adolescents with generalized anxiety disorder (GAD), social phobia, separation anxiety disorder, and panic disorder. Although we focus on psychopharmacologic treatments, the best outcomes generally are observed with multimodal treatments that combine psychotherapy and pharmacotherapy.

Generalized anxiety disorder

Researchers have evaluated SSRIs, benzodiazepines, and buspirone in pediatric patients with GAD. In a double-blind, placebo-controlled trial of 22 patients age 5 to 17, sertraline, 50 mg/d, was associated with improvement in Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impression-Severity (CGI-S), and Clinical Global Impression-Improvement (CGI-I) scores over 9 weeks.[8] The Child-Adolescent Anxiety Multimodal Study compared cognitive-behavioral therapy (CBT) to sertraline or sertraline plus CBT in 488 patients age 7 to 17, 78% of whom had GAD.[9] Sertraline monotherapy was superior to placebo and not statistically different from CBT, while combination

Figure 1

The pediatric anxiety disorders triad: Comorbidity is common



In the Child-Adolescent Multimodal Treatment Study, GAD was the most common disorder; however, GAD, SAD, and SoP were highly comorbid

GAD: generalized anxiety disorder; SAD: separation anxiety disorder; SoP: social phobia

Source: Reference 9

treatment was superior to both monotherapy conditions in improving CGI score. In both trials, sertraline was well tolerated.

One study evaluated fluoxetine, 5 to 40 mg/d, or CBT in 14 youths with GAD; both treatments improved symptoms.[10] In a study of 320 GAD patients age 6 to 17, venlafaxine extended-release (XR) initiated at 37.5 mg/d was associated with improved HAM-A scores.[11] In general, venlafaxine was well tolerated; adverse effects included increased blood pressure, asthenia, pain, anorexia, somnolence, weight loss, and possibly treatment-emergent suicidal ideation.

Two RCTs of buspirone, 15 to 60 mg/d, that evaluated 559 children and adolescents age 6 to 17 with GAD did not observe significant differences between buspirone and placebo.[12] By contrast, 2 open-label studies of youths with anxiety suggested improvement associated with buspirone.[12] Treatment-emergent adverse events included nausea, stomachache, and headache.

Clinical trials of benzodiazepines in anxious children and adolescents have yielded mixed results. A 4-week, open-label trial of alprazolam, 0.5 mg to 1.5 mg/d, in 12 adolescents with overanxious disorder—the DSM-III forerunner of GAD—found improvements in anxiety, depression, psychomotor excitation, and hyperactivity, but patients experienced sedation, activation, headache, and nausea.[13] However, a double-blind RCT in 30 youths age 8 to 16 found no statistically significant difference between alprazolam and placebo.[14] Alprazolam generally was well tolerated; fatigue and dry mouth were reported, but no withdrawal symptoms. Additionally, benzodiazepine use may be associated with tolerance and—in young children—disinhibition.

Social phobia

Researchers have evaluated paroxetine, citalopram, fluoxetine, and venlafaxine for

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Evidence suggests sertraline, fluoxetine, and venlafaxine can reduce symptoms in children and adolescents with GAD

Clinical Point

Including a benzodiazepine at the start of SSRI therapy may be a useful strategy for pediatric panic disorder

treating social phobia in pediatric patients. In an RCT, 78% of paroxetine-treated patients with social phobia responded compared with 38% for placebo over 16 weeks. Adverse events—including withdrawal symptoms—were twice as likely in patients who received paroxetine. Additionally, 4 paroxetine patients exhibited suicidal ideation vs 0 patients who received placebo.[15]

In an RCT of 293 children and adolescents age 8 to 17 with social phobia, venlafaxine XR was initiated at 37.5 mg/d and titrated to 112.5 mg/d, 150 mg/d, or 225 mg/d, depending on body weight.[16] The venlafaxine group experienced significantly improved anxiety symptoms and the medication generally was well tolerated, although 3 venlafaxine-treated patients developed suicidal ideation compared with 0 in the placebo group.

An RCT compared Social Effectiveness Therapy for Children (SET-C) and fluoxetine, 10 to 40 mg/d, for 139 patients age 7 to 17 with social phobia.[17] SET-C is a CBT for children and adolescents that focuses on increasing interpersonal skills and becoming more comfortable in social situations; it involves psychoeducation, social skills training, and exposure exercises. At endpoint, 53% of patients in the SET-C group no longer met diagnostic criteria for social phobia. Fluoxetine was well tolerated; no severe adverse events were reported.

In an open-label study of sertraline (mean dose = 123 mg/d) for 14 young persons with social phobia, 36% of patients responded and 29% partially responded at 8 weeks.[18] Adverse events generally were mild and included nausea, diarrhea, and headache. In a 12-week study, 12 pediatric patients with social phobia received citalopram, 10 to 40 mg/d, and eight 15-minute counseling sessions. At endpoint, clinicians rated 83% of patients as much improved or very much improved. The medication generally was well tolerated.[19]

Separation anxiety disorder

In a 4-week, double-blind crossover pilot study, researchers randomly assigned 15 children age 7 to 13 with separation anxiety disorder to clonazepam, up to 2 mg/d, or placebo.[20] There was no significant difference in CGI-I score between clonazepam and placebo. Side effects—including drowsiness, irritability and "oppositional behavior"—were more frequent in patients treated with clonazepam.

Panic disorder

Only 2 open-label studies of SSRIs have been conducted in pediatric patients with panic disorder. The first evaluated the effectiveness and tolerability of fluoxetine, sertraline, or paroxetine over 6 months in 12 patients; 67% no longer met criteria for panic disorder at endpoint.[21] In this study, benzodiazepines—including clonazepam and lorazepam—were used in 67% of patients at the start of SSRI treatment. The authors suggested this strategy may be clinically useful for patients with panic disorder.

In the second study, Fairbanks et al[22] examined the use of fluoxetine for 6 to 9 weeks in 16 outpatients with mixed anxiety disorders who did not respond to psychotherapy. Patients age ≤12 were given 5 to 40 mg/d and those age ≥13 received 5 to 80 mg/d. Fluoxetine was associated with clinically significant improvement in 3 of the 5 patients who had panic disorder. Although overall fluoxetine was well tolerated, drowsiness, dyssomnia, decreased appetite, nausea, and abdominal pain were the most common side effects. Fluoxetine was not associated with suicidal ideation.

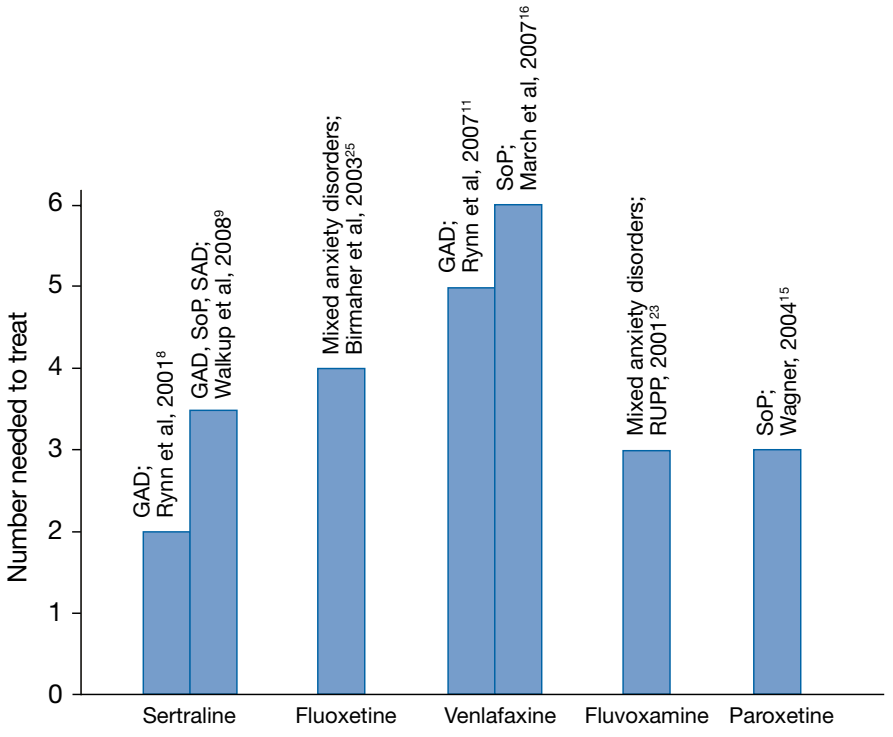
Mixed anxiety disorders

Most trials of pediatric anxiety have evaluated patients with "mixed anxiety disorders" because GAD, social phobia, and separation anxiety disorder are highly comorbid and share diagnostic features (***Figure 1, page 17***).[9] An RCT of fluvoxamine, up to 300 mg/d, in 128 pediatric patients with ≥1 anxiety disorders found significant differences in CGI-I and endpoint Pediatric Anxiety Rating Scale (PARS) scores.[23] Fluvoxamine was well tolerated but associated with increased motor activity and abdominal discomfort compared with placebo.

Two open-label trials of pediatric patients with mixed anxiety disorders suggested

Figure 2

Number needed to treat for SSRIs and SNRIs in pediatric anxiety disorders



GAD: generalized anxiety disorder; RUPP: Research Unit on Pediatric Psychopharmacology; SAD: separation anxiety disorder; SNRI: serotonin-norepinephrine reuptake inhibitor; SoP: social phobia; SSRI: selective serotonin reuptake inhibitor

fluoxetine may be beneficial. Fairbanks et al[22] documented clinical improvement in 10 of 10 patients with separation anxiety disorder, 8 of 10 with social phobia, 4 of 6 with specific phobia, 3 of 5 with panic disorder, and 1 of 7 with GAD. Birmaher et al[24] evaluated 21 pediatric patients with overanxious disorder, social phobia, or separation anxiety who had not responded to psychotherapy and were not depressed; all patients received flexibly-dosed fluoxetine for up to 10 months. Fluoxetine was well tolerated and 81% of patients improved.

Finally, in a 12-week RCT of 74 patients age 7 to 17 with GAD, separation anxiety disorder, and/or social phobia, fluoxetine, 10 to 20 mg/d, was associated with improved scores on the Screen for Anxiety Related Emotional Disorders, PARS, CGI-I, CGI-S, and Children's Global Assessment Scale.[25] A follow-up open-label trial suggested that maintenance treatment is associated with sustained improvement.[26]

Anxiety disorders with ADHD

Anxiety disorders often are comorbid with attention-deficit/hyperactivity disorder (ADHD). An RCT of patients age 8 to 17 with ADHD and comorbid anxiety found that atomoxetine was associated with improved PARS scores and ADHD symptoms.[27] The target dose was 1.2 mg/kg/d. Atomoxetine was well-tolerated; decreased appetite was the only significant adverse event in the treatment group vs placebo.

Multimodal treatment

Although this article reviews evidence for psychopharmacologic treatments, psychotherapeutic treatment of young patients with anxiety disorders has seen significant advances.[28] Most psychotherapy studies have evaluated the efficacy of CBT,[29-31] although there is evidence for psychodynamic therapy and interpersonal therapy.[32] The American Academy of Child &

Clinical Point

Fluvoxamine or fluoxetine may be helpful for pediatric patients with mixed anxiety disorders

Table

Practical dosing of SSRIs and SNRIs in pediatric patients with anxiety[a]

Medication	Initial child dose (age <12; mg/d)	Initial adolescent dose (age 12 to 17; mg/d)	Target dose (mg/d)
Citalopram	5 to 10	10	20 to 40
Escitalopram	2.5 to 5	5 to 10	10 to 20
Fluoxetine[b]	10	20	20 to 40 (children), 40 to 60 (adolescents)
Paroxetine[b]	5 to 10	10	20
Sertraline[c]	10 to 12.5	25	150
Venlafaxine	37.5	37.5	150

[a]Generalized anxiety disorder, social phobia, and separation anxiety disorder
[b]May consider cytochrome P450 genotyping for 2D6, which may suggest an alternate dosing strategy
[c]Sertraline is available in a liquid formulation (20 mg/mL)

SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Source: Adapted from reference 34

Clinical Point

A multimodal approach that incorporates psychotherapy and pharmacotherapy is more effective than monotherapy

Adolescent Psychiatry recommends a multimodal treatment approach because combination treatment appears to be more effective than monotherapy.[8,28,33] Also, clinicians who treat pediatric patients who have an anxiety disorder should evaluate the family's role on anxiety symptoms and may consider family therapy.

Treatment considerations

Evidence supports the efficacy of sertraline, citalopram, paroxetine, fluvoxamine, fluoxetine, and venlafaxine for treating children and adolescents with anxiety disorders (***Figure 2, page 19***).[8,9,11,15,16,23,25] Some practitioners suggest using differing dosing strategies for pediatric anxiety disorders compared with those used to treat adults (***Table***).[34] When considering SSRIs for children and adolescents, keep in mind the "black-box" warning regarding suicidality in these patients. Carefully monitor patients for treatment-emergent suicidality and routinely reassess for the presence and severity of suicidal ideation and suicide risk.

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Related Resources

- Connolly SD, Bernstein GA; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2007;46(2):267-283.
- Anxiety and Depression Association of America. www.adaa.org.
- American Academy of Child & Adolescent Psychiatry. www.aacap.org.

Drug Brand Names

Alprazolam • Xanax
Atomoxetine • Strattera
Buspirone • BuSpar
Citalopram • Celexa
Clonazepam • Klonopin
Fluoxetine • Prozac
Fluvoxamine • Luvox, Luvox CR
Lorazepam • Ativan
Paroxetine • Paxil, Paxil CR
Sertraline • Zoloft
Venlafaxine • Effexor, Effexor XR

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Dr. McReynolds was employed by Eli Lilly and Company from 1997 to 2005.

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Clinical Point

When prescribing SSRIs for pediatric anxiety, monitor patients for suicidality and routinely reassess suicide risk

Bottom Line

Evidence supports the use of several selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors for treating anxiety disorders in children and adolescents, including generalized anxiety disorder, social phobia, separation anxiety disorder, and panic disorder. Data on buspirone and benzodiazepines are mixed, although the latter may have an adjunctive role in managing panic disorder. Optimal treatment should include psychotherapy.