Summary of the Literature on the Treatment of Anxiety Disorders in Children and Adolescents

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Non-OCD anxiety disorders in youth are common and disabling, with 12-month prevalence between 10% to 20% in youth. Anxiety disorders increase risk for academic underachievement and are highly comorbid with other anxiety disorders, depression, ADHD, and substance abuse (1).

Screening and Assessment

The Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders highlighted evidence-informed screening and assessment tools for childhood anxiety disorders to increase early identification and monitor progress (1,2). The SCARED and SASC are free, have child and parent reports, and the SASC has a preschooler version. Using a feelings thermometer or faces barometer assists to monitor anxiety severity and impairment. Assessing baseline somatic symptoms reduces confusion with side effects during medication trials. Considering anxiety for youth with persistent somatic complaints may prevent excessive medical work-ups. Family assessment, including parental anxiety disorders, can identify environmental reinforcements for anxious and avoidant behaviors.

Treatment Planning

Treatment for children with anxiety disorders of mild severity begins with psychotherapy that includes exposure-based cognitive-behavioral therapy (CBT). Medication may be necessary for moderate to severe anxiety for acute symptom reduction, comorbid disorders, partial response to CBT, and improving outcome with combined treatment (1).

Treatment

Psychotherapy

Exposure-based CBT has received the most empirical support, and is the psychotherapy of choice for childhood anxiety disorders (1,2,3). CBT is effective in individual and group treatment. CBT for childhood anxiety disorders consists of several components: psychoeducation about anxiety and CBT, affective differentiation and somatic management skills, cognitive restructuring, practicing problem solving, exposure methods, and relapse prevention (4). Parental anxiety disorders and family accommodations that maintain the child's avoidant coping can negatively impact the success of CBT.

Pharmacological Treatments

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are first-line medications for pediatric anxiety disorders based on randomized RCTs that have established short-term efficacy (reviewed in 1,5,6,7,8). The U.S. FDA issued a black-box warning for increased relative risk for suicide adverse events for antidepressant medication in pediatric populations. The benefit/risk ratio for anxiety disorders is more favorable than that for depression, but clinicians need to monitor carefully for worsening depression, agitation, or suicidality, especially when initiating treatment and at dose changes. Side effects on SSRI medications and their management have been reviewed (9).

Separation anxiety disorder (SAD), generalized anxiety disorder (GAD), and social phobia were studied together in the following randomized placebo-controlled tri-

als (RCTs). The multi-site RUPP study (N=128) showed significant improvement on fluvoxamine (76%) over placebo (29%) in an 8 week trial with flexible dosing (50-300mg/day). Severe illness and social phobia predicted a poorer outcome (10). An open-label 6 month extension to this study showed 94% of fluvoxamine responders maintained good response, 71% of fluvoxamine non-responders responded to fluoxetine, and 56% of placebo non-responders responded to fluvoxamine.

Fluoxetine showed significant overall improvement (61%) relative to placebo (35%) in a 12 week trial with dosing at 10 or 20mg/day (11). Social phobia and GAD responded significantly better to fluoxetine, but SAD only trended toward better response. Anxiety symptoms only partially resolved in 50% of the treatment group. Higher doses of medication or a combination of treatments were suggested to improve results, and increasing the SSRI dose by the fourth week of treatment if no significant improvement.

A small, 9 week RCT with fixed low dose sertraline (50mg/day) for youth with GAD showed clinical improvement with sertraline (90%) versus placebo (10%) (12).
A multi-site, 16 week RCT in social phobia (N=322) showed significantly better response for paroxetine (78%) than placebo (39%) with flexible dosing (10-50mg/day) (13). However, there were significant adverse effects in the treatment group including insomnia, decreased appetite and vomiting. There were also concerns about worsened nervousness, hostility, and signs of potential activation in younger children; increased relative risk for treatment emergent suicidal ideations and significant discontinuation syndrome related to short-half life.

A 12 week RCT in children (N=15) with selective mutism (SM) and social phobia found significant improvement with fluoxetine on parent ratings relative to placebo, but both groups remained significantly symptomatic after treatment (14). An open trial with fluoxetine for SM in children with improvement, inversely correlated with age, supported use of graduated dosing. A controlled case series with sertraline showed positive response in children with SM. Some non-controlled studies and case reports with fluoxetine, fluvoxamine or sertraline suggested promise.

There are no RCTs in youth for medication treatment of panic disorder (5,7,8). An open-label trial of SSRIs in adolescents with panic disorder and comorbid disorders showed significant improvement with fluoxetine (20-60mg), paroxetine (20mg), or sertraline (125mg) alone or combined with short-term clonazepam or lorazepam when panic disorder was severe.

Fluoxetine in a small open trial with mixed anxiety disorders showed improvement in anxiety and panic symptoms with a mean dose of 24mg fluoxetine in children and 40mg in adolescents. A retrospective chart review in youth with panic disorder and comorbid disorders treated with paroxetine (10-40 mg/day) found significant improvement.

Very few studies have compared psychotherapy and medications. The relative 12 week efficacy of fluoxetine (10-40mg), placebo drug, and Social Effectiveness Therapy for Children (SET-C) for youth with social phobia was compared (15). Both active treatments were superior to placebo and reduced social distress and behavioral avoidance, but SET-C also enhanced social competence through improved social skills. The Child-Adolescent Anxiety Multimodal Study

(CAMS), a large (N=488) multi-site RCT, evaluated the relative and combined efficacy of 14 weeks of CBT, 12 weeks of sertraline (200mg/day), placebo drug alone, or a combination of sertraline and CBT in youth with moderate to severe SAD, GAD and/or social phobia (16). On CGI, CBT (60%) and sertraline (55%) showed greater improvement than placebo (24%), but the combination had a superior response rate (81% improved). Family preference, cost and treatment availability need to be considered in choosing treatment .
Evidence regarding long-term risks and benefits of SSRIs for youths with anxiety disorders is very limited. Clinicians can consider a medication-free trial during a low stress period for children who achieve marked improvement or remission for a full year. If relapse occurs during the slow taper or after discontinuation the SSRI should be restarted (1).

Other Medications

The safety and efficacy of medications other than the SSRIs for the treatment of childhood anxiety disorders have not been well established (8). Venlafaxine, buspirone, tricyclic antidepressants (TCAs), buspirone, and benzodiazepines have been used as clinical alternatives alone or in combination with the SSRIs. A 16 week trial of extended-release Venlafaxine (up to 225mg/day) in youth with social phobia showed significantly greater improvement on CGI for venlafaxine XR (56%) versus placebo (37%). Data was combined from two RCTs (N=320) of venlafaxine XR (up to 225mg/day) for youths with GAD. Study one showed significant improvements in anxiety and functioning measures and study two showed significant improvement only on some secondary outcome measures (17). The combined response rates were significantly greater for extended-release venlafaxine (69%) than placebo (48%). Common side effects were anorexia in children and adolescents and somnolence in adolescents. Significant increases in blood pressure, pulse, and total cholesterol were observed.
Venlafaxine may be considered for treatment of GAD after several SSRIs have failed and with careful monitoring (vital signs and cholesterol in short-term and periodic EKG in long-term treatment).
Controlled trials of TCAs for youths with anxiety disorders have demonstrated conflicting results (5,8). Clomipramine may be cautiously used alone or combined with an SSRI when there is a partial response. Although efficacious in controlled trials for childhood OCD, it has equivocal results for other anxiety disorders. Also adverse effects, cardiac conduction issues and lethality in overdose limit its usefulness. Clomipramine may be started at a low dose with close monitoring including EKGs and blood levels, and then titrated up slowly based on tolerance to side effects.

Buspirone has no RCTs that support its efficacy for children with anxiety disorders (7,8). An open trial of buspirone in youth with mixed anxiety disorders showed significant improvements in anxiety ratings and minimal side effects . Buspirone may be tolerated at lower doses in anxious children (5 to 7.5mg twice daily) than anxious adolescents (5 to 30mg twice daily).

Common side effects are lightheadedness, headache, and dyspepsia. Buspirone may be tried cautiously when SSRIs and venlafaxine fail in youth with GAD or as an adjunct medication.

Benzodiazepines have not shown efficacy in RCTs for childhood anxiety disorders (1,5,7,8). They can be clinically useful as short-term treatment for acute reduction in severe anxiety symptoms while SSRI is maximized. Benzodiazepines should be

used cautiously because of side effects and risk for physical and psychological dependency, and are contraindicated for youths with substance abuse. They are not recommended in pregnant or breastfeeding girls. Side effects include sedation, severe disinhibition with aggression and irritability, behavioral dyscontrol in adolescents, and cognitive and memory impairments that can impact learning. Withdrawal, especially if stopped abruptly, may be mild or severe.

A multisite RCT is underway to assess extended release guanfacine (1-6 mg/day) in youth with GAD, SAD or social phobia.

Psychopharmacologic treatment for very young children

The AACAP Preschool Psychopharmacology Working Group developed guidelines for psychopharmacological treatment in early childhood (18). Preschoolers benefit from much lower dosing of SSRIs than older children. Preschoolers with anxiety disorders can start with at least 12 weeks of treatment with psychotherapy. If response is not adequate then fluoxetine liquid at low dose (1mg) can be added, with target dosing of 5-8 mg/day. Alternative SSRIs if fluoxetine fails are sertraline or fluvoxamine.

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References

1. American Academy of Child and Adolescent Psychiatry: Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry 2007, 46: 267-283.
2. Velting ON, Setzer NJ, Albano AM: Update and advances in assessment and cognitive-behavioral treatment of anxiety disorders in children and adolescents. Professional Psychology: Research and Practice 35:42-54, 2004.
3. Compton SN, March JS, Brent D, et al: Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. J Am Acad Child Adolesc Psychiatry 43:930-959, 2004.
4. Gosch EA, Flannery-Schroeder E, Mauro CF, Compton SN: Principles of cognitive-behavioral therapy for anxiety disorders in children. J Cognitive Psychotherapy: An International Quarterly 2006, 20(3): 247-262.
5. Reinblatt SP, Riddle MA: The pharmacological management of childhood anxiety disorders: a review. Psychopharmacology 2007, 191:67-86.
6. Seidel L, Walkup JT: Selective serotonin reuptake inhibitor use in the treatment of pediatric non-obsessive-compulsive disorder anxiety disorders. J Child Adolesc Psychopharmacology 2006, 16:171-179.
7. Strawn JR, Sakolsky DJ, Rynn MA: Psychopharmacologic treatment of children and adolescent with anxiety disorders. Child Adolesc Psychiatric Clin N Am 2012, 21: 527-539.
8. Connolly SD, Suarez L, Sylvester C: Assessment and treatment of anxiety disorders in children and adolescents. Current Psychiatry Reports 2011, 13(2): 99-110.

9. Murphy TK, Segarra A, Storch EA, Goodman WK: SSRI adverse events: how to monitor and manage. International Review of Psychiatry 2008, 20(2): 203-208.

10. Research Units on Pediatric Psychopharmacology Anxiety Study Group (RUPP): Fluvoxamine for the treatment of anxiety disorders in children and adolescents. N Engl J Med 344:1279-1285, 2001.

11. Birmaher B, Axelson DA, Monk K, et al: Fluoxetine for the treatment of childhood anxiety disorders. J Am Acad Child Adolesc Psychiatry 42:415-423, 2003.

12. Rynn MA, Siqueland L, Rickels K: Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. Am J Psychiatry 158:2008-2014, 2001.

13. Wagner KD, Berard R, Stein MB, et al: A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety. Arch Gen Psychiatry 61:1153-1162, 2004.

14. Black B, Uhde TW:Treatment of elective mutism with fluoxetine: a double-blind, placebo-controlled study. J Am Acad Child Adoelsc Psychiatry 33:1000-1006, 1994.

15. Beidel DC, Turner SM, Sallee FR, Ammerman RT, Crosby LA, Pathak S: SET-C versus fluoxetine in the treatment of childhood social phobia. J Am Acad Child Adolesc Psychiatry 2007, 46(12):1622-1632.

16. Walkup JT, Albano AM, Piacentini J, et al.: Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. N Engl J Med 2008, 359: 2753-2766.

17. Rynn MA, Riddle MA, Yeung PP, et al: Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: Two placebo-controlled trials. Am J Psychiatry 2007, 164:290-300.

18. Gleason MM, Egger HL, Emslie GJ, et al.: Psychopharmacological treatment for very young children; contexts and guidelines. J Am Acad Child Adolesc Psychiatry 2007, 46(12); 1532-1572.