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Treatment of comorbid anxiety and autism spectrum disorders

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Summary

Clinically significant anxiety occurs frequently among individuals with autism spectrum disorders (ASDs) and is linked to increased psychosocial, familial, behavioral and academic impairment beyond the core autism symptoms when present. Although efforts are underway to establish empirically supported treatments for anxiety among individuals with ASDs, this remains an emerging research area. This literature review summarizes available information on the efficacy of pharmacological and psychosocial approaches for treating anxiety and repetitive behaviors in children, adolescents and adults with ASDs. Specifically, we evaluate evidence for the use of cognitive–behavioral therapy and selective serotonin-reuptake inhibitors. Evidence is growing in support of using cognitive–behavioral therapy to treat anxiety in youths with ASDs; however, mixed evidence exists for its application in treating repetitive behaviors, as well as the use of selective serotonin-reuptake inhibitors for anxiety in youths with ASDs. We conclude the article with a discussion of the strength of current information and next steps in research.

Prevalence rates of autism spectrum disorders (ASDs), including Asperger's disorder, pervasive developmental disorders not otherwise specified and autistic disorder, have risen dramatically over the past several decades [1]. Recent estimates suggest that one in every 91 American children (one in 58 boys) is affected by an ASD [1–4], with indications of similarly high prevalence rates outside of the USA [5]. Core features of ASDs include verbal and nonverbal communication impairments, qualitative impairments in social interaction and the presence of maladaptive routines, repetitive behaviors and atypical interests or fixations [6]. Symptoms of ASDs are associated with varying degrees of impairment across multiple domains of functioning [7].

One factor linked to increased impairment beyond core ASD symptoms is the presence of anxiety [8]. Up to 80% of children with ASDs experience clinically significant anxiety [9–11], with high comorbidity rates for social phobia, generalized anxiety disorder (GAD),

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obsessive–compulsive disorder (OCD) and separation anxiety disorder (SAD) having been observed (30, 35, 37 and 38%, respectively) [9,10,12,13]. The presence of clinically significant anxiety is associated with compounded functional impairment beyond a single ASD diagnosis [14]. Anxiety comorbidity is associated with greater ASD symptom severity and concomitant impairments in psychosocial functioning [15–19]. For example, patients with ASDs and comorbid anxiety are at increased risk for displaying externalizing behavior problems [20], social avoidance [16,18–20], difficulties establishing/maintaining peer relationships, sleep problems and disruptions in family functioning [21,22]. Among youths with ASDs and anxiety, these problems are also present in school settings, with studies reporting increased disruptive behavior, noncompliance with teacher demands and disengagement from peer-centered activities [23–27].

Youths with ASDs often also display repetitive behaviors with some phenotypic resemblance to behaviors performed by youth with certain anxiety disorders (e.g., compulsions) [10,15–17]. For example, ritualistic behaviors such as counting, checking, repeating, tapping, rigid adherence to routines and repeatedly reinstating certain words, facts or expressions are seen in both ASDs and OCD [28,29]. In both populations, these rituals may be performed to exert greater control over the environment and reduce anxiety, or may be performed for intrinsic reasons (e.g., self-stimulation or lacking identifiable function). Therefore, this review investigates treatments aimed at addressing anxiety and repetitive behaviors in youths with ASDs, given the phenomenological overlap between these behaviors [10].

Psychosocial treatment of comorbid ASD & anxiety

Cognitive–behavioral therapy treatment of anxiety

In 1993, a task force appointed by the Society for Clinical Psychology (American Psychological Association, Division 12) developed a set of criteria for establishing empirically validated treatments (now termed empirically supported treatments [ESTs]). Current guidelines require ESTs to demonstrate superiority to a placebo in at least two well-designed and controlled studies, equivalence to a well-established treatment in several independent and well-designed and controlled studies and/or efficacy in many single-subject controlled studies [30]. Additionally, studies that support an EST must clearly delineate various treatment procedures (e.g., published manuals/treatment protocols) to allow for independent replication.

Among clinical trials that investigate the efficacy of psychotherapy for treating anxiety in typically developing youths and adults [31–35], cognitive–behavioral therapy (CBT) has consistently been shown to be superior to the respective control conditions and, as a result, has been categorized as a ‘well-established’ treatment for anxiety in children [36–39] and adults [40]. A number of randomized clinical trials (RCTs) have also investigated the efficacy of CBT for treating OCD in pediatric [41,42] and adult populations [43,44], with such trials indicating the superiority of CBT to control conditions. CBT generally includes psychoeducation, cognitive restructuring, somatic management, exposure with response prevention, problem solving and relapse prevention [45,46], although the specific combination of components may be modified to match a patient's developmental or cognitive level[47-49].

CBT treatment of anxiety in ASD

Although CBT is considered a first-line treatment for anxiety disorders [37,40,50], only recently have efforts focused on adapting treatment to meet the unique needs of youths with ASDs. As a result, a limited number of studies have examined the application of CBT for

youths with ASDs and anxiety [51–57]. With the exception of two single-subject case studies [58,59], no studies of CBT for anxiety in adults with ASDs have been published.

Most treatment studies for youths with comorbid ASDs and anxiety symptoms employ a CBT approach to address deficits associated with ASD symptomology (e.g., social interaction impairments, repetitive behaviors and restricted interests). The protocols include core CBT components (e.g., psychoeducation, emotional awareness, exposure, coping skills and problem solving) with varied modifications, such as increased caregiver involvement and tailoring of materials or discussion to the cognitive ability of the child in question. For example, CBT protocols have been augmented with the inclusion of increased caregiver involvement, an emphasis on personalizing treatment around a child's interests, skill-building protocol to help shape social skills in children with ASDs and parent- and teacher-managed contingency systems [55–57,60].

Three RCTs have investigated the use of CBT for youths with ASDs and comorbid anxiety symptoms. Sofronoff *et al.* randomly assigned 71 children (age range: 10–12 years) with Asperger's disorder and comorbid anxiety symptoms to individual CBT, family-based CBT or a waitlist control condition [61]. Children included in the trial did not meet criteria for an anxiety disorder *per se*, but did display elevated anxiety levels at pretreatment. In addition to core CBT elements (e.g., psychoeducation, exposure and relapse prevention), the protocol was modified to allow for increased focus on emotional awareness, as well as tailoring skill-building exercises to match the child's restricted interests. Although both CBT arms displayed significant decreases in parent-reported anxiety, youths in the family-based CBT condition experienced a significantly greater decrease in parent-reported anxiety than the youths in the individual CBT condition. In addition, children in both CBT conditions used significantly more coping strategies than their waitlist counterparts.

Chalfant *et al.* randomized 47 youths (age range: 8–13 years) with ASDs and comorbid anxiety disorders (e.g., GAD, SAD, social phobia or separation anxiety) to a 12-week group-based CBT group or waitlist control condition [51]. The CBT program was adapted from the ‘Cool Kids’ protocol [62], a group anxiety treatment program consisting of emotional and physiological symptom identification, cognitive restructuring, coping statements and exposure. At post-treatment, CBT was superior to the waitlist arm on all anxiety symptom reports (e.g., self-report, parent and teacher). Furthermore, 71% of youths who received CBT no longer met diagnostic criteria for an anxiety disorder at post-treatment, whereas all youths in the waitlist condition still met diagnostic criteria [51]. However, the study therapists administered the diagnostic outcome measures, and hence were not blind to conditions.

In the Wood *et al.* trial, 40 youths (age range: 7–11 years) with ASDs and comorbid anxiety disorders (e.g., SAD, social phobia or OCD) were randomized to family-based CBT or waitlist control conditions [56]. The CBT treatment protocol was adapted from a family-based anxiety intervention program (Building Confidence [63]) incorporating coping skills and *in vivo* exposure components. Treatment modifications included use of social coaching, incorporation of special interests, parent and teacher involvement, playdate hosting and school-based peer coaching. Thirteen out of 14 children (92.8%) who completed treatment were treatment responders (e.g., receiving a rating of completely recovered, very much better or much better on the Clinical Global Impressions – Improvement Scale at post-treatment) as compared with two out of 22 youths (9%) in the waitlist condition (results were similar when accounting for subject attrition). Significant group differences were found in favor of youths receiving CBT for clinician-administered anxiety severity ratings and parent-reported anxiety symptoms (d = 2.46 and 1.23, respectively [d = Cohen's d, a measure of effect size in which the difference between two means is divided by the pooled

standard deviation for the data]). Treatment gains were maintained at 3-month follow-up [56], which highlights the durability of this treatment approach. Parent-reported autism symptoms declined in the treatment (but not waitlist) group [57]; similarly, children in the treatment group exhibited greater improvements in daily living skills as assessed on the Vineland interview in comparison with waitlist children [64].

Table 1 provides a comparison of the three RCTs discussed above [51,56,61]. Collectively, the results obtained from case reports [52,60] and CBT trials lend support to the utility of treating anxiety symptoms in youths with ASDs. Common modifications to CBT protocols that display promise for treating youths with ASDs include simplified or reduced cognitive restructuring, the use of targeted social skills and/or coaching and increased caregiver and teacher involvement. However, additional work is needed to better utilize credible control groups, as well as to explore psychometrically sound methods for assessing treatment response with respect to anxiety. Further, research is needed to examine the efficacy of CBT for treating comorbid ASD and anxiety symptoms in children and adults [58], which is of particular importance given the changing interpersonal relationship settings across the developmental lifespan.

Currently, we are investigating the efficacy of a modified CBT protocol for treating comorbid ASDs and anxiety in early adolescents (age range: 11–14 years) [56,57]. In addition to including core CBT components (e.g., affective education, exposure and cognitive restructuring), our treatment protocol emphasizes the use of social coaching and the development of emotion regulation skills crucial to social functioning. After conclusively establishing efficacy, subsequent trials will need to examine patient characteristics that moderate CBT (and selective serotonin-reuptake inhibitors [SSRIs]) treatment outcome (e.g., diagnosis, cognitive functioning and social relatedness/motivation).

SSRI treatment of anxiety & ASD

SSRI treatment of anxiety

The US FDA has approved the use of several SSRIs for treating anxiety in adults (e.g., fluoxetine, escitalopram, fluvoxamine, paroxetine and sertraline). Among children, fluoxetine is approved for treating childhood depression and pediatric OCD, fluvoxamine and sertraline are approved for treating pediatric OCD and escitalopram is approved for treating childhood depression.

Several large RCTs support the efficacy of SSRIs for treating anxiety in youths and adults without ASDs. The Research Units for Pediatric Psychopharmacology (RUPP) Anxiety Disorders Study Group showed that fluvoxamine was superior to placebo in reducing anxiety symptoms in youths with GAD, social phobia, and SAD (d = 1.10) [65]. Active participants (n = 74) displayed greater symptom reductions relative to a placebo control group in a second RCT that investigated the efficacy of fluoxetine for treating GAD, social phobia and SAD, although the strength of this effect was less robust (d = 0.40) [66]. More recently, the Child/Adolescent Anxiety Multimodal Study (CAMS) examined the efficacy of sertraline, CBT and combined CBT and sertraline for youth (n = 488) with GAD, social phobia and SAD [36]. All treatment combinations were superior to a placebo control. Combination therapy (d = 0.86) was superior to CBT (d = 0.31) and sertraline (d = 0.45) monotherapies.

Studies on the efficacy of SSRIs for treating anxiety in adults tend to focus on the treatment of specific anxiety disorders. Results of these investigations suggest that SSRIs are superior to placebos for treating social phobia [67], OCD [68], panic disorder [69], post-traumatic stress disorder [70] and GAD [71]. No meta-analytic studies exist that investigate the

efficacy of SSRIs for treating specific phobias, although individual RCTs suggest that SSRIs may be superior to a placebo and may potentially display clinical utility [72,73].

SSRI treatment of ASDs

Antidepressant medications (i.e., serotonin-reuptake inhibitors [SRIs]), including SSRIs, are the most commonly prescribed medication class for individuals with ASDs [74]. Approximately 32% of children and adults with ASDs are prescribed an SSRI [75], and the use of SSRIs with people with ASD has steadily increased over time. A review of community surveys in North Carolina, USA, found a 16% increase in SSRI use from 1993 to 2001, with 21% of patients with ASDs taking an SSRI in 2001 [76]. Overall, fluoxetine, paroxetine and sertraline accounted for the majority (61%) of antidepressant medications that were prescribed to individuals with ASDs[77].

Despite their wide use, results of a recent Cochrane review questioned the efficacy of SSRIs for treating ASD symptoms [78]. This review included seven studies (five included children only) that investigated the efficacy and tolerability of three commonly prescribed SSRIs (fluoxetine, fluvoxamine and citalopram). Overall, this review concluded that no convincing evidence exists for the efficacy of SSRIs for treating children with ASDs, and evidence of their clinical utility with adults is limited. Furthermore, Williams *et al.* suggest that the use of SSRIs to treat comorbid conditions (e.g., anxiety, repetitive behaviors and aggression) is not well established and must be determined on a case-by-case basis [78].

SSRI treatment of comorbid anxiety & ASDs

Clinically, some data suggest that SSRIs may have utility, especially for youths with comorbid ASDs and anxiety/compulsive behaviors [79,80]. Although a precise association between serotonin activity and the presence of ASD symptoms has not been established, SSRIs may regulate the dysfunctional serotonin activity associated with the presence of compulsive behaviors and anxiety in individuals with ASDs [81]. However, research supporting this potential treatment indication is needed, and most studies investigating the use of SSRIs in individuals with ASDs involve small and poorly characterized samples with varying efficacy end points and targeted symptoms [82].

In the following sections, we review RCTs (n = 4), as well as an expanding body of retrospective and open-label clinical trials, to help elucidate the potential utility of antidepressant medications for treating ASDs and related symptoms (e.g., anxiety and compulsive/repetitive behaviors). Table 2 displays studies investigating the efficacy of SSRIs for treating individuals with ASDs and comorbid anxiety and/or repetitive behaviors.

Fluoxetine—Fluoxetine is approved by the FDA for treating OCD and depression in adults and typically developing youths. To date, two RCTs have investigated the efficacy of fluoxetine for reducing ASD symptoms and compulsive/repetitive behaviors in youths. Hollander *et al.* conducted a 20-week, placebo-controlled crossover study of fluoxetine (doses ranged from 0.8 to 2.5 mg/kg/day) for children with ASDs (n = 45; age range: 5–16 years) [83]. At post-treatment, while both conditions reduced repetitive behavior, the reduction was significantly greater (z = -2.852; standard error = 0.246; p = -0.004) in fluoxetine than in the placebo condition. No between-group differences were observed on a measure of general autism symptomology. The frequency and severity of adverse side effects did not differ significantly between fluoxetine and placebo conditions.

Preliminary results were recently released from the Study of Fluoxetine in Autism (SOFIA), the largest treatment study conducted in patients with ASD symptoms [101]. This study was conducted across 19 Autism Clinical Trial Network sites and aimed to reduce repetitive

behaviors in youths with ASDs. Participants (n = 158; age range: 5–17 years) received a new low-dose (2–14 mg) melt-in-mouth form of fluoxetine (NPL-2008) that was designed to treat repetitive behaviors in youths with ASDs or a placebo. There were no significant group differences in repetitive behaviors between the NPL-2008- or placebo-treated groups. The full analysis of the primary and secondary data from SOFIA is ongoing, but preliminary results indicate that NPL-2008 was well tolerated, and no serious adverse events were reported [101].

Although no large studies have investigated the efficacy of fluoxetine for treating ASDs and anxiety symptoms in adults, Buchsbaum *et al.* conducted a 16-week placebo-controlled single-blind crossover trial of fluoxetine (dose range: 10–40 mg daily) in six adults with ASDs who displayed elevated anxiety levels (no participants had formal anxiety disorder diagnoses) [84]. Decreases in ASD symptoms were inconsistent across participants, yet fluoxetine was associated with general reductions in anxiety symptoms and repetitive behaviors. Only one participant experienced minor side effects (e.g., headaches) associated with fluoxetine.

Fluvoxamine—The FDA has approved fluvoxamine for treating OCD in children and adults. However, few studies have explored its efficacy for treating individuals with ASDs with or without comorbid mood or anxiety symptoms. Martin *et al.* conducted an open-label study of low-dose fluvoxamine (1.5 mg/kg/day) in 18 youths with high-functioning pervasive developmental disorder (PDD) and co-occurring anxiety and compulsive symptoms (age range: 7–18 years) [85]. Most participants (15 out of 18) completed the 10-week study, but only three experienced significant reductions in their ASD or anxiety symptoms. Thirteen participants (72%) reported at least one side effect during treatment, including severe behavioral activation that led to treatment discontinuation (n = 3), akathisia/agitation (n = 9), sleep difficulties (n = 9), headaches (n = 6), appetite changes (n = 4), abdominal discomfort (n = 3) and rhinitis (n = 2).

In contrast to the lackluster results obtained with youths, one study suggests that fluvoxamine may have some utility for treating adults with ASDs and related conditions. An early double-blind placebo-controlled study on the efficacy of fluvoxamine for treating ASD symptoms found 53% of participants (n = 15) receiving fluvoxamine (276.7 mg/day) to be treatment responders compared with 0% of the control group (n = 15) [86]. Participants receiving fluvoxamine also experienced reductions in repetitive thoughts and behaviors, the use of repetitive language and aggression relative to the placebo arm. However, this study did not assess participants' anxiety levels before, during or after treatment.

Escitalopram—Escitalopram is FDA approved for treating depression in children and adults and GAD in adults. Among patients with ASDs, Owley *et al.* conducted a 10-week, open-label study of escitalopram (mean dose: 11.1 mg/kg/day) in 28 youths (age range: 6–17 years) with autism (n = 20), Asperger's disorder (n = 5) and PDD not otherwise specified (n = 3) [87]. A total of 61% of participants were treatment responders and displayed a decrease in impulsivity and improvements in overall psychosocial functioning. A total of 78% of participants experienced dose-related side effects (e.g., hyperactivity, aggression or irritability), and 36% were unable to tolerate relatively low escitalopram doses (10 mg daily). No association was observed between dose and weight, although a small relationship was observed between dose and age. No published studies on the efficacy of escitalopram for treating ASDs and/or comorbid ASDs and anxiety symptoms in adults exist.

Citalopram—Citalopram, a medication with a molecular structure that mirrors the structure of escitalopram, is FDA-approved to treat depression in neurotypical adults, but has no indications for use with children or adolescents. A retrospective study of citalopram

(n = 17; age range: 4–15 years; mean dose: 19.7 mg daily) in youth with ASD found that 59% of participants displayed a positive treatment response [88]. Overall, the greatest reductions were noted in anxiety and aggression, whereas limited reductions were observed in core ASD symptoms. Similarly, a second retrospective study of citalopram (mean dose: 16.9 mg daily) in children and adolescents (n = 15; age range = 6–16 years) found 73% of participants displayed a positive treatment response [89]. The greatest symptom reductions were in anxiety, repetitive behaviors, and irritability; reported side effects were generally mild (e.g., headaches, sedation).

Recently, the Studies to Advance Autism Research and Treatment (STAART) Autism Network conducted a multisite trial on the efficacy of citalopram (mean dose: 16.5 mg/day) versus placebo for high levels of repetitive behavior in 149 children and adolescents (age range = 5–17 years) with ASD [90]. In contrast to Couturier and Nicolson [88] and Namerow *et al.* [89] citalopram did not result in reductions in compulsive/repetitive behavior. No significant differences were noted in treatment response rates at 12 weeks between the citalopram (32.9%) and placebo groups (34.2%). However, as a secondary outcome, youths who received citalopram were less irritable than youths in the placebo group (anxiety was not assessed). Although discontinuation rates in drug and placebo groups were modest and equivalent (17% over 12 weeks), citalopram was associated with numerous adverse effects including increased energy, disinhibition, hyperactivity, insomnia, and diarrhea. Activation effects were generally managed by dosage reductions.

Sertraline—Sertraline is FDA approved to treat a variety of mood and anxiety disorders in adults and children with OCD. However, no placebo-controlled studies have been published on the efficacy of sertraline among patients with ASDs. An early case series on the efficacy of sertraline found eight out of nine children with autism (age range: 6–12 years; dose range: 25–50 mg) displayed significant decreases in anxiety, irritability, inflexibility or ‘need for sameness’ following treatment [91]. Three children experienced marked anxiety reductions. Two children experienced behavioral activation and three children experienced a resurgence of symptoms 3–7 months after initial symptom reductions. Although this study provides preliminary support for sertraline in treating youths with comorbid ASDs and anxiety, care is needed in interpreting results given the small sample size and absence of standardized symptom measures and a control group [79].

McDougle *et al.* tested the efficacy of sertraline (doses ranged from 50 to 200 mg daily) in an open-label study on adults (n = 42) with autism (n = 22), Asperger's disorder (n = 6) and PDD not otherwise specified symptoms (n = 14) [92]. A total of 57% of participants were treatment responders, and treatment was associated with decreases in aggressive and repetitive behaviors. However, no individuals diagnosed with Asperger's disorder responded to treatment, and treatment was discontinued for three participants who experienced severe agitation. Aside from these participants, sertraline was generally well tolerated and relatively few side effects were observed.

Other SRIs—In addition to SSRIs, research is needed to test the efficacy of other SRIs for treating comorbid ASDs and anxiety/repetitive behaviors. Mixed data exist regarding the role of clomipramine in reducing repetitive behaviors in individuals with autism. Participants (n = 24; age range: 6–23 years) who received clomipramine (mean dose: 129 mg daily) in one RCT displayed decreases in repetitive and self-injurious behaviors relative to controls [93]. However, clomipramine has been associated with the presence of significant side effects [94], and a second RCT (n = 36; age range: 10–36 years; dose range: 25–128.4 mg daily) did not support its clinical utility for treating repetitive behaviors in individuals with ASDs [95]. The use of serotonin–norepinephrine- reuptake inhibitors for treating ASDs and comorbid conditions also warrants empirical attention. One open-label

study of venlafaxine (n = 10; age range: 3–21 years; dose range: 6.25–50 mg daily) found decreases in repetitive behaviors in individuals with ASDs [96], although tolerability may be a concern in this population [97].

Conclusion & future perspective

This review of the literature focuses on the efficacy of pharmacological and psychosocial approaches for treating anxiety in children, adolescents and adults with ASDs. Although no treatments for comorbid ASDs and anxiety meet the American Psychological Association's guidelines for efficacy [30], a small but growing number of studies support the use of CBT for children with comorbid ASDs and anxiety symptoms. However, research is needed to extend these findings from children to adolescents and adults, and to examine the efficacy of CBT and SRI treatments against credible control conditions (e.g., active therapies and/or pill placebos) across all age groups.

Data supporting the use of antidepressant medications to treat comorbid ASDs and anxiety are limited, despite the prevalent use of these drugs [75]. Specifically, SSRIs have not been consistently linked to improvements in core ASD symptoms (e.g., communication and social skills deficits, repetitive behaviors and stereotypies) or anxiety and repetitive behaviors in youths [78]. Following promising results obtained in preliminary studies using citalopram to treat ASDs and varied comorbid concerns (e.g., anxiety, repetitive behaviors and aggression) [88,89], the STAART Autism Network conducted a large RCT on the use of an SSRI for treating comorbid ASDs and repetitive behaviors in children and adolescents [90]. Although this investigation failed to show a separation between placebo and citalopram on the primary outcome, some preliminary findings within this study, as well as in open trials, suggest that SSRIs may have an indication for treating comorbid anxiety.

While it is possible that SSRIs may have efficacy for anxiety in ASDs, care is needed when prescribing medications for youths with ASDs. High rates of behavioral activation (e.g., agitation, irritability, aggression and disinhibition) and diminished tolerability have been reported across trials [85,87,90], which may suggest that youths with ASDs are more vulnerable to side effects compared with their typically developing peers. It is unclear if this pattern holds for adults with ASDs. Therefore, the use of SSRIs should be determined on a case-by-case basis, and dosing schedules that rely on slower titration may yield the greatest tolerability [79].

Across pharmacological and psychosocial studies, measurement of anxiety remains a limitation. Several psychosocial treatment studies have used psychometrically sound measures of anxiety severity [56], but none have used a clinician-rated measure of anxiety severity to gauge treatment response. Among pharmacotherapy studies, treatment response has been assessed through global improvements in functioning, tolerability, the absence of side effects and omnibus behavior rating scales. However, these studies have generally been limited by a lack of a specific treatment target, and measures of anxiety used within the study – if any – have been psychometrically weak. Accordingly, it will be important for future studies to evaluate clinician-, parent- (for children) and self-report measures of anxiety symptomology among individuals with ASDs.

In conclusion, research on effective treatments for comorbid ASDs and anxiety/repetitive behaviors is emerging, but much research still is needed to establish these approaches. Some RCTs have been conducted on the effectiveness of CBT and SSRI medications, while others are ongoing, and more will need to be conducted to establish or refute these treatment approaches. To date, studies across both treatment modalities have limitations. Although several RCTs of CBT have been conducted, there are issues with the credibility of the control conditions and concerns about appropriate measurement. In medication trials, there

are few RCTs available, and of these, anxiety is not adequately targeted or assessed. Anxiety and repetitive behaviors can have different antecedents and serve different functions. Therefore, future studies that aim to elucidate the efficacy of SSRI or CBT treatments may benefit from separating and targeting these symptoms differently. Nevertheless, if the past two decades are any indication of what is to come, the next decade will likely be marked by many exciting developments, ultimately leading to improvements in treatments for anxiety and repetitive behaviors in individuals with ASDs.

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Practice points

- Cognitive–behavioral therapy that is adapted for the unique characteristics of youths with autism spectrum disorders (ASDs) and comorbid anxiety shows excellent promise. However, further research with more methodologically rigorous controls is required.
- Antidepressant medications have demonstrated preliminary efficacy in targeting anxiety in youths with ASDs. However, results have been mixed, and more conclusive trials are needed.
- Children with ASDs may be at higher risk for adverse reactions associated with medications targeting anxiety. The use of slow-titration dosing schedules may be one way of more safely administering pharmacotherapy.
- Use multiple sources of information (e.g., child-, parent- and clinician-report measures) for assessing anxiety and psychosocial functioning in youths with ASDs.

Table 1

Studies examining cognitive-behavioral therapy for treating individuals with autism spectrum disorders and comorbid anxiety

Study (year)	Design	Treatment duration	Sample	Diagnoses	Outcome measures	Treatment outcomes	Ref.
Sofronoff *et al.* (2005)	Two CBT conditions (individual or family) vs waitlist control	Six sessions	n = 71 (23 individual, 25 family, 32 waitlist) 10–12 years of age	Asperger's disorder and comorbid anxiety symptoms	CAST, SCAS-P, nonstandardized measures	Family condition had greater decrease in reported anxiety than individual condition Both conditions had significantly greater decrease in reported anxiety than waitlist Both conditions had significantly greater coping strategy use than waitlist	[61]
Chalfant *et al.* (2007)	Group CBT vs waitlist control	12 sessions	n = 47 (28 CBT, 19 waitlist) 8–13 years of age	ASD and comorbid GAD, SAD, social phobia, specific phobia or panic disorder	RCMAS, SCAS, CATS, SCAS-P, SDQ	CBT superior to waitlist on all reports 71% of CBT condition no longer met diagnostic criteria for an anxiety disorder (vs 0% of waitlist condition)	[51]
Wood *et al.* (2009)	Family CBT vs waitlist control	16 sessions	n = 40 (17 treatment, 23 waitlist) 7–11 years of age	ASD and comorbid SAD, social phobia or OCD	CGI-I, ADIS-C/P, MASC	78.5% of CBT condition met CGI-I criteria (vs 9% of waitlist condition) CBT condition showed greater decrease in clinician-reported (d = 2.46) and parent-reported (d = 1.23) anxiety [†] CBT condition showed greater observed use of living skills compared with waitlist condition	[56]

[†]d = Cohen's d, a measure of effect size in which the difference between two means is divided by the pooled standard deviation for the data.

ADIS-C/P: Anxiety Disorders Interview Schedule for DSM-IV–Child and Parent Version; ASD: Autism spectrum disorder; CAST: Childhood Asperger Syndrome Test; CATS: Children's Automatic Thoughts Scale; CBT: Cognitive–behavioral therapy; CGI-I: Clinical Global Impressions – Improvement; d: Cohen's d; GAD: Generalized anxiety disorder; MASC: Multidimensional Anxiety Scale for Children; OCD: Obsessive–compulsive disorder; RCMAS: Revised Children's Manifest Anxiety Scale; SAD: Separation anxiety disorder; SCAS: Spence Children's Anxiety Scale; SCAS-P: Spence Children's Anxiety Scale – Parent Report; SDQ: Strengths and Difficulties Questionnaire – Parent/Teacher Report.

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Table 2

Studies examining selective serotonin-reuptake inhibitors for treating individuals with comorbid autism spectrum disorder symptoms and anxiety and/or repetitive behaviors

Study (year)	Design	Sample	Outcome measure(s)	Treatment outcomes	Side effects	Ref.
Hollander *et al.* (2005)†	Placebo-controlled	n = 39≠ (20 fluoxetine, 19 placebo)	CY-BOCS, CGI-A	Decreases in repetitive behaviors (ES = 0.76)	Limited side effects reported	[83]
Buchsbaum *et al.* (2001)	Single-blind crossover	n = 6 (fluoxetine)	Y-BOCS, HRSA	Participants displayed reductions in anxiety and obsessions on average	Headaches reported in one participant	[84]
Martin *et al.* (2003)	Prospective open-label	n = 18≠ (fluvoxamine)	CY-BOCS, CGI-Severity, SCARED	No significant reductions in ASDs or anxiety symptoms	50% reported behavioral activation, akathisia, sleep and headaches	[85]
McDougle *et al.* (1996)≠	Placebo-controlled	n = 30 (15 fluvoxamine, 15 placebo)	Y-BOCS, CGI-Severity	53% displayed reductions in ASD symptoms	Mild sedation and nausea	[86]
Steingard *et al.* (1997)	Open-label	n = 9≠ (sertraline)	Nonstandardized	89% displayed reductions in ASD symptoms	Behavior deteriorations and stomach aches	[91]
McDougle *et al.* (1998)	Prospective open-label	n = 41 (sertraline)	Y-BOCS, CGI-Severity	57% displayed decreases in repetitive behaviors	Anorexia, weight gain, sedation, agitation, anxiety, alopecia and tinnitus	[92]
Couturier *et al.* (2002)	Retrospective chart review	n = 17≠ (citalopram)	CGI-Severity	59% displayed decreases in anxiety and/or aggression	Agitation, tics and insomnia	[88]
Namerow *et al.* (2003)	Retrospective chart review	n = 15≠ (citalopram)	CGI-Severity	73% displayed improvement in ASD symptoms	33% reported ‘mild’ side effects including appetite changes and headaches	[89]
King *et al.* (2009)†	Placebo-controlled crossover	n = 149≠ (73 citalopram, 76 placebo)	CY-BOCS, CGI-Severity	No significant reductions in ASDs or anxiety symptoms	Impulsivity, poor concentration, insomnia, hyperactivity, stereotypy, diarrhea and dry skin	[90]

†Randomized controlled study design.

≠ChiId sample.

ASD: Autism spectrum disorder; CGI-A: Clinical Global Impressions –Autism Scale; CGI-Severity: Clinical Global Impressions – Severity Scale; CY-BOCS: Children's Yale–Brown Obsessive–Compulsive Scale; ES: Effect size; HRSA: Hamilton Rating Scale for Anxiety; SCARED: Screen for Child Anxiety-Related Emotional Disorders; Y-BOCS: Yale–Brown Obsessive–Compulsive Scale.