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An update on anxiety in youth with autism spectrum disorders

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Abstract

Purpose of review—Anxiety is one of the most common co-occurring psychiatric conditions in youth with autism spectrum disorders (ASDs). This article reviews recent evidence as well as earlier relevant studies regarding the characteristics, assessment, and treatment of anxiety in youth with ASD.

Recent findings—It is well established that the prevalence of anxiety in youth with an ASD is significantly greater than the prevalence of anxiety in the general population. Recent studies have highlighted the importance of informant, method, and instrument when measuring anxiety in this population. Despite the high prevalence, findings to date have been unable to identify any consistent risk factors for anxiety. New psychological treatments, including modified cognitive behavioral therapy for youth with high functioning ASD and co-occurring anxiety, are emerging. Pharmacological data, however, are scant. Existing studies show that youth with ASD are at increased risk for behavioral activation when taking SSRIs.

Summary—Clinicians working with youth with ASD are encouraged to routinely screen for anxiety. Until further data are available, clinical judgment is needed when prescribing treatments, particularly selective serotonin reuptake inhibitors, which require close monitoring of side-effects. Research on risk factors, pathophysiology, and treatment of this condition is needed.

Keywords

anxiety; autism spectrum disorders; children

INTRODUCTION

Anxiety disorders and symptoms are common co-occurring conditions in youth with autism spectrum disorders (ASD) [1]. Research on the prevalence and clinical characteristics of this condition has soared during the past decade. This review summarizes the literature on

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Conflicts of interest

None.

anxiety in youth with ASD with emphasis on studies published within the past 18 months and areas for future research in the field.

PREVALENCE AND PHENOTYPE OF ANXIETY IN AUTISM SPECTRUM DISORDER

The following sections review recent data on the prevalence and phenomenology of anxiety as well as its relationship to core symptoms of ASD in youth with ASD. Recent conceptualizations of anxiety as well as measurement issues are emphasized.

Prevalence studies in children

Data on the prevalence of anxiety in individuals with ASD have varied widely, ranging from 22 to 84% [2–6]. A recent meta-analysis found that the prevalence of at least one anxiety disorder among children with ASD was 39.6%. Specific phobia (29.8%), obsessive-compulsive disorder (OCD) (17.4%) and social anxiety disorder (16.6%) were the most common types [1]. In a recent study of 108 high-functioning children with ASD enrolled in treatment trials for anxiety, almost all (91.6%) met criteria for two or more anxiety disorders, with greatest prevalence of social phobia (41.7%) and generalized anxiety disorder (25.9%) [7■].

Studies published within the past 18 months have examined symptom prevalence in large and population-based samples. In a population-based sample of 863 children with ASD, 43% had frequent ‘anxiety, fears, and phobias’; however, the clinical significance of these symptoms was not assessed [8■]. In a sample of 1429 children with ASD, 46% were at or above the clinically elevated range on the Child Behavior Checklist (CBCL) Anxiety Problems scale, compared with only 9% of typically developing (TD) siblings [9■]. Consistent with previous findings, these studies indicate that children with ASD are at increased risk for anxiety (compared with prevalence of 2.2–27% among TD children [10]).

Several new studies have investigated the effects of measurement on observed prevalence of anxiety in ASD. Kaat *et al.* [11■] found that prevalence estimates of anxiety disorders differ substantially depending on criteria for psychiatric caseness. Reliance on a single reporter (parent or teacher) on the Child and Adolescent Symptom Inventory – 4th Edition (CASI-4R) resulted in lower rates, whereas consideration of a combination of parent- and teacher-report yielded substantially higher prevalence. Similar differences were found depending on whether symptom, impairment, or combination criteria were utilized (47–70%). Kerns *et al.* [12■] separately assessed the prevalence of ‘traditional’ DSM-defined anxiety disorders and ‘atypical’ anxiety symptoms (more closely related to ASD symptoms). Of the 63% demonstrating impairing anxiety, 48% showed traditional symptoms, whereas 15% showed only ‘atypical’ symptoms. The results of these studies highlight the importance of considering rater, sample, method, and criteria in estimating prevalence of anxiety.

Anxiety phenomenology and relationship to autism spectrum disorder symptoms

Distinguishing anxiety from core ASD symptoms presents a challenge to accurate assessment. Recent studies have addressed this by examining the relationship between

symptom constructs. Renno and Wood [13■] used a multitrait-multimethod approach to investigate discriminant and convergent validity of anxiety and ASD symptoms. These findings indicated that anxiety and ASD symptoms were separable constructs and that anxiety severity was independent of ASD severity. However, additional phenomenological considerations may also be important. Kerns *et al.* [12■] found that language ability was associated with traditional DSM-defined anxiety, whereas ASD severity was associated with atypical anxiety. Additionally, Hallett *et al.* [14■] found differential relationships between particular types of anxiety and ASD symptoms. Social anxiety was negatively correlated with social and communication impairment, whereas panic and OCD symptoms were positively correlated with the restricted and repetitive behaviors (RRBs).

A number of other recent studies have specifically focused on the relationship between anxiety and RRB. In a sample of 1429 children with ASD [9■], anxiety was associated with greater RRB; yet anxiety and insistence on sameness appeared to be distinct constructs. Stratis and Lecavalier [15■] also found a significant relationship between anxiety and RRB, with the strongest relationship being between anxiety and ritualistic/sameness behavior. Lidstone *et al.* [16■] also found that anxiety was associated with insistence on sameness, and that sensory over-responsivity and sensory avoiding were related to both. This is consistent with recent as well as prior data showing a significant relationship between anxiety and sensory over-responsivity in children with ASD [17,18■,19]. These findings suggest that for some children with ASD and anxiety, repetitive behaviors (particularly sameness behaviors) may serve to reduce arousal by reducing sensory input.

RISK FACTORS AND CORRELATES OF ANXIETY IN AUTISM SPECTRUM DISORDER

The high prevalence of anxiety in youth with ASD has prompted research to identify risk factors and correlates for this condition. Most of the research has yielded mixed findings because of heterogeneity in the samples as well as the methods used to assess anxiety. The sections below discuss recent findings pertaining to potential factors that may contribute to the development and maintenance of anxiety.

Age and gender

Data examining the effects of age on anxiety have yielded inconsistent findings. Some studies report that anxiety increases with age [20■,21–22], whereas other data report that anxiety decreases from childhood to adulthood [23]. Other studies report no associations between age and anxiety in youth with ASD [24–26]. A recent meta-analysis looked more specifically at the types of anxiety disorders that may be associated with age and found that older children were at risk for generalized anxiety disorder, whereas younger children had higher rates of OCD and separation anxiety disorder [1]. Results on the effect of gender are also mixed with some studies reporting no influence [20■,26] and others reporting gender differences [2].

Cognitive functioning

Previous studies have found a positive association between IQ and anxiety in children with ASD [21,22,26]. Consistent with this, Rieske *et al.* [27■] found that higher cognitive ability was associated with increased anxiety among infants and toddlers with ASD. In a study of older children with ASD, higher verbal IQ was associated with greater anxiety, but nonverbal IQ was unrelated [9■]. Regarding specific types of anxiety, Hallett *et al.* [14■] found that social anxiety was positively correlated with IQ, whereas separation anxiety was negatively correlated with IQ. These results highlight the differential impact of cognitive and verbal ability on the experience and behavioral manifestations of anxiety among children with ASD. It is possible that individuals with stronger cognitive abilities have greater awareness of their social and adaptive impairments, leading to increased anxiety.

Cognitive processes related to anxiety

A number of recently published studies have reported on potential cognitive mechanisms of anxiety in youth with ASD. These results have direct implications for the efficacy of treatment strategies, particularly within cognitive behavioral therapy (CBT) models. In one of the first such studies, Hollocks *et al.* [28■] examined attentional biases in children with ASD and anxiety. Threat-related attentional biases are common in individuals with anxiety [29], and are often targets in CBT treatments for anxiety. Surprisingly, there was no association between anxiety and attentional bias to threat in the ASD group. The authors hypothesized that the attentional bias task may not have been a valid measure in the ASD population, or that individuals with ASD may have more idiosyncratic fears.

Other studies have found evidence of anxious cognitive processes among high functioning children with ASD. Sharma *et al.* [30■] found that children with ASD had more negative expectations about the future, more negative beliefs about their abilities, and greater self-blame than TD children. These maladaptive cognitive appraisals were associated with increased anxiety. Other studies found that negative automatic thoughts [31■], anxious cognitive style [12■], and intolerance of uncertainty [32■] predicted anxiety among children with ASD, similar to typically developing children. Together, the majority of recent studies have indicated that anxious cognitive processes may be fruitful intervention targets for children with ASD.

Emotion dysregulation

Recently, there has been interest in examining whether emotion dysregulation is a risk factor for anxiety and other types of psychopathology in children and adolescents with ASD. Emotion regulation refers to a multistep process that involves evaluating and expressing one's emotions to meet the demands of the environment [33]. Emotion dysregulation is therefore the inability to adjust or control one's emotions. Mazefsky *et al.* [34■] hypothesized that emotion regulation deficits may be intrinsic to ASD and can be conceptualized as a transdiagnostic condition that is present in both anxiety and ASD. In a study of emotion regulation strategies, Mazefsky *et al.* [35■] found that adolescents with high-functioning ASD were more likely to use maladaptive and involuntary emotion regulation skills (e.g., rumination, increased arousal, shutting down) compared with typically developing controls. White *et al.* [36■] recently published an extensive review that

parsed out the various sociocognitive, physiological, and neurobiological mechanisms that moderate the relationship between emotion regulation deficits and anxiety. The authors proposed a developmental model linking ASD, emotion dysregulation, and anxiety.

Physiological correlates

There has been considerable enthusiasm to search for psychophysiological markers for anxiety in youth with ASD as such biomarkers may assist in diagnosis given the challenges associated with self-report. Toward this end, several recent studies have examined psychophysiological responses in anxious youth or during stressful conditions. Hollocks *et al.* [37] is one of the few studies that formally assessed anxiety in their sample. Findings showed that youth with high-functioning ASD and a co-occurring anxiety disorder exhibited a blunted heart rate and cortisol response after a psychosocial stress test compared with youth with ASD without anxiety and a healthy control sample; blunted physiological responses were correlated with increased anxiety symptoms. Other studies report similar findings reflecting overactivity of the hypothalamic-pituitary-adrenal axis. [38,39]. Findings pertaining to autonomic system arousal also suggest heightened physiological activity. For example, Kushki *et al.* [40] reported sympathetic overarousal and reduced parasympathetic tone in children with ASD who were completing a Stroop task.

New studies examining fear conditioning and fear-potentiated startle responses, which reflect enhanced arousal and anxious states, are emerging. Using a simple discrimination paradigm, South *et al.* [41] found that skin conductance responses positively correlated with social anxiety and reduced ASD severity in the ASD group. Chamberlain *et al.* [42] reported increased startle responsivity during a threat-modulated startle paradigm suggesting that ASD may be characterized by heightened arousal in response to threat contexts rather than specific cues. These findings contrast with other data reporting no group differences in threat-potentiated startle responses in ASD and control groups [43,44]. Further research is needed to better understand these threat responses, and their potential role in diagnostic assessment.

Genetic risk

Anxiety disorders result from an interaction between genetic and environmental influences [45,46]. About 60% of children with an anxiety disorder will have a parent with an anxiety disorder and conversely 80% of anxious parents will have a child with an anxiety disorder [47].

A few studies have examined the relationship between familial emotional disorders and anxiety in youth with ASD. Most recently, Conner *et al.* [48] showed that several genes may be associated with risk for anxiety and ASD. This finding is consistent with prior data reporting a similar association. Mazefsky *et al.* [49] found that maternal phobic anxiety and hostility conferred risk for anxiety in adolescent probands with ASD. Cohen and Tsiouris [50] reported that recurrent maternal depression, which started prior to any child birth, was associated with higher functioning ASD, increased behavior problems, and an internalizing behavioral style in offspring with ASD.

Several previous studies have examined relationships between genetic markers and anxiety in youth with ASD. Preliminary evidence implicates several genes associated with risk for anxiety in ASD. These include the dopamine transporter gene (*DAT1*, [51]), D4 receptor gene [52], *MAO-A* gene [53,54], glutamate transporter gene (*SLC1A1*, [55]). Sample sizes in these genetic studies as well as the aforementioned family studies are small and therefore the results must be viewed as preliminary.

Neuroimaging correlates

Very few neuroimaging studies have examined the neural correlates of anxiety in youth with ASD and none have established anxiety disorder status in their sample. The majority of functional magnetic resonance neuroimaging evidence shows that childhood anxiety disorders are associated with increased amygdala activity [56]. Affective neuroscience research has documented these findings using tasks that elicit evaluation of facial expressions of fear and anger. In ASD, some data show heightened amygdala activation in response to emotional faces, however because anxiety was not assessed in the participants, it is difficult to discern whether the heightened activity was secondary to anxiety [57,58]. Kleinmans *et al.* [59] administered a face-matching task to adults with ASD and reported that anxiety was positively correlated with amygdala activity in the ASD but not control group. Weng *et al.* [60], however, did not find any association between anxiety and amygdala activity in adolescents with ASD compared with controls when performing a gender identification task.

Structural neuroimaging data on anxiety in ASD are scant. In a recent structural neuroimaging study, Corbett *et al.* [61] reported that smaller right amygdala volume was associated with younger age as well as increased social anxiety. This finding contrasts with that of Juranek *et al.* [62] who found that increased total and right amygdala volumes positively correlated with anxiety and depressive symptoms.

In summary, delineating the neurobiological correlates of anxiety in ASD is important for development of novel treatments. Given the role of the amygdala in other psychological and behavioral processes, a more complex and nuanced understanding of the amygdala is needed to understand its role in anxiety in this population [63]. Other regions implicated in anxiety also deserve attention, including the ventral medial prefrontal cortex, anterior cingulate, and hippocampus [56].

ASSESSMENT CONSIDERATIONS

Accurate assessment of anxiety among children with ASD is challenging because of symptom overlap with other psychiatric disorders, difficulties with self-report, and a lack of well validated tools. A number of recent studies have examined the psychometric properties of anxiety measures in children with ASD. Equivalence (the extent to which a measure operates similarly across clinical groups) is an especially important property for tools originally developed for the general population.

White *et al.* [64] examined measurement equivalence of the Multidimensional Anxiety Scale for Children (MASC) using confirmatory factor analysis. Similar latent factors of anxiety

were found across both ASD and TD groups; however, the relations among factors were different across groups. These data suggest that anxiety is a separate construct from ASD, but that children with ASD may experience anxiety in an atypical manner as compared with the general population.

The Screen for Child Anxiety Related Emotional Disorders (SCARED) and the Spence Children's Anxiety Scale (SCAS) were also originally developed to assess anxiety in TD children. van Steensel *et al.* [65] found that the SCARED showed acceptable psychometric properties in high-functioning children with ASD as compared with TD children, including good internal consistency and moderate convergent validity. Inter-rater agreement between children with ASD and their parents was adequate, but somewhat smaller than for TD children. Sensitivity was strong for both groups, but specificity for particular anxiety diagnoses was lower in the ASD group.

Regarding psychometric properties of the SCAS in children with ASD, Magiati *et al.* [66] found that internal consistency was high for both parent-report and child-report versions, and that there was moderate-to-strong agreement across subscales (with lowest agreement for social phobia and panic/agoraphobia). Better agreement was found on items assessing observable behavioral manifestations of anxiety. Two other studies found strong psychometric properties for the SCAS in children with ASD, including good parent-child concordance [31], good convergent validity, and strong sensitivity and specificity [67].

Finally, two recent systematic reviews focused specifically on the psychometric properties of anxiety measures for children with ASD. Wigham and McConachie [68] concluded that three tools demonstrated the best psychometric properties: the SCAS, the Revised Child Anxiety and Depression Scale (RCADS), and the SCARED. However, the authors noted limited evidence regarding sensitivity to change or validity for use in children with ASD. Lecavalier *et al.* [69] also noted significant limitations in the current evidence, and concluded that four measures were appropriate (with conditions) in this population: the CASI-4R, the MASC, the Pediatric Anxiety Rating Scale, and the Anxiety Disorders Interview Schedule. Three measures were deemed to be potentially appropriate: the Anxiety, Depression and Mood Scale, the RCADS, and the SCARED. The discrepant conclusions of these two reviews highlight the impact of measurement limitations on the study of anxiety in ASD. General consensus across the field is that there is a strong need for ASD-specific anxiety measures as well as rigorous studies of the psychometric properties of new and existing tools.

CURRENT TREATMENTS

In typically developing children, large-scale multisite clinical trials show that combined treatment with selective serotonin reuptake inhibitors (SSRIs) and CBTs are efficacious treatments for youth with anxiety disorders [70]. Similar types of treatment studies for anxiety disorders in youth with ASD are lagging and as such there are currently no established clinical pathways to guide clinicians in their management of anxiety in this population [71].

When treating anxiety, it is important to identify and modify any psychosocial, contextual, and medical factors that could be aggravating anxiety symptoms. For example, a sudden change in supports at school or a new behavioral aide may suddenly trigger an increase in anxiety symptoms. If anxiety symptoms persist after all these various factors have been addressed, specific anxiety-focused therapies as well as pharmacological interventions should be considered based on the severity of anxiety in the child, as well as consideration of psychosocial factors, provider availability, and geographic proximity.

The literature on pharmacological interventions for anxiety in youth with ASD is scant. Only four studies exist. These studies are outdated, include heterogeneous groups of children, do not precisely characterize the anxiety phenotype, and employ either a retrospective chart review or open-label design. Two of these studies demonstrated anxiety reduction with citalopram [72,73] and one demonstrated no benefits of fluvoxamine [74]. Most notable is the emergence of various adverse effects, particularly behavioral activation as well as akathisia and agitation, which occurred in 50% of the sample taking fluvoxamine. This finding is consistent with the high rates of behavioral activation reported by King *et al.* [75] in a citalopram study of repetitive behaviors that showed no group differences between the ASD and control groups on the primary outcome measure. The weak evidence for SSRIs efficacy, as well as high rate of reported side-effects, suggest cautious use of these medications in youth with ASD.

Preliminary evidence suggests that modified CBT may be efficacious for youth with high-functioning ASD and anxiety. Several recent reviews discuss the specific methods and data for modified CBT in this population [76,77,78]. Modified CBT protocols can be administered in either individual or group-based formats, and usually include parent involvement. ASD-specific adaptations include use of visual supports to reinforce learning, modules to address emotional dysregulation, and strategies to help children reduce perseveration on special interests. Response rates for short-term modified CBT trials in ASD ranged from 38 to 71% with the majority of effect sizes being over 0.80. These response rates are fairly comparable with those reported in CBT studies of typically developing children [79]. Large-scale trials with longer duration are needed to determine whether efficacy is sustained.

Although CBT is most appropriate for higher functioning children with ASD, behavioral treatments for anxiety may be effective for children across functional levels [80]. These treatments are usually prescribed for stimulus or contextual-specific anxiety. The same techniques used in typically developing children are modified and applied to youth with ASD. These include graduated exposure and reinforcement strategies, accompanied by modeling and prompting techniques to promote compliance with the protocols.

CONCLUSION

Anxiety is highly prevalent in youth with ASD and can lead to significant distress and impairment. The field is beginning to understand the phenotype of anxiety in this population and is now actively pursuing efforts to precisely measure this construct by developing new instruments and modifying existing ones. Current research is also focused on identifying

specific correlates and risk factors for anxiety in children with ASD order to identify vulnerable youth and develop preventive interventions. Treatments for anxiety in youth with ASD are lacking, although there is promise that modified CBT may be effective for a subgroup of children with ASD. Large-scale treatment studies examining the efficacy of medications, specialized therapies, and their combination are desperately needed.

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KEY POINTS

- Anxiety is highly prevalent in youth with ASD and can manifest as DSM-defined anxiety symptoms and disorders or atypical anxiety related to ASD symptoms.
- Measurement of anxiety in youth with ASD is challenging because of symptom overlap with other disorders, limitations in self-report, and lack of specific anxiety instruments designed to measure anxiety in this population.
- Research on risk factors and mechanisms of anxiety in ASD is emerging.
- Modified CBT shows promise in treating anxiety in youth with high-functioning ASD.
- Randomized placebo controlled trials investigating the efficacy of SSRIs and other medications to treat anxiety in youth with ASD are lacking.