

A Systematic Review of Treatments for Anxiety in Youth with Autism Spectrum Disorders

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Abstract This study systematically examined the efficacy and safety of psychopharmacological and non-psychopharmacological treatments for anxiety in youth with autism spectrum disorders (ASD). Four psychopharmacological, nine cognitive behavioral therapy (CBT), and two alternative treatment studies met inclusion criteria. Psychopharmacological studies were descriptive or open label, sometimes did not specify the anxiety phenotype, and reported behavioral activation. Citalopram and buspirone yielded some improvement, whereas fluvoxamine did not. Non-psychopharmacological studies were mainly randomized controlled trials (RCTs) with CBT demonstrating moderate efficacy for anxiety disorders in youth with high functioning ASD. Deep pressure and neurofeedback provided some benefit. All studies were short-term and

included small sample sizes. Large scale and long term RCTs examining psychopharmacological and non-psychopharmacological treatments are sorely needed.

Keywords Anxiety · Autism spectrum disorders · Treatments · Children · Adolescents

Introduction

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders characterized by qualitative impairments in social and communication skills as well as restricted interests and stereotyped behavior (American Psychiatric Association 2013). The prevalence of ASD has dramatically increased during the past decade with recent

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estimates indicating that 1 in 88 children has ASD, favoring males with a 5:1 gender ratio (Centers for Disease Control and Prevention 2012). Providing comprehensive and coordinated services for youth with ASD is therefore a national priority.

Anxiety disorders and symptoms are amongst the most common co-occurring conditions in youth with ASD, with recent studies indicating that roughly 40 % of children with ASD meet criteria for at least one anxiety disorder (Simonoff et al. 2008; see reviews by MacNeil et al. 2009, White et al. 2009, van Steensel et al. 2011). This prevalence is higher than the 5–32 % prevalence of anxiety disorders in typically developing (TD) controls (Costello et al. 2005; Merikangas et al. 2010). Children with ASD also have a higher prevalence of anxiety disorders compared to other clinical groups, e.g., ADHD (Gau et al. 2010), intellectual disabilities (Dekker and Koot 2003), language impairment (Gillott et al. 2001), and Down's syndrome (Evans et al. 2005). In addition to anxiety disorders, parent- and self-report data indicate higher rates of anxiety symptoms in youth with ASD compared to TD children (Bradley et al. 2004). Anxiety in youth with ASD can exacerbate social deficits, impair daily living skills and negatively impact relationships with peers, teachers, and family (Drahota et al. 2011; Kim et al. 2000). Data from TD children indicates that untreated childhood anxiety can lead to long term psychopathology (Pine et al. 1998). Children with ASD may have similar long term vulnerabilities given their underlying social, cognitive, and language impairments.

Evidence for treatment of childhood anxiety disorders in TD children is robust and consists of cognitive behavioral therapies, selective serotonergic reuptake inhibitors, or their combination (e.g., Walkup et al. 2008). In contrast, evidence for treatment of anxiety in youth with ASD is still emerging. A number of reviews have reported on treatments for anxiety in youth with HFA. Several of these reviews collectively support the efficacy of cognitive behavioral therapy (CBT) for youth with high functioning ASD (HF-ASD) (Lang et al. 2010; Moree and Davis 2010; Nadeau et al. 2011; Danial and Wood 2013; Rudy et al. 2013; Sukhodolsky et al. 2013). Some reviews have reported on the shortage of pharmacological data and the need for further clinical trials (Nadeau et al. 2011; Rudy et al. 2013). One study reviewed instruments used to evaluate treatment response in youth with HFA (Wigham and McConachie 2014).

The primary aim of this report is to examine the evidence for psychopharmacological and non-psychopharmacological treatments for anxiety in youth with ASD using an established rating system that evaluates the strength of evidence (Guyatt et al. 2008; US Preventive Services Task Force Procedure Manual 2008). An expert panel of physicians and psychologists, who are part of the Autism Speak Autism Treatment Network (AS ATN) Anxiety Workgroup

and specialize in the care of children with ASD, first formulated a set of key questions pertaining to efficacy. The panel then conducted a systematic search of the data. The strength of evidence for each question was then systematically graded. Key questions for this review were as follows:

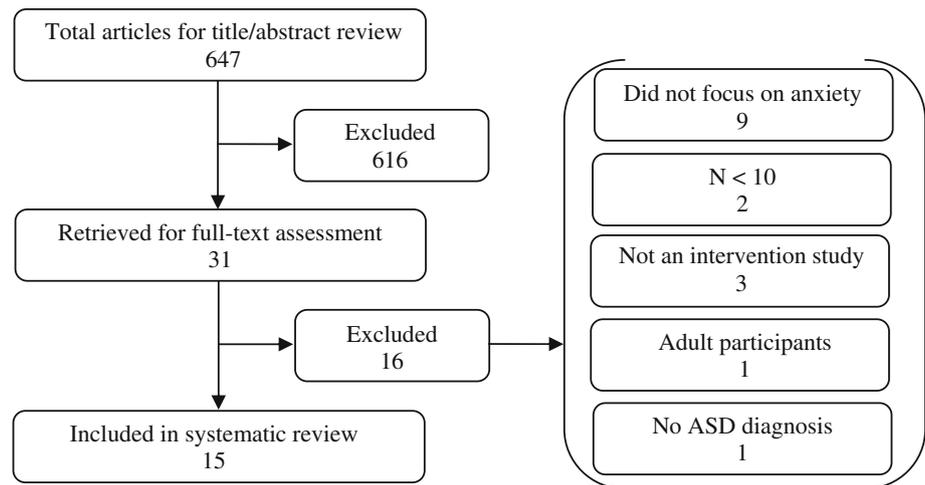
1. What is the evidence supporting the efficacy and safety of psychopharmacological treatments for anxiety in youth with ASD?
2. What is the evidence supporting the efficacy and safety of non-psychopharmacological treatments?
3. What are the types of anxiety disorders and symptoms that are targeted in treatment trials?
4. Are there specific types of anxiety disorders and symptoms that are more responsive to treatment?
5. What are the demographic, cognitive, and clinical determinants (e.g., ASD symptoms) of treatment response?
6. What anxiety assessment measures are sensitive to change in treatment studies?

Although previous reviews have been published on this topic, none of these reviews examine both the pharmacological and non-pharmacological evidence in a comprehensive and integrated way. For example, some reviews focus primarily on CBT treatments (e.g., Danial and Wood 2013; Sukhodolsky et al. 2013). Others include the pharmacological evidence but do not report detailed study information (e.g., Rudy et al. 2013) or exclusively focus on anxiety (Nadeau et al. 2011 report on anxiety and repetitive behaviors). Some reviews (e.g., Rudy et al. 2013) do not report on how anxiety was measured or the types of anxiety disorders examined or that respond to treatment; this information is relevant for both researchers as well as clinicians working with youth with ASD. Finally, none of the previous reviews have organized the evidence according to an a priori set of key questions, nor have they applied an established grading system to rate the strength of the evidence for both pharmacological and non-pharmacological treatments. Data on the strength of the evidence can help clinicians appraise the literature based on a defined set of criteria, while also providing general guidelines when making treatment recommendations. The current review therefore critically evaluates the literature using a clinically focused framework.

Method

Search Procedures

We searched MEDLINE, PsycINFO, and EMBASE (published from database start date to June 2013) for articles combining three groups of relevant key words, Medical

Fig. 1 Systematic multi-stage review process

Subject Headings (MeSH) and Emtree terms (see Fig. 1 for search procedures). The three categories of key words pertained to ASD, anxiety, and treatments. Anxiety terms included anxiety disorders and symptoms from the Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth and fifth editions (American Psychiatric Association 2000, 2013). Treatment terms included categories of medications, generic names for medications, types of psychosocial treatments, ASD specific treatments, and terms related to complementary and alternative treatments. (All search terms as well as the systematic search strategy are available upon request.)

Included articles met all the following criteria: (1) the study focused on an intervention for children and adolescents with ASD and anxiety, (2) had at least 10 human subjects, (3) included subjects age 18 years or younger, (4) was written in English, and (5) was published in or after 1994, when Asperger's Disorder entered the DSM IV. In order to be inclusive of all articles, the terms 'ASD' and 'anxiety' were not operationally defined when abstracting articles but rather the methods to assess these conditions were critically analyzed as part of the review. Articles that were a review, opinion, dissertation, editorial, book chapter, or descriptive piece were excluded. Additionally, studies that focused only on the treatment of repetitive behaviors (King et al. 2009) without mention of anxiety were excluded because it could not be determined with certainty whether the repetitive behaviors were secondary to anxiety. The initial search resulted in 647 articles for title and abstract screening.

Multiple investigators independently screened a subset of the 647 titles and abstracts using a standardized screening sheet that assessed inclusion and exclusion criteria. This step resulted in 31 manuscripts for full-text review, all of which were reviewed in-depth using the same inclusion and exclusion criteria noted above. Studies that

still met all criteria were selected for inclusion in this review and subsequently abstracted. Twenty percent of the articles overlapped amongst the investigators to ensure consistency and validate the process. If disagreements arose, the two primary reviewers, along with a third investigator (either RV or AN), discussed the discrepancies to arrive at a consensus regarding article inclusion or exclusion. Data abstraction elements included study design, sample size, population description, intervention, and outcome measures. This step resulted in a final set of 15 studies.

Data Quality Assessment

The investigators evaluated the evidence for each key question using select criteria from the US Preventive Services Task Force (USPSTF; USPSTF 2008) and Grading of Recommendations Assessment, Development and Evaluation (GRADE; Guyatt et al. 2008). Using both sets of criteria allowed for a more qualitative assessment of the evidence, which was necessary given the limited literature on the topic (particularly for psychopharmacological studies). Critical appraisal questions from the USPSTF criteria were used to guide the evaluation of the evidence for each key question; these questions pertained to aspects of research design (internal validity), generalizability and applicability (external validity) and other study methods including the number and size of the study. The USPSTF criteria were also used to rate the strength of the evidence (low, moderate, high) for each key question. The GRADE approach was used to assess the evidence in four domains: risk of bias, consistency, directness, and precision. Risk of bias (low, medium, and high) refers to various aspects of study design with randomized controlled trials (RCTs) resulting in the least bias. If studies varied in their risk for bias, studies with lower bias were preferentially weighted.

Table 1 Psychopharmacological treatment studies for anxiety in children and adolescents with autism spectrum disorders^a

Study	N	Age (years)	Anxiety diagnoses ^b	Study design	Medication	Study duration	Outcome measures ^c	Results ^d	Adverse events (n)	Drop outs (n)
Buitelaar et al. (1998)	22	6–17	Diagnoses not specified	Open label	Buspirone (15–45 mg/day, M = 29.3 mg/day)	6–8 weeks; 2–12 month follow up	CGI (unblind)	41 % had a marked response and 32 % had a moderate response	Sedation (2), mild agitation (2), nausea (1), abnormal involuntary movements (1)	Lack of response (1)
Couturier and Nicolson (2002)	17	4–15	Diagnoses not specified	Chart review	Citalopram (5–40 mg/day, M = 19.7 mg)	M = 7.4 months, range 1–15 months	CGI (unblind)	59 % showed improvement		Agitation (2), tics (1), insomnia (1)
Martin et al. (2003)	18	7–18	GAD, SAD, SoP, OCD, school phobia, and panic/somatic symptoms	Open label	Fluvoxamine (37.5–175 mg/day, M = 66.7 mg/day)	10 weeks	CGI-I (unblind) C-YBOCS SCARED-P	Group did not improve as a whole. Females were more likely to respond compared to males (100 vs. 29 %)	Akathisia, agitation, behavioral activation (9), sleep problems (9), headaches (6), change in appetite (4), abdominal discomfort (3), rhinitis (2)	Behavioral activation (3)
Namerow et al. (2003)	15	6–16	Rigidity, stereotypies, repetitive behaviors, preoccupations with routines	Chart review	Citalopram (5–40 mg/day, M = 16.9 mg)	M = 219 days (SD = 167 days)	CGI-I CGI-S (unblind)	66 % had improvement in anxiety symptoms	Headaches, sedation, aggression, agitation, and lip dyskinesia (5)	Side effects (2), lack of efficacy (2)

^a All studies included participants with various ASD subtypes including autistic disorder, Asperger's syndrome, and pervasive developmental disorder not otherwise specified. All studies except Buitelaar et al. (1998) included participants with comorbid intellectual disability

^b OCD: Obsessive compulsive disorder, GAD: Generalized anxiety disorder, SAD: Separation anxiety disorder, SoP: Social Phobia

^c CGI: Clinical Global Impressions scale, CGI-I: Clinical Global Impressions scale—Improvement, CGI-S: Clinical Global Impressions scale—Severity, C-YBOCS: Children's Yale-Brown Obsessive Compulsive Scale, SCARED-P: Screen for Child Anxiety and Related Emotional Disorders, parent report

^d Namerow et al. (2003) and Martin et al. (2003) reported results from the ITT analysis

Table 2 Non-psycho pharmacological treatments for anxiety in children with autism spectrum disorders^a

Study	N	Age (years)	% Caucasian	Anxiety diagnoses ^b	Study design ^c	Treatment groups ^d	Study duration	Outcome measures ^e	Results ^f	Drop outs (n)
<i>Cognitive behavioral studies</i>										
Chalfant et al. (2007)	47	8–13	Not reported	SoP (20) GAD (14) SAD (8) SP (3) PD (2)	RCT	Group CBT versus WL	12 weeks	ADIS-C/P RCMAS-C SCAS-C/P	71.4 % in the CBT group were diagnosis free versus 0 % in the WL group. CBT group had fewer anxiety symptoms as per SCAS parent (d = 4.11) and child (d = 2.74) report	Parent work schedules (2), relocation (1), treatment ineffective (1)
McNally et al. (2013)	22	8–14	55 %	GAD (18) SAD (8) SoP (15) SP (15) OCD (2)	RCT	Individual CBT versus WL control	16 weeks; 2 month follow up	ADIS-P SCAS-C/P	58 % in CBT group were diagnosis free versus 0 % in WL group. CBT group had reduction in SCAS-P scores (d = 1.17) but not SCAS-C scores	None reported
Reaven et al. (2009)	33	8–14	81 %	GAD (22) SAD (6) SoP (5)	CT	Group CBT versus WL	12 weeks	SCARED-C/P KSADS-PL	CBT group had a reduction in SCARED-P total (d = 0.88) and subscale scores (GAD, SAD, social, school, panic scores). No reduction as per SCARED-C	busy schedules and family crisis (2)
Reaven et al. (2012)	50	7–14	84 %	GAD SoP SAD SP	RCT	Group CBT versus TAU	12 weeks; 3 and 6 month follow up	ADIS-P CGI-I (blind) CGI-S SCARED-C/P	As per CGI-I, 50 % in CBT group responded versus 8.7 % in WL group (d = 1.03) As per CGI-S, reduction in anxiety severity seen across all disorders (d = 0.66–0.87) As per ADIS-P, significant reduction in GAD. As per SCARED C/P, reduction in scores at 3 and 6 months	3 in the treatment group due to unspecified reason
Sofronoff et al. (2005)	71	10–12	Not reported	GAD, SAD, SoP, SP, Panic/ Agoraphobia and OCD symptoms	RCT	Individual CBT versus parent/child sessions versus WL	6 weeks	SCAS-P SWQ-P	Both treatment groups showed a decrease in SCAS-P (individual: d = 0.48; family: d = 1.29) versus WL as well as a decrease in SAD, GAD, OCD, and SoP symptoms	2 in the treatment and 3 in the WL group for unspecified reasons

Table 2 continued

Study	N	Age (years)	% Caucasian	Anxiety diagnoses ^b	Study design ^c	Treatment groups ^d	Study duration	Outcome measures ^e	Results ^f	Drop outs (n)
Storch et al. (2013)	45	7–11	84 %	SoP (18) GAD (14) SAD (9) OCD (4)	RCT	Individual CBT versus TAU	16 weeks; 3 month follow up	ADIS-C/P CGI-I (blind) CGI-S (blind) PARS MASC-P CBCL RCMAS-C	38 % in CBT group were diagnosis free versus 5 % in TAU group; reduction in anxiety in CBT group as per all clinician-rated measures ($d = 0.84-1.06$). Gains maintained at 3 months	7 in the treatment group: distance from clinic (2) and without any specified reason (5)
Sung et al. (2011)	70	9–16	0 %	GAD, SAD, SoP, OCD, panic/AG, and injury and symptoms.	RCT	Group CBT versus social recreational program	16 weeks; 3 and 6 month follow up	CGI-S (blind) SCAS-C	Both groups had reduction in anxiety severity, and SCAS-C total anxiety and generalized anxiety symptoms after treatment and at 6 months	6 due to lack of interest, schedule conflicts, preference for other services, medication changes for other psychiatric conditions
White et al. (2013)	30	12–17	87 %	SoP (23) GAD (19) SP (16) OCD (4) SAD (1) PD (1) PTSD (1)	RCT	Individual and group CBT/ social skills intervention versus WL	14 weeks; 3 month follow up	CGI-I (blind) CASI-Anx PARS	No significant reduction in anxiety in the treatment group on the CASI-Anxiety and PARS	2 in treatment group; decrease in teasing and social anxiety (1), increased self-harm, and recurring suicidal behavior (1); 3 in the WL group due to unspecified reason
Wood et al. (2009)	40	7–11	48 %	SoP (35) SAD (24) GAD (19) OCD (17) PTSD (1)	RCT	Individual CBT versus WL	16 weeks; 3 month follow up	ADIS-C/P MASC-C/P CGI-I (blind)	64.3 % in CBT group were diagnosis free versus 9.1 % in the WL group. CBT group had decrease in MASC-P versus WL ($d = 1.23$) but not MASC-C	1 in the treatment group and 2 in the CBT for unspecified reasons
<i>Alternative treatment studies</i>										
Edelson et al. (1999)	12	4–13	Not reported	Diagnosis not specified	CT	Deep pressure versus placebo	6 weeks (twice a week)	CPRS derived anxiety scales	Treatment group had significant reduction in tension and marginal reduction in anxiety	Separation anxiety (1), refusal to participate in galvanic skin response (1)

Table 2 continued

Study	N	Age (years)	% Caucasian	Anxiety diagnoses ^b	Study design ^c	Treatment groups ^d	Study duration	Outcome measures ^e	Results ^f	Drop outs (n)
Jarusiewicz (2002)	24	4–13	Not reported	Diagnosis not specified	CT	Neurofeedback versus WL	6–8 months	Parent interview	Treatment group had reduction in anxiety	Family factors (7), illness (1)

^a In all studies, various autism spectrum disorder diagnoses were included, i.e., autistic disorder, Asperger’s syndrome, and pervasive developmental disorder not otherwise specified
^b RCT refers to randomized controlled trial. CT refers to non-randomized controlled trial
^c GAD: Generalized anxiety disorder, SAD: separation anxiety disorder, SoP: social phobia, SP: specific phobia, OCD: obsessive compulsive disorder, PD: panic disorder, PTSD: post-traumatic stress disorder, AG: agoraphobia
^d WL: Waitlist, TAU: Treatment as usual
^e ADIS C/P: Anxiety Disorders Interview Schedule, RCMAS: Revised Children’s Manifest Anxiety Scale, SCAS: Spence Children’s Anxiety Scale, CPRS: Conners Parent Rating Scale, CGI-S: Clinical Global Impressions scale-Severity, CGI-I: Clinical Global Impressions scale-Improvement, CASI-Anx: Child and Adolescent Symptom Inventory-4 ASD Anxiety Scale, CATS: Children’s Automatic Thoughts Scale, K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version
^f Results report % that are diagnosis free of their primary anxiety disorder

Other dimensions included the consistency of the findings (consistent, inconsistent, unknown), how directly the findings related to the key question (direct, indirect), and whether the findings offered clinically useful conclusions (precise, imprecise).

Results

Among the 15 included studies reporting treatments for anxiety in youth with ASD, four were psychopharmacological (Table 1) and eleven were non-psychopharmacological (Table 2) trials. Table 3 presents the strength of evidence for each key question.

The methods used to assess ASD varied across studies. In psychopharmacological studies, ASD was diagnosed primarily by clinician interview, which was based on DSM criteria (Buitelaar et al. 1998; Couturier and Nicolson 2002; Martin et al. 2003; Namerow et al. 2003). One pharmacological study used the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 2002) as part of the ASD assessment (Martin et al. 2003). Among the non-psychopharmacological studies, seven included the ADOS as part of the clinical assessment (McNally et al. 2013; Reaven et al. 2009, 2012; Storch et al. 2013; Sung et al. 2011; White et al. 2013; Wood et al. 2009). Four studies relied on previous clinical evaluations documenting a diagnosis of HF-ASD (Chalfant et al. 2007; Edelson et al. 1999; Jarusiewicz 2002; Sofronoff et al. 2005).

The results are organized by key question. The responses to each key question are presented below.

1. What is the evidence supporting the efficacy and safety of psychopharmacological treatments for anxiety in youth with ASD?

Study characteristics Participants were a heterogeneous group with respect to age and the presence of intellectual disability. Three studies examined the efficacy of selective serotonin reuptake inhibitors (SSRIs; Couturier and Nicolson 2002; Martin et al. 2003; Namerow et al. 2003) and one focused on buspirone (Buitelaar et al. 1998). The two citalopram studies were chart reviews whereas buspirone and fluvoxamine were tested in open label trials. The studies had small sample sizes (range 15–22 participants), lacked control groups and blinded evaluators at follow up. Duration of treatment was variable across studies (6 weeks to 15 months).

Evidence The two citalopram studies demonstrated a reduction in anxiety. Couturier and Nicolson (2002) reported that 10 of 17 (59 %) of participants demonstrated a decrease in target symptoms, which included anxiety, aggression, stereotypies, and preoccupations. Four (24 %) children did not respond to citalopram. Namerow et al.

Table 3 Strength of evidence for treatment of anxiety in youth with ASD

Quality of the Studies							Strength of evidence
Number of studies	Total number of participants	Study design	Risk of bias	Consistency	Directness	Precision	
1. <i>What is the evidence supporting the efficacy and safety of psychopharmacological treatments for anxiety in youth with ASD?</i>							
4	72	Chart review Open label	Medium	Inconsistent	Direct	Imprecise	Low
2. <i>What is the efficacy and safety of non-pharmacological treatments?</i>							
11	444	RCT (8) Nonrandom (1)	Low	Consistent	Direct	Imprecise	Moderate
3. <i>What are the types of anxiety disorders and symptoms that are targeted in treatment trials?</i>							
5	184	N/A	Medium	Inconsistent	Direct	Imprecise	Low
4. <i>Are there specific profiles of anxiety that are more responsive to treatment?</i>							
5	239	RCT (1)	Low	Unknown	Indirect	Imprecise	Moderate
5. <i>What are the determinants of treatment response?</i>							
1	18	Open label (1)	High	Unknown	Indirect	Imprecise	Low
6. <i>What anxiety assessment measures are sensitive to change in treatment studies?</i>							
15	516	Controlled (11) Descriptive (4)	Medium	Inconsistent	Direct	Imprecise	Low

The strength of the evidence was evaluated using criteria from USPSTF and GRADE

Risk of bias: Based on study design for each key question (low, medium, high)

Consistency: Consistency of results across studies in relation to the key question (consistent, inconsistent, unknown)

Directness: Degree to which the findings are directly related to the key question (direct, indirect)

Precision: Degree to which the findings offer clinically useful conclusions (precise, imprecise)

Strength of evidence: Overall strength of the findings (low, moderate, high)

(2003) reported a reduction in PDD-related anxiety symptoms with citalopram in 10 of 15 (66 %) children. These symptoms included preoccupations with nonfunctional routines, repetitive behaviors or stereotypies, and difficulty with deviations in daily routines. Fluvoxamine lacked efficacy in treating anxiety or obsessive–compulsive disorder (OCD) symptoms for the overall group, although females were significantly more likely to respond compared to males (4 out of 4 females responded versus 4 out of 14 males; Martin et al. 2003). Buspirone resulted in a reduction in anxiety in 16 of 22 (73 %) participants, all of whom maintained these gains at follow up (Buitelaar et al. 1998).

Adverse events Citalopram resulted in mild to severe side effects, resulting in discontinuation in 6 of 32 (19 %) children. Fluvoxamine resulted in side effects in 13 of 18 (72 %) children with behavioral activation occurring in 9 (50 %) of children. Buspirone resulted in mild side effects.

Conclusions Based on the small number and sample sizes of existing studies, as well as the lack of placebo comparison groups, the strength of evidence is low. The SSRI data indicate a high rate of adverse events, particularly behavioral activation.

2. What is the evidence supporting the efficacy and safety of non-psychopharmacological treatments?

Study characteristics Eight CBT studies were RCTs (Chalfant et al. 2007; McNally et al. 2013; Sung et al. 2011; Reaven et al. 2012; Sofronoff et al. 2005; Storch et al. 2013; White et al. 2013; Wood et al. 2009). One study lacked randomization (Reaven et al. 2009). Three CBT studies included an active control group, of which two consisted of a treatment as usual control group (TAU; Reaven et al. 2012; Storch et al. 2013) and one included a social recreation (SR) control group (Sung et al. 2011). The SR group participated in various activities that used ASD friendly techniques to promote self-development and social skills, intellectual stimulation, and motor development. Six studies included a waitlist (WL) control group (Chalfant et al. 2007; McNally et al. 2013; Reaven et al. 2009; Sofronoff et al. 2005; White et al. 2013; Wood et al. 2009). Duration of CBT ranged from 6 to 16 weeks. Four studies included a follow up assessment 2–6 months after treatment (McNally et al. 2013; Storch et al. 2013; Sung et al. 2011; Wood et al. 2009). Sample sizes for all CBT studies were small (range 22–71 participants).

The CBT format varied and consisted of individual CBT (McNally et al. 2013; Storch et al. 2013; Wood et al. 2009), group based CBT (Chalfant et al. 2007; Reaven et al. 2009, 2012; Sung et al. 2011), and both individual and group

CBT sessions (Sofronoff et al. 2005; White et al. 2013). All CBT protocols included the standard CBT components employed in TD children (e.g., awareness of emotional and physiological symptoms, cognitive strategies to identify and cope with anxious thoughts, and behavioral strategies such as deep breathing). Adaptations for the ASD population included the use of visual supports, concrete language, as well as modules to address special interests, social skills, and emotion regulation.

Participants in all CBT trials included youth who were high functioning, which was usually defined as either an IQ of approximately >70 , a clinical diagnosis of high functioning autism or Asperger's, or efforts to speak during the ADOS even if the conversation was limited (e.g., Reaven et al. 2009). Participants were usually 7 to 14 years old, except for two studies that included older adolescents (Sung et al. 2011; White et al. 2013). When reported, samples were predominantly Caucasian (McNally et al. 2013; Reaven et al. 2009, 2012; Storch et al. 2013; White et al. 2013). One study included a mixed race sample (Wood et al. 2009) and another involved a sample of Chinese children (Sung et al. 2011).

Two studies examined alternative treatments. One compared the effects of neurofeedback versus WL control treatment (Jarusiewicz 2002). Another compared the effects of deep pressure versus WL treatment (Edelson et al. 1999). Deep pressure was administered through Grandin's Hug Machine, a device that allows for self-administration of lateral body pressure.

Evidence Seven RCTs demonstrated that CBT was superior to both WL and TAU in terms of reducing anxiety disorders (Chalfant et al. 2007; McNally et al. 2013; Reaven et al. 2012; Storch et al. 2013; Wood et al. 2009) and symptoms (Reaven et al. 2009; Sofronoff et al. 2005). The percentage of children who were diagnosis free ranged from 38 to 71.4 % and the majority of effect sizes were greater than 0.80. Sung et al. (2011) reported that both the CBT and SR groups had a reduction in anxiety symptoms. White et al. (2013) reported some improvement in the treatment group but the change was not significantly different from the control group.

Edelson et al. (1999) showed a significant reduction in tension and a marginally significant reduction in anxiety with treatment compared to placebo. Tension was defined as the presence of rigidity, twitches, jerks, and shakes. Neurofeedback also resulted in a greater reduction in anxiety compared to the control group (Jarusiewicz 2002).

Adverse events White et al. (2013) reported that a total of five children dropped out. Two children in the intervention group dropped out. One child dropped out due to a decrease in teasing by peers and social anxiety, and the other dropped out due to worsening self-harm, suicidal ideation, and suicide attempts requiring emergency room

visits. Both adverse events were unrelated to study treatment. Three children in the WL group dropped out.

Conclusions Seven studies support the efficacy of modified CBT in youth with HF-ASD. The data, however, are collectively limited by their small sample sizes and shortage of studies with an active intervention control group. Data on alternative treatments are scant. The strength of evidence for using CBT to treat anxiety in HF-ASD is moderate.

3. What are the types of anxiety disorders and symptoms that are targeted in treatment trials?

Study characteristics Different methods were used to assess anxiety across the included studies. Among the psychopharmacological studies, one study indicated that anxiety diagnoses were established by clinical evaluation using DSM-IV criteria, which involved an interview of the parent and child, as well as a review of previous records (Namerow et al. 2003). One study administered the Screen for Child Anxiety and Related Disorders (SCARED; Birmaher et al. 1999; Martin et al. 2003), which is an established anxiety scale for TD children, to the parent. Two studies did not report how anxiety was assessed (Buitelaar et al. 1998; Couturier and Nicolson 2002).

Several CBT studies used the Anxiety Disorders Interview Schedule (ADIS; Silverman and Albano 1996), a gold standard instrument that assesses anxiety in TD youth; some studies administered the parent version only (ADIS-P; Reaven et al. 2012; McNally et al. 2013), whereas others integrated data from both the parent and child report (ADIS-C/P; Chalfant et al. 2007; Storch et al. 2013; White et al. 2013; Wood et al. 2009). Other CBT studies used anxiety scales designed for TD children (Reaven et al. 2009; Sofronoff et al. 2005; Sung et al. 2011). Only one study included an anxiety measure that was adapted for youth with ASD (White et al. 2013). This measure, the Child and Adolescent Symptom Inventory-4 ASD Anxiety Scale (CASI-Anx; Sukhodolsky et al. 2008), is a 20-item parent-report anxiety symptom scale that excluded symptoms that overlapped with ASD.

Evidence Among the pharmacological studies, two used the general term 'anxiety' without specification (Buitelaar et al. 1998; Couturier and Nicolson 2002), one examined PDD-related anxiety symptoms (e.g., rigidity, stereotypies, repetitive behaviors, preoccupations with routines) (Namerow et al. 2003), and one examined DSM IV anxiety symptoms (Martin et al. 2003).

Studies using the ADIS indicate that generalized anxiety disorder (GAD), separation anxiety disorder (SAD), and social phobia (SoP) were the most common disorders. Studies using anxiety scales report symptoms of the same three disorders (Reaven et al. 2012; Sofronoff et al. 2005).

The alternative treatment studies used the general term ‘anxiety’.

Conclusions Anxiety assessment was more rigorous in CBT compared to psychopharmacological studies and indicated that GAD, SAD, and SoP were the most common anxiety disorders. Sample sizes were small and only one study used an ASD specific anxiety instrument (White et al. 2013), which precludes firm conclusions about the most prevalent phenotypes. The strength of evidence is therefore low.

4. Are there specific types of anxiety disorders or symptoms that are more responsive to treatments?

Study characteristics Only five studies reported which specific anxiety disorders and symptoms responded to treatment (Namerow et al. 2003; Reaven et al. 2009, 2012; Sofronoff et al. 2005; Sung et al. 2011). All but one study (Namerow et al. 2003) used anxiety instruments for TD children.

Evidence Using the Spence Child Anxiety Scale-Parent Report (SCAS-P; Nauta et al. 2004), Sofronoff et al. (2005) reported a significant decrease in GAD, SAD, SoP, panic, and OCD symptoms in both the child only and the child and parent intervention groups but not the WL group. Reaven et al. (2009) similarly demonstrated that the mean subscale scores on the SCARED were lower after treatment for the following symptoms: generalized anxiety, separation anxiety, panic, and social anxiety. In a later study using the ADIS-P, Reaven et al. (2012) showed that GAD remitted with CBT; the data also showed that ADIS-P clinician severity ratings for SAD, SoP, and specific phobia significantly decreased. Using the child version of the Spence Child Anxiety Scale (SCAS-C; Spence 1998), Sung et al. (2011) reported a reduction in both total anxiety and generalized anxiety symptoms in both the treatment and SR groups. In a chart review study, Namerow et al. (2003) reported that citalopram improved ASD-related anxiety symptoms (e.g., nonfunctional routines, repetitive behaviors, stereotypies, and difficulty with change).

Conclusions The data show that GAD, SAD, and SoP all respond to CBT. One study showed improvement in ASD-related anxiety symptoms. The evidence for any specific type of anxiety disorder being more or less responsive to treatment is low. The strength of evidence based on the CBT data is moderate.

5. What are the demographic, cognitive and clinical determinants of treatment response?

Study characteristics One study reported on the determinants of treatment response (Martin et al. 2003).

Evidence Females were significantly more likely to respond to fluvoxamine compared to males (4 out of 4 females responded versus 4 out of 14 males; Martin et al. 2003).

Conclusions The strength of evidence regarding predictors of treatment response is low.

6. What anxiety measures are sensitive to change in treatment studies?

Study characteristics The Clinical Global Impressions scale (CGI; Guy 1976) was the primary outcome measure in all psychopharmacological studies (Buitelaar et al. 1998; Couturier and Nicolson 2002; Martin et al. 2003; Namerow et al. 2003) and in five of nine CBT studies (Reaven et al. 2012; Storch et al. 2013; Sung et al. 2011; White et al. 2013; Wood et al. 2009). Other clinician-rated measures included the Pediatric Anxiety Rating Scale (PARS; Storch et al. 2013; RUPP 2002) and the ADIS (Chalfant et al. 2007; McNally et al. 2013; Reaven et al. 2012; Storch et al. 2013; Wood et al. 2009). Eight CBT studies used a parent-report anxiety measure (Chalfant et al. 2007; McNally et al. 2013; Reaven et al. 2009, 2012; Sofronoff et al. 2005; Storch et al. 2013; White et al. 2013; Wood et al. 2009) and six studies included a child self-report measure to assess outcome (Chalfant et al. 2007; McNally et al. 2013; Reaven et al. 2009; Storch et al. 2013; Sung et al. 2011; Wood et al. 2009). One of the alternative treatment studies used a parent-report anxiety measure to assess outcome (Edelson et al. 1999), while the other used a parent interview (Jarusiewicz 2002).

Evidence The CGI was sensitive to treatment effects in all but one medication study (Martin et al. 2003). Across medication studies, rater qualifications and information used to guide ratings were not described, ratings were not blind to treatment, and in some cases, were retrospective (Buitelaar et al. 1998; Couturier and Nicolson 2002; Martin et al. 2003).

Among the non-pharmacological studies, the CGI demonstrated sensitivity to treatment effects in three CBT studies (Reaven et al. 2012; Storch et al. 2013; Wood et al. 2009) but did not show treatment effects in two studies (Sung et al. 2011; White et al. 2013). In five studies, the CGI was completed by independent raters blind to treatment condition (Reaven et al. 2012; Storch et al. 2013; Sung et al. 2011; White et al. 2013; Wood et al. 2009). The PARS showed large treatment effects in one study (Storch et al. 2013). The ADIS was effective in demonstrating both response and remission of anxiety disorders (Chalfant et al. 2007; McNally et al. 2013; Reaven et al. 2012; Storch et al. 2013; Wood et al. 2009), as well as reduction in anxiety severity (Reaven et al. 2012; Storch et al. 2013; Wood et al. 2009) and interference ratings (McNally et al. 2013; Reaven et al. 2012).

When using anxiety scales, treatment results differed based on parent and child informant status. In terms of parent-report measures, the SCAS-P demonstrated treatment effects across several studies (Chalfant et al. 2007;

McNally et al. 2013; Sofronoff et al. 2005). The parent version of the SCARED also showed treatment effects (Reaven et al. 2009) that were maintained 3 and 6 months later (Reaven et al. 2012). The CASI-Anx did not show treatment effects (White et al. 2013). The parent version of the Multidimensional Anxiety Scale for Children (MASC; March et al. 1999) was sensitive to treatment in one study (Wood et al. 2009) but not another (Storch et al. 2013).

Child-report anxiety scales also demonstrated variability in showing treatment response and seemed even less sensitive than parent-rated scales. The SCAS-C did not demonstrate treatment effects in two studies (McNally et al. 2013; Sung et al. 2011), but did show effects in a third (Chalfant et al. 2007). The child-report of the Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds and Richmond 1978) demonstrated treatment effects in one study (Chalfant et al. 2007), but not another (Storch et al. 2013). Other child-report measures including the SCARED-C (Reaven et al. 2009) and the MASC-C (Wood et al. 2009) were not sensitive to treatment.

Studies using child- and parent-report versions of the same measure typically yielded discordant results. For example, the parent versions of the SCARED, MASC, and SCAS showed treatment effects, while the child versions did not (McNally et al. 2013; Reaven et al. 2009; Wood et al. 2009). One study showed consistency across both parent and child-report of the SCAS (Chalfant et al. 2007).

Conclusions The ADIS showed some sensitivity to treatment, whereas the CGI, as well as parent and child anxiety measures, yielded discrepant data. The strength of evidence for this question is low.

Discussion

Anxiety is a significant problem for youth with ASD. Successful treatment of this condition could dramatically improve both short- and long-term outcomes in this population. Findings from this systematic review show that despite the burden of anxiety in youth with ASD, there is a dire shortage of treatments for this condition. Responses to key questions pertaining to the current state of treatment outcome research are discussed below.

Evidence for Psychopharmacological Treatments (Question 1)

Large randomized controlled medication trials for anxiety in youth with ASD are lacking, and the existing studies are minimally informative regarding treatment efficacy due to study limitations. The data, however, do highlight that youth with ASD may be particularly vulnerable to

behavioral activation with certain SSRIs. Behavioral activation is a well-known side effect of SSRIs in children and is characterized by a cluster of symptoms including increased activity level, impulsivity, insomnia, or disinhibition without manic symptoms (Reinblatt et al. 2009). Other treatment data in youth with ASD similarly show high rates of SSRI-induced behavioral activation (King et al. 2009). The SSRIs are amongst the most commonly prescribed medications in youth with ASD (Hsia et al. 2014). There are, however, no large scale RCTs examining their efficacy for treatment of anxiety in youth with ASD, and as such, there are no data to guide evidence based prescribing of these medications. Concern therefore exists regarding the overprescribing of SSRIs and risk of subjecting children to potential side effects, especially activation.

Evidence for Non-psychopharmacological Treatments (Question 2)

The CBT data indicate that up to 71.4 % of youth with HF-ASD responded to treatment, which is consistent with the data in TD children with anxiety disorders (Walkup et al. 2008). One limitation of the CBT data, however, is that only three of the nine CBT studies included an active control group (Reaven et al. 2012; Storch et al. 2013; Sung et al. 2011). One of these studies included an SR control group that appeared structurally equivalent to the treatment group in terms of offering a variety of ASD training techniques and modules but not anxiety specific treatments (Sung et al. 2011). Results of this study showed a reduction in anxiety in both the CBT and control groups. While this study possessed other limitations, the design highlights the importance of selecting active control groups that possess common elements of CBT and are lacking only in the key CBT ingredients being studied (Safer and Hugo 2006). Another point to note is that although CBT was well-tolerated, some subjects dropped out, primarily due to practical reasons. In naturalistic settings where there is no incentive to continue with treatment, compliance may be even more problematic than in research studies. This may particularly impact group therapies given that missing even one session could potentially interrupt skill acquisition. Taken together, the CBT data are promising but must be viewed as preliminary.

Anxiety Profiles and Determinants of Treatment Response (Questions 3, 4, 5)

Almost every study used anxiety instruments designed for TD children yet none of the studies discussed how these instruments were adapted for youth with ASD. For example, there was no discussion of how overlapping symptoms

between anxiety and ASD were parsed (e.g., social avoidance, rigidity, and repetitive behaviors). Aside from the ‘ASD-related anxiety symptoms reported by Namerow et al. (2003), it is also unclear whether anxiety related to ASD symptoms (e.g., anxiety related to transitions) was coded as part of a DSM IV anxiety disorder or considered symptoms inherent to ASD. Moreover, no studies discussed the methods used to ensure that participants understood the anxiety questions being asked. Helping parents and children disentangle symptoms during the assessment process is important for delineating valid anxiety phenotypes.

A variety of DSM IV anxiety disorders and symptoms appeared responsive to modified CBT techniques particularly GAD, SAD, and SoP, which is consistent with findings in TD children (Walkup et al. 2008). Data on other determinants of treatment response are lacking. In pharmacological studies, lack of a precise phenotype as well as small sample sizes precluded such analyses. The CBT studies collected more comprehensive phenotypic data but these were not used to examine predictors of treatment response. It is important to note that the success of CBT requires a certain degree of emotional awareness, somatic perception, and theory of mind. Some children with HF-ASD, with their gifted memories, can learn techniques in a rote fashion that can to some extent make up for deficits in those areas. Given the clinical heterogeneity among youth with HF-ASD, it will be important to know what prerequisite social, emotional, and behavioral characteristics confer treatment advantage.

Measures of Treatment Response (Question 6)

There were no measures that consistently demonstrated responsiveness to treatment. The CGI demonstrated responsiveness to treatment across several medication and CBT studies but not others. The CGI has been widely used in medication trials and is a cost and time efficient means of measuring treatment response (Martin et al. 2010). However, critiques of this measure cite its limited evidence of validity or reliability (Busner et al. 2009; Forkmann et al. 2011). Even in cases when the CGI was completed by examiners blind to treatment condition, much of the information used to guide CGI ratings was provided by parents. In WL control studies, parents are equally likely to be affected by bias, particularly since they are not blind to treatment condition (Cunningham et al. 2013; Mohr et al. 2009). Some anxiety measures were sensitive to treatment but the data were discrepant across studies and informants. The lack of appropriate measures and wide variation in outcome measurement therefore limits our ability to compare results across studies, which compromises the strength of evidence.

Future Research Directions

There are a number of critical areas for future treatment research on anxiety and ASD. Foremost, all but one study used anxiety measures that were designed for TD children. As such, there is a desperate need to develop reliable and valid psychiatric instruments to assess anxiety in youth with ASD in order to precisely define the anxiety construct, as well as to differentiate between ASD and anxiety symptoms (e.g., CASI-Anx, Sukhodolsky et al. 2008). Until such instruments are developed, it is recommended that clinicians and researchers adapt instruments used in TD children to account for the cognitive and socioemotional challenges associated with ASD.

Second, there is a pressing need for large rigorous clinical trials examining psychopharmacological and non-psychopharmacological treatments of anxiety. The paucity of these studies limits our ability to determine whether medications are efficacious and safe, how medication efficacy compares to non-psychopharmacological treatments, and whether combination treatment is more effective than monotherapy. Given the emotional and financial stresses associated with caring for a child with ASD, coupled with the shortage of mental health providers for this population, it will also be important to develop psychosocial treatments that are feasible, portable, and generalizable.

Research on the efficacy of anxiety treatments across the lifespan and across functional levels is lacking. The CBT studies to date have been limited to school age children with HF-ASD. Additional research is needed to determine whether modified CBT procedures would broaden the reach of these interventions to children and adolescents with cognitive or verbal impairment. Additionally, research on treatments for adults with ASD and co-occurring anxiety is strongly needed.

In future clinical trials, it will be important to delineate specific anxiety phenotypes in order to develop targeted treatments and to help elucidate mediators and moderators of treatment response. Measures of improvement that minimize or eliminate reporter bias are also needed, particularly in studies in which raters (either parents or clinicians) are not blind to treatment condition (Lecavalier et al. 2013). Many of the existing studies included primarily Caucasian children (McNally et al. 2013; Reaven et al. 2009, 2012; Storch et al. 2013; White et al. 2013; Wood et al. 2009). Including youth who are racially, ethnically, and socioeconomically diverse will strengthen the generalizability of treatments.

Finally, most treatment trials examined short-term treatment efficacy. Long-term follow up is needed to determine if length of treatment is related to maintenance of treatment gains and improved functional outcomes.

Clinical Implications

Findings from this review will provide clinicians with data regarding the strength of the evidence for treatment of anxiety in youth with ASD. These data can be used to make decisions regarding treatment recommendations. For example, clinicians may refer youth with ASD and co-occurring SAD, GAD, and SoP to a therapist with expertise in administering specialized CBT techniques for this population. Insurance constraints as well as the shortage of specialized CBT providers for youth with ASD in certain locations, however, may compromise access to CBT treatment for this population.

Given the limited pharmacological evidence base for treatment of anxiety, it will be important for clinicians to implement a conservative approach in their choice and dosing of medications, as well as monitoring of adverse events. This is especially true when prescribing SSRIs, which can result in high rates of behavioral activation in this population.

Another point to note is that many studies demonstrated treatment response using the parent-report but not child-self-report measures. In TD children, limited parent-child agreement regarding the diagnosis of anxiety disorders in children is an established finding (Choudhury et al. 2003; Comer and Kendall 2004). Due to the internalizing nature of anxiety, children may be more likely to report anxiety whereas parents may have difficulty recognizing these symptoms. In youth with ASD, there is the additional concern that child self-report may be compromised due to difficulty recognizing internal emotional states (e.g., Losh and Capps 2006; Lopata et al. 2010). Some data however indicate that youth with HF-ASD may be able to reliably report anxious symptoms (e.g., Farrugia and Hudson 2006; Ozsivadjian et al. 2014). Multi-informant approaches are therefore recommended in the assessment of child anxiety in youth with ASD (e.g., MacNeil et al. 2009; White et al. 2009) as some youth may be able to offer information about their internalizing symptoms.

Summary

The findings of this systematic review highlight the shortage of treatment studies for anxiety in youth with ASD. Preliminary evidence suggests that modified CBT may be efficacious for youth with HF-ASD. Pharmacological data are extremely limited.

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