Relationship between Anxiety, Depression, Somatic Complaints, and Age in Children with Autism and Children with ADHD

Susan D. Mayes, Peter Castagna, Raman Baweja[*], Taranjeet Jolly and Daniel A. Waschbusch

Department of Psychiatry and Behavioral Health, Penn State College of Medicine, USA

Abstract: No study has analyzed internalizing and somatic symptoms and age in large samples of children with autism and ADHD. Mothers rated 1,436 children with autism and 1,056 with ADHD-Combined or ADHD-Inattentive, 2-17 years of age, on 25 Pediatric Behavior Scale internalizing and somatic symptoms. Generalized and separation anxiety scores were significantly higher in autism than in ADHD-C and ADHD-I, social anxiety was higher in autism than in ADHD-C, and feeling sad and depressed was higher in autism than in ADHD-I. Children with ADHD-C and ADHD-I did not differ from each other, except that sleep disturbance was greater in ADHD-C and social anxiety was greater in ADHD-I. Across age groups, generalized anxiety was often or very often a problem for 49% with autism, 29% with ADHD-C, and 26% with ADHD-I. Corresponding percentages for social anxiety were 32%, 15%, and 24%; separation anxiety 40%, 22%, and 21%; and depressed 22%, 15%, and 9%. No symptoms significantly decreased with age, and in all three diagnostic groups, depression, low self-esteem, and somatic complaints increased with age. Generalized anxiety also increased with age in autism. The frequency of clinically significant anxiety and depression was high in all three diagnostic groups (particularly autism) and was overall higher in the 13-17 year age group than at younger ages, indicating that anxiety and depression may increase with age in ADHD and autism, making early diagnosis and treatment critical.

Keywords: Internalizing symptoms, somatic problems, autism, ADHD.

PREVALENCE OF ANXIETY AND DEPRESSION IN AUTISM AND ADHD

Parent ratings of anxiety and depression are higher in children with ADHD than in typical controls, with a nonsignificant difference between children with ADHD-Combined presentation (ADHD-C) and ADHD-Inattentive presentation (ADHD-I) across studies [1-5]. Parent ratings of anxiety and depression are also significantly higher in children with autism than in community controls [6-11]. Strikingly, children with autism and normal intelligence did not differ from children with an anxiety disorder in maternal ratings of anxiety [4]. A meta-analysis of 31 studies indicated that, overall, 40% of children and adolescents with autism have at least one type of anxiety disorder [12]. In contrast to anxiety, the prevalence of major depressive or dysthymic disorders in autism is lower, ranging from 1% to 29% across studies [13-16].

A literature review by Mitchison and Njardvik [17] revealed that approximately 25% of children and adolescents with ADHD have an anxiety disorder and 20% have depression. In a study using self-report measures completed by 112 8- to 15-year-olds with ADHD, 42% scored above the anxiety cut-off on the Manifest Anxiety Scale for Children and 21% scored above the cut-off on the Children's Depression

Inventory [17]. Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) diagnoses among 309 6- to 18-year-olds with ADHD-C and ADHD-I, respectively, were 23% and 21% for dysthymic disorder and 12% and 19% for generalized anxiety disorder with a nonsignificant difference between the two ADHD subtypes [2]. However, much lower K-SADS percentages (1% anxiety disorder and 1% depression) were reported for 1,269 children with ADHD in another study [18].

Only two studies were located comparing the prevalence of anxiety and depression in children with autism versus ADHD. Parent ratings of anxiety (but not depression) were significantly higher in 233 children with high functioning autism than in 490 with ADHD-C and 188 with ADHD-I [4]. In a study using the Structured Clinical Interview for DSM-IV Childhood Diagnoses [19], 40 children with pervasive developmental disorder-NOS or Asperger's disorder did not differ significantly from 40 children with ADHD in frequency of major depressive or dysthymic disorder (12% and 5%, respectively), but an anxiety disorder was more common in autism (28% vs. 10%). Aside from the limitation of very small sample sizes, the authors noted that comorbidity percentages were lower than in other studies and that some children with ADHD may have had autism because children with ADHD were not assessed for possible autism.

Age and Anxiety and Depression

A review of general population studies showed an increase in the incidence of depression, panic disorder,

*Address correspondence to this author at the Department of Psychiatry H073, Penn State College of Medicine, 500 University Dr. Hershey, PA 17033, USA; Tel: (717) 531-8314; Fax: (717) 531-6850; E-mail: rbaweja@pennstatehealth.psu.edu

and agoraphobia and a decrease in separation anxiety disorder from childhood to adolescence [20]. In contrast, normative data for the self-report Revised Children's Manifest Anxiety Scale-2 (RCMAS-2) indicated a small but systematic decline with age in total anxiety, physiological anxiety, worry, and social anxiety [21]. Most cross-sectional autism studies revealed that increasing age was associated with an increase in symptoms of depression [15, 22-25] and anxiety [24, 26]. However, two small studies did not reveal age differences in the frequency of anxiety and depressive disorders in 50 children with autism [27] or the presence of any internalizing disorder in 40 children with autism and in 40 with ADHD [19].

Relationship between Anxiety, Depression, and Somatic Symptoms

Studies revealed large and significant correlations between self-ratings of anxiety and depression in children referred for an ADHD evaluation [21] and between parent ratings of anxiety and depression in children with autism [24]. Moderate and significant correlations were found between somatic complaints (e.g., aches and pains) and parent ratings on the anxiety-depression subscale in both the normative and clinical Child Behavior Checklist samples [28] and between somatic complaints and parent ratings of anxiety and ratings of depression in children with autism [24]. In both the normative and clinical samples, the RCMAS-2 physiological anxiety subscale score (which includes problems with concentration, nightmares, sleep disturbance, aches, and feeling sick, tired, or mad) had large correlations with worry and social anxiety scores [21].

Purpose

As noted in the preceding literature review, the prevalence of internalizing symptoms and disorders varied markedly between studies. This is due in part to differing measurement instruments (e.g., diagnostic interviews vs. rating scales), informants, criteria for clinical significance, and age ranges. Sample sizes were small in most studies, and prevalence data cited in recent reviews primarily involved results from only a few studies from the 1990s, predating DSM changes in symptoms and criteria for diagnosing anxiety and depression in children. Further, no articles were located investigating the prevalence of anxiety or depression in ADHD as a function of age, with the exception of a study of only 40 children with ADHD [19], which showed a nonsignificant relationship between age and

the presence of an internalizing disorder (without assessing anxiety and depression separately).

Our study is the first to analyze large samples of children with autism, ADHD-C, and ADHD-I to (1) determine the relationship between symptoms of anxiety (i.e., generalized, social, and separation), depression, low self-esteem, suicide ideation and attempts, and specific somatic complaints, (2) compare symptom frequencies between diagnostic groups (autism, ADHD-C, and ADHD-I), and (3) examine symptom frequencies relative to age. Diagnoses were based on comprehensive clinical evaluations considering all possible child psychiatric diagnoses. This is important because many children with autism are initially diagnosed with only ADHD without ruling in or out autism [29, 30]. Further, many prior studies failed to analyze ADHD-C and ADHD-I separately, which is critical because of differences in symptom profiles and comorbidity between the two subtypes.

METHOD

Sample

The study was approved by the Institutional Review Board, which waived informed consent because analyses were conducted retrospectively on existing clinical data. The sample comprised 2,492 children referred to a psychiatry diagnostic clinic, 1,436 with autism (with or without ADHD) and 1,056 with ADHD without autism. The children were 2-17 years of age (M = 7.4, SD = 3.2) with IQs ranging from 9 to 149 (M = 96.6, SD = 22.5). In all, 90.7% were white, 74.1% were male, 36.6% had a parent with a professional or managerial occupation, and 33.8% were treated with a psychotropic medication (most often a stimulant, antipsychotic, SSRI, and/or alpha agonist). Demographic data for each diagnostic group are reported in Table **1**.

All children underwent a diagnostic evaluation by a licensed PhD psychologist. The evaluation included a diagnostic interview with the parents, parent and teacher questionnaires and rating scales (Pediatric Behavior Scale, PBS) [31], review of educational records, administration of psychological tests (IQ, achievement, and neuropsychological), and clinical observations of the child during the evaluation. All children in the ADHD group had a DSM-IV or DSM-5 (whichever version was current when the child was evaluated) diagnosis of ADHD and fulfilled the following criteria: (1) symptoms of ADHD observed during

Table 1:   Demographic Data for Children with Autism, ADHD-C, and ADHD-I

	Autism $n = 1436$	ADHD-C $n = 747$	ADHD-I $n = 309$	F/χ^2	p	$\phi/M\,d$
Age (*M/SD*)	6.6/3.3	8.2/2.7	9.2/2.8	128.6	<.0001	.54
IQ (*M/SD*)	92.1/24.9	102.7/17.0	103.0/16.8	72.6	<.0001	.32
Male	79.0%	72.0%	56.3%	70.9	<.0001	.17
Parent occupation[1]	34.1%	36.7%	48.5%	23.0	<.0001	.10
White	90.6%	90.1%	92.9%	2.1	1.0	.03
On psychotropic medication	34.1%	38.9%	20.4%	33.5	<.0001	.12

[1]One or both parents have a professional or managerial position.

psychological testing and (2) ratings of short attention span or distractible as often or very often a problem on the PBS by at least two raters (mother, father, teacher). Children were classified with ADHD-C if the median mother, father, and teacher rating on the PBS impulsive and hyperactive items was often or very often a problem. Children were classified with ADHD-I if the median impulsive and hyperactive rating was less than often a problem.

Children in the autism sample had a DSM-IV or DSM-5 diagnosis of autism (i.e., autistic disorder, Asperger's disorder, or autism spectrum disorder) and a score in the autism range on the Checklist for Autism Spectrum Disorder (CASD) [32]. The CASD is a 30-item diagnostic measure normed and standardized on 2,469 children (1-18 years, IQs 9-146) with autism, other clinical disorders, and typical development [32]. In the national standardization study, the CASD identified children with and without autism with 99.5% accuracy. The CASD differentiates children with autism from children with intellectual disability, learning disability, traumatic brain injury, language disorder, ADHD, ODD, anxiety disorder, apraxia of speech, and reactive attachment disorder [32-35]. Concurrent validity is strong with high diagnostic agreement (93%-98%) between the CASD and the Childhood Autism Rating Scale, the Gilliam Asperger's Disorder Scale, and the Autism Diagnostic Interview-R [36, 37]. Children with autism who also had ADHD symptoms were only included in the autism sample. These children were not given an additional clinical diagnosis of ADHD if they were evaluated at the time of the DSM-IV because the DSM-IV did not permit an ADHD diagnosis with autism. In the autism sample, 79.5% had elevated (often or very often a problem) maternal ratings on the total ADHD subscale (ADHD-C) and 9.1% had elevated ratings on attention deficit but not on impulsivity/ hyperactivity (ADHD-I).

Instrument and Variables

The 165 items on the PBS were rated by mothers on a 4-point scale (0 = almost never or not at all, 1 = sometimes, 2 = often, and 3 = very often a problem). The PBS assesses multiple psychological problems including anxiety, depression, somatic complaints, oppositional behavior, conduct problems, irritability/anger, and ADHD. The PBS corresponds well with established measures of psychopathology [38, 39] and has been used to diagnose and differentiate psychological problems in several published studies [4, 34, 40-42]. The 25 PBS symptom scores analyzed in this study were generalized anxiety (anxious, worried, fearful), social anxiety (shy), separation anxiety (clings to adults, too dependent), sad and depressed, low self-confidence and self-esteem, feels worthless, feels guilty, apathetic, preoccupied with death, suicide ideation, suicide attempts, sluggish and lacks energy, tires easily, sleeps more than normal, sleeps less than normal, trouble falling asleep, wakes during the night, feels sick, headaches, stomachaches, other body aches and pains, eats too much, poor appetite, diarrhea, and constipated.

Data Analyses

Relationships between the 25 symptom raw scores were determined with exploratory factor analysis (principal axis factoring with an oblique rotation) and cluster analysis (Pearson correlation matrix). The study focused on single scores reflecting the primary symptoms of generalized anxiety disorder (i.e., worried, anxious, fearful), social anxiety (shy), separation anxiety (clingy, overly dependent), and depression (feels sad or depressed) and composite scores derived from factor analysis of the remaining internalizing and somatic symptoms. Differences in symptom and factor scores between the three diagnostic groups (autism, ADHD-C, and ADHD-I) were investigated with

ANCOVA, post hoc *t*-tests, and Cohen's *d.* Because of significant differences between diagnostic groups on most demographic variables and medication status (Table **1**), the significant variables were covaried in ANCOVA when comparing differences in symptom scores between diagnostic groups.

Linear relationships between age and symptom scores were determined using partial correlations and explained variance. Age was not significantly ($p > .01$) related to demographic variables in the autism, ADHD-C, and ADHD-I samples, including IQ ($r = .00 - .08$), sex ($t = 0.46 - 1.59$), race ($t = 0.5 - 2.7$), and parent occupation ($t = 0.3 - 2.5$). However, children prescribed psychotropic medication were older than children not treated with medication ($t = 3.37 - 17.8$, $p < .01$). Therefore, psychotropic medication status was controlled using partial correlations when correlating age and symptom scores. Symptom raw scores did not differ significantly between girls and boys within each diagnostic group ($t = 0.0 - 2.6$, $p > .05$), except that one of the 25 symptoms (poor appetite) was greater in boys than in girls in the autism sample only ($t = 4.5$) but the effect size was small ($d = 0.28$). Therefore, data for

girls and boys were combined in all analyses. All reported *p*-values are 2-tailed, and *p*-values were interpreted using a Bonferroni correction for the number of comparisons made.

RESULTS

Relationships between Symptom Scores

Exploratory factor analysis of the 25 symptom scores in the total sample yielded seven discrete factors (Table **2**): (1) anxiety (generalized, social, and separation anxiety), (2) depression (sad/depressed, low self-esteem and self-confidence, feels worthless, and feels guilty), (3) suicide ideation (preoccupied with death, suicide ideation, and suicide attempts), (4) fatigue (sluggish/lacks energy, tires easily, and sleeps more than normal), (5) sleep disturbance (sleeps less than normal, trouble falling asleep, and wakes during the night), (6) aches (feels sick, headaches, stomachaches, and other body aches), and (7) appetite disturbance (eats too much and poor appetite). Three symptoms (constipation, diarrhea, and apathy) had small factor loadings (.01 - .29) and were not included

Table 2:   Factor Loadings for the Total Sample (*N* = 2492)

	Factor						
	Anxiety	**Depression**	**Suicide ideation**	**Fatigue**	**Sleep disturbance**	**Aches**	**Appetite disturbance**
Generalized anxiety	.43						
Social anxiety	.66						
Separation anxiety	.66						
Sad, depressed		.40					
Low self-esteem		.77					
Feels worthless		.91					
Feels guilty		.67					
Preoccupied with death			.47				
Suicide ideation			.83				
Suicide attempt			.50				
Sluggish, lacks energy				.74			
Tires easily				.60			
Sleeps more than normal				.43			
Sleeps less than normal					.80		
Difficulty falling asleep					.72		
Wakes during the night					.63		
Feels sick						.72	
Stomachaches						.94	
Headaches						.52	
Other body aches						.49	
Eats too much							-.42
Poor appetite							.63

on any factor. Notably, factor cross-loading of the 25 symptoms was minimal, with values ranging from .01 - .26 and 90.9% (120/132) < .10.

For the total sample, inter-correlations between all symptom scores were positive, with the exceptions of negative relationships between poor appetite and eats too much and between sleeps less and sleeps more than normal. The three anxiety symptoms (generalized, social, and separation anxiety) were highly correlated with each other (r = .36 - .43, p < .0001). The correlation between sad/depressed and generalized anxiety was also medium to large (r = .42, p < .0001), whereas correlations between sad/depressed and social and separation anxiety were small to medium (r

= .22 and .20, p < .0001). Low self-esteem/feels worthless and guilty was strongly correlated with sad/depressed and with generalized anxiety (r = .57 and .46, p < .0001) and less so with social and separation anxiety (r = .23 and .21, p < .0001). Sad/depressed was more strongly correlated with suicide ideation (.36), preoccupation with death (.34), and suicide attempts (.20) than were the three anxiety symptoms (.01 - .19), with the exception of a correlation of .29 between preoccupation with death and generalized anxiety.

Correlations were small to medium between sleep disturbance and generalized anxiety, separation anxiety, and sad/depressed (r = .23, .23, and .20, p <
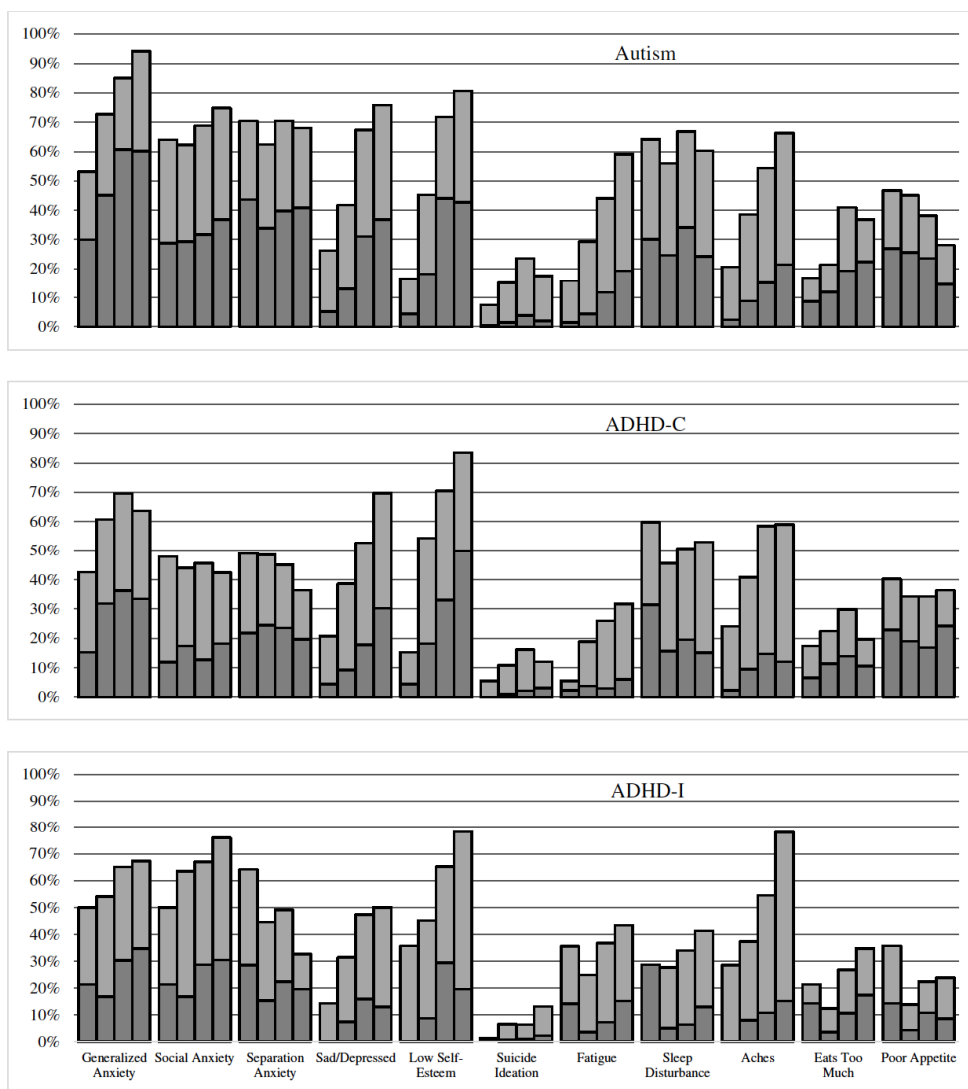

Figure 1: Frequency of Internalizing and Somatic Symptoms by Age in Children with Autism, ADHD-C, and ADHD-I.

Key: For each problem, the first column depicts 2-5 years, followed by 6-8 years, 9-12 years, and 13-17 years. For each bar, the darker portion represents often or very often a problem and the lighter part represents sometimes a problem. Note: For ADHD-I, 0% were rated as having suicide ideation sometimes or more in the 2-5 year group.

.0001), and small between sleep disturbance and social anxiety ($r = .10$, $p < .0001$). Generalized, social, and separation anxiety and sad/depressed had small correlations with sleeps more than normal ($r = .09 - .15$, $p < .0001$). The four somatic symptoms comprising the aches factor (feels sick, headache, stomachache, and other body aches) were highly inter-correlated (.42 - .66) and had medium correlations with sad/depressed (.29 - .34, $p < .0001$), slightly smaller correlations with generalized anxiety (.25 - .29, $p < .0001$), and negligible correlations with social and separation anxiety (.08 - .14, explaining less than 2% of the variance).

Symptom Frequencies by Diagnosis and Age

Mean symptom and factor scores for children with autism, ADHD-C, and ADHD-I by diagnostic and age groups are presented in Figure **1**. The symptom scores are ratings of the primary symptoms of generalized, social, and separation anxiety disorders (i.e., worry, shy, and clingy/overly dependent) and depression (i.e., sad/depressed). The remaining scores are composites ratings on the factors representing the other PBS internalizing and somatic symptoms.

Differences in Symptom Scores between Diagnostic Groups

Differences in symptom and factor scores between children with autism, ADHD-C, and ADHD-I (Table **3**)

were nonsignificant for: (1) low self-esteem, feels worthless, and feels guilty, (2) suicide ideation, suicide attempts, and preoccupation with death, (3) feels sick, headaches, stomachaches, and other body aches and pains, and (4) eats too much. All other symptom and factor scores were significantly higher for children with autism than for children with ADHD-C and/or ADHD-I. Differences between ADHD-C and ADHD-I were nonsignificant except that sleep disturbance was greater in ADHD-C than in ADHD-I and social anxiety was greater in ADHD-I than in ADHD-C.

Relationship between Symptom Scores and Age

In all three diagnostic groups, increasing age was significantly associated with increasing depression, low self-esteem, and aches, with correlations ranging from .20 to .43 explaining 4.0% - 18.5% of the variance (Table **4**). For children with autism only, increasing age was also related to increasing generalized anxiety and fatigue ($r = .24$ and .32, explained variance 5.8% and 10.2%). The remaining correlations in the three diagnostic groups were small, ranging from .02 to .18 (explained variance 0.0% - 3.2%).

DISCUSSION

Relationships between Symptom Scores

Factor analysis revealed seven distinct and clinically defensible factors without significant cross-loading. The

Table 3: Mean Symptom or Factor Scores[1] for Children with Autism, ADHD-C and ADHD-I

	Autism M (SD)	ADHD-C M (SD)	ADHD-I M (SD)	F (d≥.3)	post hoc[2]
Generalized anxiety	1.27 (1.08)	1.04 (1.02)	0.90 (0.90)	55.3(.4,.6)	A>C,I
Social anxiety	1.08 (1.01)	0.66 (0.87)	0.98 (0.92)	49.3(.4,.3)	A,I>C
Separation anxiety	1.27 (1.11)	0.81 (1.02)	0.71 (0.92)	42.7(.4,.5)	A>C,I
Sad, depressed	0.60 (0.84)	0.60 (0.81)	0.54 (0.78)	18.7(.3)	A>I
Low self-esteem[3]	0.66 (0.85)	0.90 (0.87)	0.82 (0.77)	4.10	NS
Suicide ideation[4]	0.17 (0.37)	0.16 (0.35)	0.10 (0.31)	8.9	NS
Fatigue[5]	0.36 (0.56)	0.27 (0.48)	0.41 (0.60)	25.3(.3)	A>C
Sleep disturbance[6]	1.01(0.91)	0.75 (0.82)	0.45 (0.60)	46.5(.3,.6,.3)	A>C>I
Aches[7]	0.38 (0.56)	0.51 (0.61)	0.52 (0.63)	0.3	NS
Eats too much	0.42 (0.85)	0.41 (0.83)	0.32 (0.70)	6.4	NS
Poor appetite	0.82 (1.09)	0.63 (0.98)	0.30 (0.68)	12.4(.3)	A>I

[1]0 = almost never or not at all, 1 = sometimes, 2 = often, 4 = very often a problem.
[2]Bonferroni *t*-test comparisons $p < .05$ and Cohen's $d \geq .3$ based on estimated marginal means, A = autism, C = ADHD-C, I = ADHD-I.
[3]Low self-esteem, feels worthless, feels guilty.
[4]Suicide ideation, attempts, preoccupation with death.
[5]Sluggish, tires easily, sleeps more than normal.
[6]Sleeps less than normal, difficulty falling asleep, wakes during the night.
[7]Feels sick, headaches, stomachaches, other body aches and pains.

Table 4:   Correlations between Age and Symptom or Factor Scores for Children with Autism, ADHD-C and ADHD-I

	Autism	ADHD-C	ADHD-I
Generalized anxiety	.24[1]	.08	.12
Social anxiety	.05	-.02	.11
Separation anxiety	-.05	-.05	-.03
Sad, depressed	.29[1]	.28[1]	.20[2]
Low self-esteem[3]	.43[1]	.36[1]	.26[1]
Suicide ideation[4]	.12[1]	.12	.03
Fatigue[5]	.32[1]	.17[1]	.16
Sleep disturbance[6]	-.09	-.08	.09
Aches[7]	.28[1]	.21[1]	.27[1]
Eats too much	.14[1]	.05	.18
Poor appetite	-.13[1]	-.05	.06

[1]$p < .0001$, [2]$p = .003$, all other correlations $p > .01$.
[3]Low self-esteem, feels worthless, feels guilty.
[4]Suicide ideation, attempts, preoccupation with death.
[5]Sluggish, tires easily, sleeps more than normal.
[6]Sleeps less than normal, difficulty falling asleep, wakes during the night.
[7]Feels sick, headaches, stomachaches, other body aches and pains.

factors depicted a strong relationship between the cardinal symptoms of the three anxiety disorders (generalized, social, and separation anxiety) as distinct from the depression factor (which included sad and depressed, poor self-concept, feels worthless, and feels guilty). Suicide ideation and attempts and preoccupation with death comprised a single factor separate from but moderately correlated with the depression factor. The remaining items comprised four somatic factors (fatigue, sleep disturbance, aches, and appetite disturbance).

Inter-correlations between all individual symptom scores were positive, indicating that all internalizing and somatic symptoms increased or decreased with each other. The only exceptions were expected negative relationships between poor appetite and eats too much and between sleeps less and sleeps more than normal. Although generalized, social, and separation anxiety were highly correlated with each other, their relationships with other symptoms revealed patterns that differed between the three anxiety symptoms. Generalized anxiety had a strong association with sad/depressed, whereas the association with sad/depressed was small for social and separation anxiety. Generalized anxiety and sad/depressed (unlike social and separation anxiety) were both strongly related to low self-esteem and were moderately correlated with aches and preoccupation with death. Unlike sad/depressed, however, generalized anxiety had small correlations with suicide

ideation and attempts. In contrast to children who are depressed, children with generalized anxiety may not have suicide ideation or attempts but may be preoccupied with death because they are worried about harm befalling themselves or others. Taken together, these findings suggest that generalized anxiety and feeling sad and depressed have a high risk of co-occurrence and share features, particularly low-self-esteem, that need to be considered in a clinical evaluation. Social and separation anxiety have a more specific focus than generalized anxiety and have less overlap with other internalizing or somatic symptoms. However, given the strong association between the three types of anxiety symptoms, all three should be assessed clinically and ruled in or out when symptoms of one are present.

Differences and Similarities in Symptom Scores between Diagnostic Groups

Previous research shows that children with autism and children with ADHD-C have similarly high levels of externalizing problems. Across studies, 51% to 68% of children with autism and children with ADHD-C met criteria for ODD [43-47]. For children with ADHD-I, the prevalence of ODD was far lower [41, 44, 48-51] and children with ADHD-I did not differ significantly from typical controls in maternal ratings of oppositional, aggressive, and explosive behavior [41]. In contrast to the pattern for externalizing problems, internalizing problems in our study were more common in autism than in both ADHD-C and ADHD-I and when present,

were more likely to be severe in autism compared to ADHD-C and ADHD-I. A previous study of children with normal intelligence showed that maternal anxiety ratings did not differ between children with autism and children without autism who had a primary anxiety disorder [4]. In our study, symptom scores for children with ADHD-C and children with ADHD-I did not differ significantly, except that sleep disturbance was greater in ADHD-C than in ADHD-I and social anxiety was greater in ADHD-I than in ADHD-C. These findings may be related to core symptom differences between the two ADHD subtypes, as children who are hyperactive have difficulty settling for sleep and children who are socially anxious are inhibited which may curb impulsivity and hyperactivity.

Remarkably, generalized anxiety (worried, fearful, and anxious) was often or very often a problem for 49% of children with autism and at least sometimes a problem for 76%. Additionally, social anxiety was often or very often a problem for 32% (68% at least sometimes), separation anxiety was often or very often a problem for 40% (68% at least sometimes), and sad and depressed was often or very often a problem for 22% (53% at least sometimes). Additionally, another study reported that unusual and irrational fears or phobias were present in 41% of children with autism [52]. Many of the reported fears were the same as those described by Kanner [53] when he introduced autism as a childhood diagnosis (including fear of vacuum cleaners, elevators, mechanical toys, and the wind), suggesting that specific fears have endured over time. Children with autism perceive, experience, and react to the world differently than children without autism. The higher levels of anxiety and depression in autism found in our study relative to children with ADHD may in part occur because children with autism are distressed by input or situations that other children can tolerate, such as change, activity interruptions, certain sounds, new foods, a child entering their personal space, or an object that is not in the right location [32]. This creates stress and anxiety for the child in these situations and in anticipation of such situations (e.g., fearing to go to school because there may be a fire drill or because of a noisy and crowded cafeteria). It is important to be aware of the very high prevalence of anxiety in autism because its presence increases degree of impairment and because anxiety is treatable, whereas the core symptoms of autism are not [19].

Although the prevalence of anxiety and depression was higher in autism than in ADHD-C and ADHD-I, more than half of children with ADHD-C and children with ADHD-I had generalized, social, and/or separation anxiety at least sometimes and these symptoms were often or very often a problem for approximately one-third. Depression was at least sometimes a problem for 45% with ADHD-C and 36% with ADHD-I and often or very often a problem for 15% and 9%, respectively. Further, the majority of children with autism, ADHD-C, and ADHD-I had low self-esteem at least sometimes (54%, 56%, and 56%), which was often or very often a problem for 27%, 26%, and 14%, respectively.

Sleep disturbance (i.e., difficulty falling and staying asleep and sleeping less than normal) was also sometimes or more a problem for the majority of children with autism and ADHD-C (62% and 52%) and for 33% with ADHD-I and was often or very often a problem for 28%, 20%, and 13%, respectively. In contrast, a minority of children with autism, ADHD-C, and ADHD-I had scores that were sometimes or more a problem on the remaining suicide ideation, fatigue, aches, and appetite disturbance factors.

Relationship between Symptom Scores and Age

In all three diagnostic groups, older age (controlling for psychotropic medication use which was more common in older children) was significantly associated with increasing sadness and depression; low self-esteem, feels worthless, and feels guilty; and aches (feels sick, headaches, stomachaches, and other body aches). The majority of children with autism, ADHD-C, and ADHD-I in the 13-17 year age group, were sad and depressed and had generalized anxiety, low self-esteem, and aches at least sometimes. Low self-esteem was remarkably high in the 13-17 year age group in children with autism, ADHD-C, and ADHD-I (81%, 83%, and 78% at least sometimes, 43%, 50%, and 20% often or very often, respectively).

For the autism sample only, increasing age was also related to increasing generalized anxiety and fatigue (i.e., sluggish, tires easily, and sleeps more than normal). Fatigue in children with autism may represent avoidant behavior. Both avoidant behavior and generalized anxiety may increase with age in autism because of increasing demands for peer interaction and participation in school and community activities. Correlations between age and the remaining symptoms (social and separation anxiety, suicide ideation or attempts and preoccupation with death, sleep disturbance, eating too much, and poor appetite) in children with autism, ADHD-C, and ADHD-I were all small.

None of the internalizing and somatic symptoms significantly decreased with age, and the frequency of most internalizing symptoms in children with autism, ADHD-C, and ADHD-I was higher in the 13-17 year age group than at younger ages, suggesting that internalizing symptoms do not decrease with age and, instead, become more prevalent. In the 13-17 year autism age group, 94% were worried, anxious, and fearful, 75% had social anxiety, 67% had separation anxiety, 76% were sad and depressed, and 81% had low self-esteem at least sometimes. Although anxiety and feeling sad and depressed were overall higher in autism than in ADHD-C and ADHD-I, significant percentages of children with ADHD-C and ADHD-I experienced anxiety and depression, which did not decrease with age. The majority of 13- to 17-year-olds with ADHD-C and ADHD-I at least sometimes had generalized anxiety (64% and 67%, respectively), sadness and depression (70% and 50%), and low self-esteem (83% and 78%), and 76% of children with ADHD-I had social anxiety.

Our study has several limitations. Symptom scores were based exclusively on maternal report, age analyses were cross-sectional and not longitudinal, and the samples were from a single clinical site. Therefore, study findings need to be replicated with other samples and should include longitudinal data and additional measures of internalizing problems reported by multiple informants. Although medication status was controlled in our statistical analyses, medication is a potentially confounding factor that needs to be investigated in future studies, particularly the influence of specific medications. Some psychotropic medications can disturb sleep (e.g., stimulants) and others can improve sleep (e.g., alpha agonists and antipsychotics). Psychotropic use also differs between diagnostic groups. For example, children with ADHD-I are less likely to be medicated than children with ADHD-C or children with autism [54].

CONCLUSIONS AND CLINICAL SIGNIFICANCE

Most children with autism have ADHD and many children with autism are initially diagnosed with only ADHD, making it imperative to assess both disorders in children presenting with symptoms of either. Given the high prevalence of generalized, social, and separation anxiety and depressive symptoms in ADHD-C, ADHD-I, and autism found in our study, clinicians should assess anxiety and depression when evaluating children presenting with symptoms of autism and/or ADHD. Further, the finding that these symptoms do not decline

with age and possibly increase, makes early identification and treatment critical. Moreover, children receiving a diagnosis of autism and/or ADHD at an early age should be monitored for the development of an internalizing disorder. Gillberg *et al*. [49] emphasize that clinicians providing ADHD services should not only have expertise in ADHD but also in other disorders, an assertion supported by results from our study. The same applies to clinicians providing autism services. Several evidence-based interventions are available to reduce anxiety and depression in children, including those with ADHD and with autism. These include treatment with medication such as an SSRI [55-59] and cognitive-behavior and exposure therapy [59-63]. The causes of anxiety and depression in autism and in ADHD may differ in some ways and may be related to the core symptoms of both disorders. For example, for children with autism it may be necessary to help the child cope with situations that cause anxiety (e.g., change or certain sensory experiences). For children with ADHD, research has shown that treating the ADHD symptoms with stimulant medication reduces anxiety and depression [64]. More research on diagnostic specific interventions is needed.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

FUNDING

None.

COMPLIANCE WITH ETHICAL STANDARDS

The study was approved by the Institutional Review Board, which waived informed consent because analyses were conducted retrospectively on existing clinical data.

REFERENCES

[1]   Barkley RA, DuPaul GJ, McMurray MB. Comprehensive evaluation of attention deficit disorder with and without hyperactivity as defined by research criteria. J Consulting Clin Psychol 1990; 58: 775-789.
      https://doi.org/10.1037/0022-006X.58.6.775

[2]   Elia J, Ambrosini P, Berrettini W. ADHD characteristics: I. Concurrent co-morbidity patterns in children and adolescents. Child Adolesc Psychiatry Mental Health 2008; 2: 1-15.
      https://doi.org/10.1186/1753-2000-2-15

[3]   Gross-Tsur V, Goldzweig G, Landau YE, Berger I, Shmueli D, Shalev RS. The impact of sex and subtypes on cognitive and psychosocial aspects of ADHD. Dev Med Child Neurol 2006; 48: 901-5.
      https://doi.org/10.1017/S0012162206001976

[4]   Mayes SD, Calhoun SL, Murray MJ, Ahuja M, Smith LA. Anxiety, depression, and irritability in children with autism relative to other neuropsychiatric disorders and typical development. Res Autism Spectrum Disord 2011; 5: 474-85. https://doi.org/10.1016/j.rasd.2010.06.012

[5]   Meinzer MC, Pettit JW, Viswesvaran C. The co-occurrence of attention-deficit/hyperactivity disorder and unipolar depression in children and adolescents: A meta-analytic review. Clin Psychol Rev 2014; 34: 595-607. https://doi.org/10.1016/j.cpr.2014.10.002

[6]   Bellini S. Social skill deficits and anxiety in high-functioning adolescents with autism spectrum disorders. Focus Autism Other Dev Disabil 2004; 19: 78-86. https://doi.org/10.1177/10883576040190020201

[7]   Gadow KD, DeVincent CJ, Pomeroy J, Azizian A. Comparison of DSM-IV symptoms in elementary school-age children with PDD versus clinic and community samples. Autism 2005; 9: 392-415. https://doi.org/10.1177/1362361305056079

[8]   Hurtig T, Kuusikko S, Mattila M-L, Haapsamo H, Ebeling H, Jussila K, *et al*. Multi-informant reports of psychiatric symptoms among high-functioning adolescents with Asperger syndrome or autism. Autism 2009; 13: 583-98. https://doi.org/10.1177/1362361309335719

[9]   Kim JA, Szatmari P, Bryson SE, Streiner DL, Wilson FJ. The prevalence of anxiety and mood problems among children with autism and Asperger syndrome. Autism 2000; 4: 117-32. https://doi.org/10.1177/1362361300004002002

[10]   Mazzone L, Postorino V, De Peppo L, Fatta L, Lucarelli V, Reale L, *et al*. Mood symptoms in children and adolescents with autism spectrum disorders. Res Develop Disabil 2013; 34: 3699-708. https://doi.org/10.1016/j.ridd.2013.07.034

[11]   Russell E, Sofronoff K. Anxiety and social worries in children with Asperger syndrome. Australian New Zealand J Psychiatry 2005; 39: 633-8. https://doi.org/10.1080/j.1440-1614.2005.01637.x

[12]   Van Steensel FJA, Bögels SM, Perrin S. Anxiety disorders in children and adolescents with autistic spectrum disorders: A meta-analysis. Clin Child Family Psychol Rev 2011; 14: 302-17. https://doi.org/10.1007/s10567-011-0097-0

[13]   Green J, Gilchrist A, Burton D, Cox A. Social and psychiatric functioning in adolescents with Asperger syndrome compared with conduct disorder. J Autism Dev Disord 2000; 30: 279-93. https://doi.org/10.1023/A:1005523232106

[14]   Leyfer OT, Folstein SE, Bacalman S, Davis NO, Dinh E, Morgan J, *et al*. Comorbid psychiatric disorders in children with autism: Interview development and rates of disorders. J Autism Dev Disord 2006; 36: 849-61. https://doi.org/10.1007/s10803-006-0123-0

[15]   Rosen TE, Mazefsky CA, Vasa RA, Lerner MD. Co-occurring psychiatric conditions in autism spectrum disorder. Internat Rev Psychiatry 2018; 30: 40-61. https://doi.org/10.1080/09540261.2018.1450229

[16]   Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry 2008; 47: 921-9. https://doi.org/10.1097/CHI.0b013e318179964f

[17]   Mitchison GM, Njardvik U. Prevalence and gender differences of ODD, anxiety, and depression in a sample of children with ADHD. J Attention Disord 2019; 23: 1339-45. https://doi.org/10.1177/1087054715608442

[18]   Buitelaar JK, Barton J, Danckaerts M, Friedrichs E, Gillberg C, Hazell PL, *et al*. A comparison of North American versus non-North American ADHD study populations. Eur Child Adolesc Psychiatry 2006; 15: 177-81. https://doi.org/10.1007/s00787-005-0523-2

[19]   Van Steensel FJA, Bögels SM, deBruin EI. Psychiatric comorbidity in children with autism spectrum disorders: A comparison with children with ADHD. J Child Family Studies 2013; 22: 368-76. https://doi.org/10.1007/s10826-012-9587-z

[20]   Costello EJ, Copeland W, Angold A. Trends in psychopathology across the adolescent years: What changes when children become adolescents, and when adolescents become adults? J Child Psychol Psychiatry 2011; 52: 1015-25. https://doi.org/10.1111/j.1469-7610.2011.02446.x

[21]   Reynolds CR, Richmond BO. Revised Children's Manifest Anxiety Scale-2 manual: Los Angeles: Western Psychological Services. 2012.

[22]   Ghaziuddin M, Weidmer-Mikhail E, Ghaziuddin N. Comorbidity of Asperger syndrome: A preliminary report. J Intellectual Disabil Res 1998; 42: 279-83. https://doi.org/10.1111/j.1365-2788.1998.tb01647.x

[23]   Brereton AV, Tonge BJ, Einfeld SL. Psychopathology in children and adolescents with autism compared to young people with intellectual disability. J Autism Dev Disord 2006; 36: 863-70. https://doi.org/10.1007/s10803-006-0125-y

[24]   Mayes SD, Calhoun SL, Murray MJ, Zahid J. Variables associated with anxiety and depression in children with autism. J Dev Physical Disabil 2011; 23: 325-37. https://doi.org/10.1007/s10882-011-9231-7

[25]   Vickerstaff S, Heriot S, Wong M, Lopes A, Dossetor D. Intellectual ability, self-perceived social competence, and depressive symptomatology in children with high-functioning autistic spectrum disorders. J Autism Dev Disord 2007; 37: 1647-64. https://doi.org/10.1007/s10803-006-0292-x

[26]   Weisbrot DM, Gadow KD, DeVincent CJ, Pomeroy J. The presentation of anxiety in children with pervasive developmental disorders. J Child Adolesc Psychopharmacol 2005; 15: 477-96. https://doi.org/10.1089/cap.2005.15.477

[27]   Mattila ML, Hurtig T, Haapsamo H, Jussila K, Kuusikko-Gauffin S, Kielinen M, *et al*. Comorbid psychiatric disorders associated with Asperger syndrome/high-functioning autism: A community- and clinic-based study. J Autism Dev Disord 2010; 40: 1080-93. https://doi.org/10.1007/s10803-010-0958-2

[28]   Achenbach TM, Edlebrock C. Manual for the Child Behavior Checklist Burlington, VT: University of Vermont. 1991.

[29]   Clark T, Feehan C, Tinline C, Vostanis P. Autistic symptoms in children with attention deficit-hyperactivity disorder. Eur Child Adolesc Psychiatry 1999; 8: 50-5. https://doi.org/10.1007/s007870050083

[30]   Miodovnik A, Harstad E, Sideridis G, Huntington N. Timing of the diagnosis of attention-deficit/hyperactivity disorder and autism spectrum disorder. Pediatrics 2015; 136: e830-e7. https://doi.org/10.1542/peds.2015-1502

[31]   Lindgren SD, Koeppl GK. Assessing child behavior problems in a medical setting: Development of the Pediatric Behavior Scale. Advances in behavioral assessment of children and families Greenwich, CT: JAI. 1987; pp. 57-90.

[32]   Mayes SD. Checklist for Autism Spectrum Disorder. Wood Dale, IL: Stoelting. 2012. https://doi.org/10.1037/t03996-000

[33]   Mayes SD, Calhoun SL, Waschbusch DA, Baweja R. Autism and reactive attachment/disinhibited social engagement disorders: Co-occurrence and differentiation. Clin Child Psychol Psychiatry 2017; 22: 620-31. https://doi.org/10.1177/1359104516678039

[34] Mayes SD, Calhoun SL, Mayes RD, Molitoris S. Autism and ADHD: Overlapping and discriminating symptoms. Res Autism Spectrum Disord 2012; 6: 277-85.
https://doi.org/10.1016/j.rasd.2011.05.009

[35] Tierney C, Mayes S, Lohs SR, Black A, Gisin E, Veglia M. How valid is the Checklist for Autism Spectrum Disorder when a child has apraxia of speech? J Dev Behav Pediatrics 2015; 36: 569-74.
https://doi.org/10.1097/DBP.0000000000000189

[36] Mayes SD, Calhoun SL, Murray MJ, Morrow JD, Yurich KKL, Mahr F, et al. Comparison of scores on the Checklist for Autism Spectrum Disorder, Childhood Autism Rating Scale (CARS), and Gilliam Asperger's Disorder Scale (GADS) for children with low functioning autism, high functioning autism or Asperger's disorder, ADHD, and typical development. J Autism Dev Disord 2009; 39: 1682-93.
https://doi.org/10.1007/s10803-009-0812-6

[37] Murray MJ, Mayes SD, Smith LA. Brief report: Excellent agreement between two brief autism scales (Checklist for Autism Spectrum Disorder and Social Responsiveness Scale) completed independently by parents and the Autism Diagnostic Interview-Revised. J Autism Dev Disord 2011; 41: 1586-90.
https://doi.org/10.1007/s10803-011-1178-0

[38] Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample: Prevalence and risk factors. Sleep 2009; 32: 731-6.
https://doi.org/10.1093/sleep/32.6.731

[39] Mayes SD, Gordon M, Calhoun SL, Bixler EO. Long-term temporal stability of measured inattention and impulsivity in typical and referred children. J Attention Disord 2014; 18: 23-30.
https://doi.org/10.1177/1087054712448961

[40] Conrad AL, Richman L, Lindgren S, Nopoulos P. Biological and environmental predictors of behavioral sequelae in children born preterm. Pediatrics 2010; 125: e83-9.
https://doi.org/10.1542/peds.2009-0634

[41] Mayes SD, Calhoun SL, Aggarwal R, Baker C, Mathapati S, Anderson R, et al. Explosive, oppositional, and aggressive behavior in children with autism compared to other clinical disorders and typical children. Res Autism Spectrum Disord 2012; 6: 1-10.
https://doi.org/10.1016/j.rasd.2011.08.001

[42] Waxmonsky JG, Mayes SD, Calhoun SL, Fernandez-Mendoza J, Waschbusch DA, Bixler EO. The association between disruptive mood dysregulation disorder symptoms and sleep problems in children with and without ADHD. Sleep Med 2017; 37: 180-6.
https://doi.org/10.1016/j.sleep.2017.02.006

[43] Biederman J, Faraone SV, Milberger S, Jetton JG, Chen L, Mick E, et al. Is childhood oppositional defiant disorder a precursor to adolescent conduct disorder? Findings from a four-year follow-up study of children with ADHD. J Am Acad Child Adolesc Psychiatry 1996; 35: 1193-204.
https://doi.org/10.1097/00004583-199609000-00017

[44] Faraone SV, Biederman J, Weber W, Russell RL. Psychiatric, neuropsychological, and psychosocial features of DSM-IV subtypes of attention-deficit/hyperactivity disorder: Results from a clinically referred sample. J Am Acad Child Adolesc Psychiatry 1998; 37: 185-93.
https://doi.org/10.1097/00004583-199802000-00011

[45] Efron D, Sciberras E. The diagnostic outcomes of children with suspected attention deficit hyperactivity disorder following multidisciplinary assessment. J Paediatrics Child Health 2010; 46: 392-7.
https://doi.org/10.1111/j.1440-1754.2010.01750.x

[46] King S, Waschbusch DA. Aggression in children with attention-deficit/hyperactivity disorder. Expert Rev Neurother 2010; 10: 1581-94.
https://doi.org/10.1586/ern.10.146

[47] Mayes SD, Waxmonsky J, Calhoun SL, Kokotovich C, Mathiowetz C, Baweja R. Disruptive mood dysregulation disorder (DMDD) symptoms in children with autism, ADHD, and neurotypical development and impact of co-occurring ODD, depression, and anxiety. Res Autism Spectrum Disord 2015; 18: 64-72.
https://doi.org/10.1016/j.rasd.2015.07.003

[48] Connor DF, Steeber J, McBurnett K. A review of attention-deficit/hyperactivity disorder complicated by symptoms of oppositional defiant disorder or conduct disorder. J Dev Behav Pediatrics 2010; 31: 427-40.
https://doi.org/10.1097/DBP.0b013e3181e121bd

[49] Gillberg C, Gillberg IC, Rasmussen P, Kadesjo B, Soderstrom H, Rastam M, et al. Co-existing disorders in ADHD - Implications for diagnosis and intervention. Eur Child Adolesc Psychiatry 2004; 13 Suppl 1: I80-92.
https://doi.org/10.1007/s00787-004-1008-4

[50] Milich R, Balentine AC, Lynam DR. ADHD combined type and ADHD predominantly inattentive type are distinct and unrelated disorders. Clin Psychol: Science Practice 2001; 8: 463-88.
https://doi.org/10.1093/clipsy.8.4.463

[51] Turgay A. Aggression and disruptive behavior disorders in children and adolescents. Expert Rev Neurotherapeutics 2004; 4: 623-32.
https://doi.org/10.1586/14737175.4.4.623

[52] Mayes SD, Calhoun SL, Aggarwal R, Baker C, Mathapati S, Molitoris S, et al. Unusual fears in children with autism. Res Autism Spectrum Disord 2013; 7: 151-8.
https://doi.org/10.1016/j.rasd.2012.08.002

[53] Kanner L. Autistic disturbances of affective contact. Nervous Child 1943; 2: 217-50.

[54] Mayes SD, Waxmonsky JG, Baweja R, Mattison RE, Memon H, Hameed U, et al. Symptom and demographic predictors of psychotropic medication use in ADHD and autism. Internat J Clin Psychiatry Mental Health 2019; 7: 10-20.
https://doi.org/10.12970/2310-8231.2019.07.03

[55] Coleman DM, Adams JB, Anderson AL, Frye RE. Rating of the effectiveness of 26 psychiatric and seizure medications for autism spectrum disorder: Results of a national survey. J Child Adolesc Psychopharmacol 2019; 29: 107-23.
https://doi.org/10.1089/cap.2018.0121

[56] Connolly SD, Bernstein GA. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry 2007; 46: 267-83.
https://doi.org/10.1097/01.chi.0000246070.23695.06

[57] Garland EJ, Kutcher S, Virani A, Elbe D. Update on the use of SSRIs and SNRIs with children and adolescents in clinical practice. J Canadian Acad Child Adolesc Psychiatry 2016; 25: 4-10.

[58] Pliszka SR. Psychiatric comorbidities in children with attention deficit hyperactivity disorder: Implications for management. Paediatr Drugs 2003; 5: 741-50.
https://doi.org/10.2165/00148581-200305110-00003

[59] Wang Z, Whiteside SPH, Sim L, Farah W, Morrow AS, Alsawas M, et al. Comparative effectiveness and safety of cognitive behavioral therapy and pharmacotherapy for childhood anxiety disorders: A systematic review and meta-analysis. JAMA Pediatrics 2017; 171: 1049-56.
https://doi.org/10.1001/jamapediatrics.2017.3036

[60] Banneyer KN, Bonin L, Price K, Goodman WK, Storch EA. Cognitive behavioral therapy for childhood anxiety disorders:

A review of recent advances. Current Psychiatry Reports 2018; 20: 65.
https://doi.org/10.1007/s11920-018-0924-9

[61] Higa-McMillan CK, Francis SE, Rith-Najarian L, Chorpita BF. Evidence base update: 50 years of research on treatment for child and adolescent anxiety. J Clin Child Adolesc Psychol 2016; 45: 91-113.
https://doi.org/10.1080/15374416.2015.1046177

[62] Oud M, Winter L, Vermeulen-Smit E, Bodden D, Nauta M, Stone L, *et al*. Effectiveness of CBT for children and adolescents with depression: A systematic review and meta-regression analysis. Eur Psychiatry 2019; 57: 33-45.
https://doi.org/10.1016/j.eurpsy.2018.12.008

[63] Ricciardi JN, Luiselli JK, Camare M. Shaping approach response intervention for specific phobia in a child with autism. J Applied Behav Analysis 2006; 39: 445-448.
https://doi.org/10.1901/jaba.2006.158-05

[64] MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry 1999; 56: 1073-86.
https://doi.org/10.1001/archpsyc.56.12.1073