

An exploration of concomitant psychiatric disorders in children with autism spectrum disorder

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ABSTRACT

Objective: We explored patterns of concomitant psychiatric disorders in a large sample of treatment-seeking children and adolescents with autism spectrum disorder (ASD).

Methods: Participants were 658 children with ASD (age 3–17 years; mean = 7.2 years) in one of six federally-funded multisite randomized clinical trials (RCT) between 1999 and 2014. All children were referred for hyperactivity or irritability. Study designs varied, but all used the Child and Adolescent Symptom Inventory or Early Childhood Inventory to assess Attention Deficit Hyperactivity Disorder (ADHD), Oppositional-Defiant Disorder (ODD), Conduct Disorder (CD), Anxiety Disorders, and Mood Disorders. In addition, several measures in common were used to assess demographic and clinical characteristics.

Results: Of the 658 children, 73% were Caucasian and 59% had an IQ >70. The rates of concomitant disorders across studies were: ADHD 81%, ODD 46%, CD 12%, any anxiety disorder 42%, and any mood disorder 8%. Two or more psychiatric disorders were identified in 66% of the sample. Of those who met criteria for ADHD, 50% also met criteria for ODD and 46% for any anxiety disorder. Associations between types of concomitant disorders and a number of demographic and clinical characteristics are presented.

Conclusion: In this well-characterized sample of treatment-seeking children with ASD, rates of concomitant psychiatric disorders were high and the presence of two or more co-occurring disorders was common. Findings highlight the importance of improving diagnostic practice in ASD and understanding possible mechanisms of comorbidity.

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1. Introduction

Autism spectrum disorder (ASD) is a group of heterogeneous childhood onset conditions characterized by social communication deficits, restricted interests and repetitive behaviors [1]. The estimated worldwide prevalence ranges from 6 to 14 per 1000 in children with a 4 to 5 fold higher rate in boys than girls [2]. Because ASD has an early onset and chronic course, many affected individuals require lifelong care [3]. The core features of ASD can cause substantial impairments that may be amplified by behavioral and emotional problems [4,5].

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These co-occurring problems are common complaints from parents of children with ASD and the focus of psychotropic medication and behavioral intervention in this population [6,7].

Concomitant psychiatric disorders are common in children with ASD [8–10]. In a sample of 109 children with autism spectrum disorders, Leyfer et al. [11] reported that 72% of the children (average age = 9 years; 68% IQ > 70) had at least one Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) Axis I disorder. The median number of co-occurring psychiatric disorders was three. Children in this study were consecutive cases recruited from longitudinal and neuroimaging studies, unselected for psychiatric problems. Using an epidemiological sample of 10 to 14-year olds with DSM-IV ASD ($N = 112$), Simonoff et al. [10] reported a 3-month prevalence of 70% for concomitant psychiatric disorders with 41% having had two or more diagnoses. The most common were Social Anxiety Disorder (29%), ODD (30%), and ADHD (28%). Brookman-Frazee et al. [12] reported that 92% of children with ASD ($N = 201$; mean age 9 years, range 4–14) receiving publicly funded mental health services in Southern California met criteria for another psychiatric disorder. The most frequently reported psychiatric disorders were ADHD (78%), ODD (58%), and Anxiety disorders (56%).

In contrast, a randomly selected community sample of 986 children and adolescents with intellectual disability from a Dutch province reported much lower 1-year prevalence rates, with only 41% of those screening positive for an ASD meeting criteria for any impairing DSM-IV diagnosis [13]. Therefore, although psychiatric disorders appear common in youth with ASD, the range and types of disorders common to this population merits further study. There is also a need to understand the demographic and clinical characteristics that are associated with these concomitant disorders.

The high likelihood of a second psychiatric disorder in children with one disorder is well established [14]. This observation raises questions about uncertainty of the boundaries between psychiatric diagnoses in children. The overlap and shared symptomatology across diagnostic categories is not unique to children and has led to growing interest in transdiagnostic constructs [15–17].

In this report, we explore rates, patterns, and correlates of concomitant psychiatric disorders in a large sample of well-characterized, treatment-seeking children with ASD who participated in one of six federally-funded, multisite RCTs. The children in all six studies were

recruited for disruptive behavior such as tantrums, aggression, self-injury, impulsive behavior or hyperactivity. We expected to find (a) high rates of concomitant psychiatric disorders, (b) higher rates of anxiety disorders in children with an IQ ≥ 70 , and (c) poorer response to the study intervention in children with more concomitant psychiatric disorders.

2. Methods

2.1. Participants

The sample of 658 children (585 males and 97 females, aged 3–17 years) with ASD was participants in one of six multisite RCT [18–23]. Table 1 shows key characteristics of the six studies, including treatment targets, entry criteria, and key outcome measures. All studies were approved by each site's institutional review board and written informed consent was obtained from parents or legal guardian prior to data collection. Participants were recruited from a number of sources across sites and studies, including schools, the internet, the radio, outpatient clinics, and word of mouth.

2.2. Procedure

An experienced multidisciplinary team conducted a pretreatment evaluation that included medical and developmental histories, as well as behavioral and diagnostic assessments. The diagnosis of ASD was based on the current version of the DSM at the time of the study [24,25]. In addition to clinical assessment, ASD diagnoses were supported by either the *Autism Diagnostic Interview-Revised* [26] or the *Autism Diagnostic Observation Schedule* [27]. The pretreatment assessment also included parent and clinician ratings (described below). Participants had to be healthy, meet study-specific symptom severity thresholds, and have a minimum mental age (e.g., receptive language ≥ 18 months). All drug studies required participants to be medication-free at baseline (with the exception of stable anticonvulsant treatment for seizure disorder). The parent training study [19] permitted children to be on psychotropic medication if stable with no planned changes for the duration of the six-month study.

Table 1
Key characteristics of the six multisite RCT.

Study	Aim	N	Age range	IQ evaluation	Treatment target	Outcome measures	Entry criteria	Primary finding
Aman et al. [18]	RIS alone vs. RIS + PT	124	4–14	ASB Leiter MSEL	Irritability	ABC-I HSQ CGI-I	ABC-I ≥ 18 CGI-S ≥ 4	RIS + PT > RIS
Bearss et al. [19]	PT vs PEP	180	3–6	MSEL	Irritability	ABC-I HSQ-ASD CGI-I	ABC-I ≥ 15 CGI-S ≥ 4	PT > PEP
Handen et al. [20]	ATX vs placebo and PT vs no PT	128	5–14	ASB MSEL	Hyperactivity and Inattention	CGI-I SNAP HSQ ABC	SNAP-IV M ≥ 1.5 CGI-S ≥ 4	ATX & PT > placebo
RUPP Autism Network [21]	RIS vs. Placebo	101	5–17	NR	Irritability	ABC-I CGI-I	ABC-I ≥ 18 CGI-S ≥ 4	RIS > placebo
RUPP Autism Network [22]	MPH vs. Placebo	72	5–17	SIT	Hyperactivity	ABC-H CGI-I	SNAP-IV ADHD ≥ 27 SNAP-IV H-I ≥ 10 CGI-S ≥ 4	MPH > placebo
Schahill et al. [23]	GUAN vs Placebo	62	5–14	ASB MSEL	Hyperactivity	ABC-H ADHD Rating Scale CGI-I	ABC-H ≥ 24 CGI-S ≥ 4	GUAN > placebo

Abbreviations: GUAN = guanfacine; MPH = methylphenidate; RIS = risperidone; PEP = parent education; PT = parent training; ASB = Abbreviated Stanford-Binet Intelligence Scales, fifth edition [37]; Leiter = Leiter International Performance Scale [38]; MSEL = Mullen Scale of Early Learning [39]; NR = not reported; SIT = Slosson Intelligence Test [40]; ABC-I = Aberrant Behavior Checklist-Irritability subscale; HSQ = Home Situation Questionnaire; CGI-I = Clinical Global Impression-Improvement; HSQ-ASD = Home situation Questionnaire-Autism Spectrum Disorder; CYBOCS-PDD = Children's Yale-Brown Obsessive-Compulsive Scale-Modified for Pervasive Developmental Disorders; RBS-R = Repetitive Behavior Scale-Revised; ABC-H = Aberrant Behavior Checklist-hyperactivity subscale; SNAP-IV ADHD = Swanson, Nolan, and Pelham-version IV ADHD subscale; SNAP-IV H/I = Swanson, Nolan, and Pelham-version IV Hyperactivity/Impulsivity subscale; M = mean.

2.3. Measures

2.3.1. Early Childhood Inventory (ECI)/Child and Adolescent Symptom Inventory (CASI)

The pretreatment assessment also included the ECI or CASI to screen for concomitant psychiatric conditions. These DSM-IV-referenced, parent-rated scales are designed to screen for child psychiatric disorders [28–31]. The ECI and CASI are identical except for minor differences based on age. Here we used the subscales for ADHD (18 items), ODD (8 items), CD (10 items for ECI and 15 items for CASI), major depressive disorder and dysthymia (11 items for ECI and 13 items for CASI), and ASD (12 items). The subscales for anxiety disorders (21 items for ECI and 20 items for CASI) included social phobia, generalized anxiety, and separation anxiety. We did not include specific phobia as it only includes one item. Previous studies have supported the validity of ECI and CASI subscales in children with ASD [32,33]. Items are rated 0 (never) to 3 (very often) and can be scored in two different ways: symptom severity (total of scores within diagnostic category) or symptom count (number of items rated 2 or 3 within category). In the current study, symptom counts that met or exceeded DSM-IV criteria were used to define a positive screen for each diagnostic category.

2.3.2. Aberrant Behavior Checklist (ABC)

The ABC is a 58-item parent rating comprised of five subscales: Irritability (tantrums, aggression, and self-injurious behaviors, 15 items); Social Withdrawal (response to others, initiation of interaction, 16 items); Stereotypy (mannerisms and repetitive movements, 7 items); Hyperactivity and noncompliance (16 items); and Inappropriate Speech (repetitive vocalizations, 4 items) [34]. Each item is rated 0 to 3 with higher scores indicating greater severity. Kaat et al. [35] provided evidence of validity and normative data for children with ASD.

2.3.3. Clinical Global Impression-Scale

The *Clinical Global Impression – Severity* (CGI-S) subscale is a 7-point scale ranging from 1 (normal) to 7 (among the most extremely ill patients) [36]. By convention, a score of 3 (Mild) was used to describe a child who met criteria for ASD without associated behavioral problems. A score of 4 (Moderate) was required for entry in all trials. Although the pre-treatment CGI-S score was weighted by the specific treatment target (e.g., irritability, hyperactivity), the evaluating clinician incorporated all available information to assign the score.

The *Clinical Global Impression-Improvement* (CGI-I) subscale is also a 7-point scale designed to measure overall change from baseline. Scores on the CGI-I range from 1 (Very Much Improved) through 4 (Unchanged) to 7 (Very Much Worse). In all six trials, scores of Much Improved or Very Much Improved defined positive treatment response. The CGI-I was rated by an independent evaluator, who was blind to treatment assignment. In this report, we used the CGI-I to classify treatment response at the end of the acute phase. The Handen et al. [20] study used separate CGIs for Hyperactivity/Inattention and Noncompliance, as this was a study for youth selected for ADHD. We used the CGI Hyperactivity/Inattention in this report.

2.4. Measures of intellectual functioning

Different tests were used across the studies to measure intellectual functioning. They included the *Stanford-Binet Intelligence Scales: Fifth edition* [37]; *Leiter International Performance Scale-Revised* [38], *Mullen Scales of Early Learning* [39], and *Slosson Intelligence Test* [40]. Because several different tests were used, children were classified as ≥ 70 or < 70 IQ.

2.5. Statistical methods

Each of the six data sets was examined for missing data across common measures. Minor differences in the documentation of demographic data (e.g., school placement) were resolved by consensus (LL, CMcC)

and by collapsing across levels to allow for aggregating data across studies. Descriptive statistics were calculated for all variables of interest and included means and standard deviations for continuous measures or counts and percentages for categorical data. The association of concomitant diagnoses was examined using generalized estimating equations (GEE) with a binomial distribution and a logit link [41]. The GEE approach was used to account for the correlation between participants nested within a study. Resulting association between diagnoses are presented as adjusted odds ratios with corresponding 95% confidence intervals.

The frequency of concomitant psychiatric disorders was compared across demographic and clinical subgroups using Chi-square tests. In analyses with the CGI-I, only children receiving the active treatment were included ($n = 478$). When a demographic or clinical variable was ordinal (e.g., CGI-Severity: Moderate, Marked, Severe), associations with diagnosis were tested using the Cochran Armitage test for trend. For continuous variables, such as ASD severity score and age, subjects were stratified by the median value of the sample (e.g., age ≤ 6 years vs > 6 years).

Uniform criteria were used to collapse ECI/CASI subscales for analyses. For example, the presence of any anxiety disorder was based on a positive screen for generalized anxiety, separation anxiety, or social anxiety. Similarly, the presence of any mood disorder was based on a positive screen for major depressive disorder or dysthymia. The presence of any mood or anxiety disorder was classified as *internalizing disorders*; and *externalizing disorders* comprised ADHD, ODD, or CD.

Statistical analyses were performed using SAS v. 9.4. Given the sample size and number of comparisons, statistical significance was assessed at the 0.01 level to control for false discovery rate.

3. Results

3.1. Demographics

Table 2 shows demographic and clinical characteristics of children with ASD and their caregivers. In all, 73.1% of children were non-

Table 2
Demographic and clinical characteristics of children with ASD.

Characteristics	N (%)
N = 658	
Age (years), mean \pm SD	7.2 \pm 2.6
Race	
Non-Hispanic White	481 (73.1%)
Non-Hispanic Black	65 (9.9%)
Asian	29 (4.4%)
Hispanic/Latino	54 (8.2%)
Other	29 (4.4%)
Maternal education ($n = 557$) ^a	
High school graduate or less	91 (16.3%)
Some college/trade school or 4 year degree	385 (69.1%)
Graduate or professional school	80 (14.4%)
Not in household	1 (0.2%)
Intelligence quotient ($n = 633$) ^b	
< 70	257 (40.6%)
≥ 70	376 (59.4%)
CGI-severity ($n = 656$) ^c	
Moderate (4)	199 (30.3%)
Marked (5)	327 (49.9%)
Severe or extreme (6 or 7)	130 (19.8%)
ABC, mean \pm SD	
Irritability ($n = 656$)	22.7 \pm 9.1
Social withdrawal ($n = 656$)	13.6 \pm 8.6
Stereotypic behavior ($n = 655$)	7.6 \pm 5.4
Hyperactivity/noncompliance ($n = 655$)	32.3 \pm 9.0
Inappropriate speech ($n = 654$)	5.9 \pm 3.5
CASI ASD total score ^d , mean \pm SD ($n = 654$)	20.6 \pm 7.3

CGI-improvement summarized only for patients receiving active study treatment.

^a RUPP [21] did not collect maternal education.

^b IQ not available in 25 subjects.

^c CGI not available in 2 subjects.

^d Summed score across 12 PDD items. Scores range 0–36.

Table 3
Rates of diagnosis in each study.

	RUPP [21] (n = 101)	RUPP [22] (n = 66)	Aman et al. [18] (n = 124)	Bearss et al. [19] (n = 177)	Scahill et al. [23] (n = 62)	Handen et al. [20] (n = 128)	Total (n = 658)
ADHD	72 (71.2%)	57 (86.4%)	105 (84.7%)	132 (74.6%)	59 (95.2%)	109 (85.1%)	534 (81.1%)
ADHD combined	44 (43.6%)	40 (60.6%)	79 (63.7%)	72 (40.7%)	34 (54.8%)	54 (42.2%)	323 (49.1%)
ADHD hyperactive	11 (10.9%)	5 (7.6%)	7 (1.1%)	38 (21.5%)	8 (12.9%)	9 (7.0%)	78 (11.9%)
ADHD inattentive	17 (16.8%)	12 (18.2%)	19 (15.3%)	22 (12.4%)	17 (27.4%)	46 (35.9%)	133 (20.2%)
ODD (n = 657)	42 (41.6%)	23 (35.4%)	78 (62.9%)	95 (53.7%)	20 (32.3%)	41 (32.0%)	299 (45.5%)
CD (n = 656)	19 (19.0%)	4 (6.2%)	27 (21.8%)	18 (10.2%)	4 (6.5%)	5 (3.9%)	77 (11.7%)
Any anxiety disorder (n = 657)	34 (33.7%)	30 (46.2%)	54 (43.6%)	71 (40.1%)	28 (45.3%)	58 (45.3%)	275 (41.9%)
Generalized	18 (17.8%)	19 (29.2%)	30 (24.2%)	35 (19.8%)	18 (29.0%)	40 (31.3%)	160 (24.4%)
Social	22 (21.8%)	11 (16.7%)	31 (25.0%)	27 (15.3%)	18 (29.0%)	32 (25.0%)	141 (21.4%)
Separation	9 (8.9%)	10 (15.2%)	21 (16.9%)	22 (12.4%)	10 (15.2%)	7 (5.5%)	74 (11.3%)
Any mood disorder	7 (6.9%)	4 (6.1%)	13 (10.5%)	19 (10.7%)	4 (6.5%)	2 (1.6%)	49 (7.5%)
Major depression	3 (3.0%)	1 (1.5%)	4 (3.2%)	7 (4.0%)	0 (0%)	1 (0.8%)	16 (2.4%)
Dysthymia	7 (6.9%)	4 (6.1%)	11 (8.9%)	19 (10.7%)	4 (6.5%)	1 (0.8%)	46 (7.0%)
Any externalizing disorder	75 (76.3%)	58 (89.2%)	116 (93.6%)	148 (83.6%)	59 (95.2%)	112 (87.5%)	568 (86.5%)
Any internalizing disorder	36 (35.6%)	31 (47.7%)	57 (46.0%)	78 (44.1%)	29 (46.8%)	59 (46.1%)	290 (44.1%)

Hispanic White and 59.4% had an IQ ≥ 70 . Altogether, 83.5% of mothers had attended some college/trade school.

3.2. Rates and patterns of concomitant disorders

Table 3 shows positive screen rates for all diagnostic categories. With a few exceptions, rates were quite consistent across studies. 81.2% of the total sample met criteria for any type of ADHD, with most children meeting criteria for the combined subtype (49.1%). Rates for ODD and any anxiety disorder were 45.5% and 41.9%, respectively. CD and any mood disorders occurred at 11.7% and 7.5%, respectively. As shown in Fig. 1, 66.1% of the sample had two or more concomitant psychiatric disorders. Fig. 2 depicts the diagnostic overlap in a proportional Venn Diagram for the three most frequently endorsed diagnostic categories

of ADHD, ODD, and any anxiety disorder. Among children who met criteria for ADHD only 28.1% did not meet criteria for ODD or an anxiety disorder. In the full sample, 24% met criteria for all three diagnostic categories.

Table 4a presents associations between ADHD and other diagnostic conditions. It shows significant associations with most categories. All adjusted odds ratios were above 2.0, with the exception of mood disorders. The odds ratios indicated that the odds of children with ADHD also having ODD were 2.7 times higher than children without ADHD. Similarly, the odds of having an internalizing disorder were 2.5 times higher in children with ADHD compared to those without ADHD. The odds of having CD were 3 times higher in children with ADHD compared to children without ADHD; however the p value = 0.025 and the confidence interval was quite large.

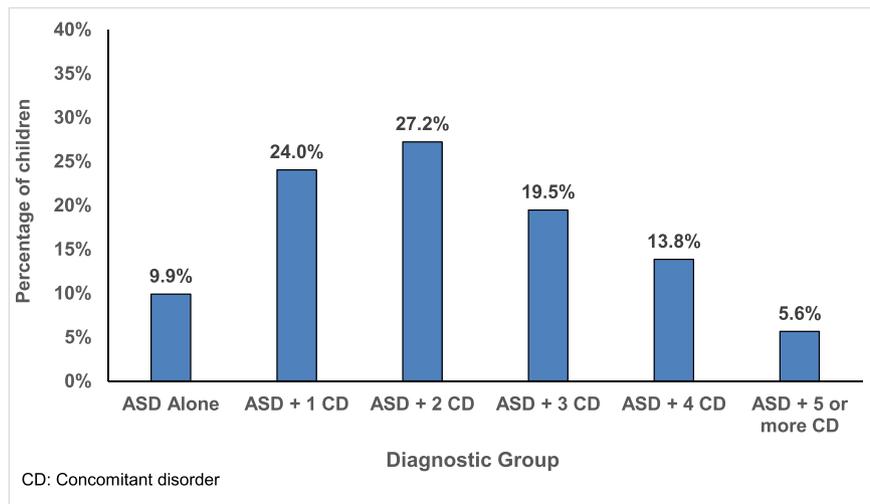


Fig. 1. Number of concomitant psychiatric diagnoses.

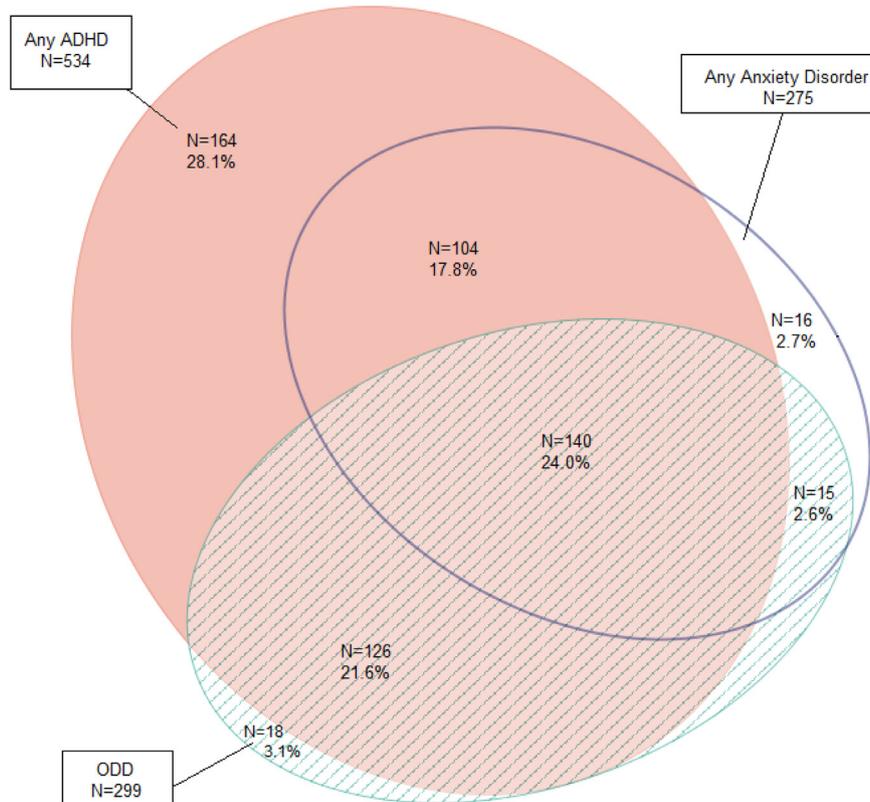


Fig. 2. Proportional Venn Diagram illustrating patterns of comorbidity.

Table 4b presents associations between anxiety disorders and other diagnostic conditions. All values are statistically significant ($p \leq 0.003$) with adjusted odds ratios > 2.0 . Odds of screening positive for an externalizing disorder were 4.2 times higher in children with an anxiety disorder compared to children without an anxiety disorder.

3.3. Demographic and clinical characteristics of participants with and without concomitant conditions

Tables 5a and 5b show demographic and clinical characteristics of children with ASD and at least one additional psychiatric disorder (note: groups are not mutually exclusive). Table 5a reveals no association between the presence of a concomitant disorder and sex. Children under the age of six years had higher rates of ODD (51.9% vs 41.1%, $p = 0.007$), but other significant associations with age were not observed. With the exception of CD and ADHD, children with a concomitant disorder and those with two or more disorders were significantly more common in children with $IQ \geq 70$.

Table 5b shows no association at the $p < 0.01$ level between diagnostic subtypes and CGI-S. Only one significant association emerged with CGI-I. Children who responded to study interventions were less likely to screen positive for ODD (37.6% positive responder vs 51.2% non-

responder, $p = 0.003$). Finally, children with more elevated ASD scores had higher rates of psychiatric problems in all categories, but only ADHD and externalizing disorders reached statistical significance at the $p < 0.01$ level.

4. Discussion

This is one of the largest studies of concomitant psychiatric disorders in children with ASD published to date. A unique aspect of the report is the well-characterized sample, with longitudinal data on treatment outcome. The findings suggest that boundaries of co-occurring DSM-defined disorders are blurry in this sample of children with ASD seeking treatment for disruptive behavior. The high frequency of multiple DSM-defined disorders has been reported in several studies of children with ASD using different methodologies [12,8–10].

The rates and patterns of probable concomitant psychiatric disorders observed in this sample were similar to those reported in children with ASD receiving publicly-funded mental health services [12]. The high rates of ODD and CD in children with ADHD have been observed in the general pediatric population and in children with ASD [14,10]. In the current sample of children with ASD, there was also a high co-occurrence of ADHD and anxiety disorders. Almost half (244 of 534)

Table 4a
Frequency of concomitant psychiatric diagnoses in children with and without ADHD^a.

	No ADHD (N = 123)	ADHD (N = 534)	Adjusted odds ratio (95% CI) ^b	p-Value
ODD	33 (26.8%)	266 (49.8%)	2.7 (1.66–4.43)	<0.001
CD	6 (4.9%)	71 (13.3%)	3.0 (1.15–7.83)	0.025
Anxiety disorder	31 (25.2%)	244 (45.7%)	2.5 (1.37–4.55)	0.003
Mood disorder	7 (5.7%)	42 (7.9%)	1.4 (0.76–2.69)	0.272
Internalizing disorder	33 (26.8%)	257 (48.1%)	2.5 (1.35–4.74)	0.004

^a Percents are percent of the column with the indicated diagnosis.
^b Adjusted for correlation of subjects nested within study.

Table 4b
Frequency of concomitant psychiatric diagnoses in children with and without an anxiety disorder.^a

	No anxiety disorder (N = 382)	Anxiety disorder (N = 275)	Adjusted odds ratio (95% CI) ^b	p-Value
Any ADHD	290 (75.9%)	244 (88.7%)	2.5 (1.37–4.55)	0.003
ODD	144 (37.7%)	155 (56.4%)	2.1 (1.39–3.28)	<0.001
CD	28 (7.4%)	49 (17.8%)	2.7 (2.13–3.51)	<0.001
Mood disorder	15 (3.9%)	34 (12.4%)	3.5 (2.47–4.82)	<0.001
Externalizing disorder	308 (80.6%)	260 (94.6%)	4.2 (1.86–9.34)	<0.001

^a Percents are percent of the column with the indicated diagnosis.

^b Adjusted for correlation of subjects nested within study.

of children with ADHD also screened positive for an anxiety disorder. The prevalence estimates for all anxiety disorders are likely understated because specific phobia was not included. The high co-occurrence of ADHD and anxiety disorders in youth with ASD was also observed by Brookman-Frazee et al. [12]. In the general pediatric population, by contrast, the review by Angold et al. [14] reported significantly lower co-occurrence of ADHD and anxiety disorders compared to the association between ADHD and ODD/CD. In their sample of 579 children with ADHD, the Multimodal Treatment Study of ADHD (MTA) observed a 34% rate of anxiety disorders (excluding specific phobia) [42]. This higher co-occurrence of ADHD and anxiety disorders in our sample of children with ASD compared to the general pediatric population may reflect the difficulties parents have in distinguishing between anxiety symptoms from ADHD symptoms such as restlessness, distractibility and disruptive behavior [43]. It may also speak to the shared etiology between disorders [44,45].

In the current sample, the rates of concomitant psychiatric disorders were higher in children with IQ ≥ 70 than children $< IQ 70$. This trend was not observed in studies by Simonoff et al. [10] or Brookman-Frazee et al. [12]. The difference across IQ groups in our sample is greatest in anxiety disorders. This is consistent with findings in a prior study in which CASI anxiety scores were significantly lower in children with IQ < 70 , presumably because the presence of language is a precondition for endorsing several anxiety items [46].

The presence of another psychiatric disorder did not drive the CGI-S ratings. For example, the rates of ADHD and anxiety disorders were similar across CGI-S ratings of Moderate, Marked or Severe. On the CGI-I, children with concomitant ODD were more likely to show a positive response. We note that these trials selected children with disruptive

behavior and ADHD. That higher levels of noncompliant and defiant behavior at baseline, the essence of ODD, predicted higher positive response rates is not surprising given that the study treatments were directed at these behaviors and selection criteria would have guaranteed substantial room for participants to show improvements. The rate of positive response was not influenced by any other diagnostic category. The minor difference in the rate of positive response for children with or without a mood disorder fell below our predetermined significance level. Even the presence of two or more concomitant disorders did not reduce the rate of positive response. In the MTA study, Jensen et al. [47] reported that the presence of multiple concomitant psychiatric disorders did affect outcome. Children with ADHD and multiple comorbid psychiatric disorders required combined mediation and behavioral intervention to respond optimally.

The results of this study raise fundamental questions about the meaning of concomitant psychiatric disorders in children with ASD. The introduction of DSM-III was an important milestone for criteria-driven categorical diagnosis. It has also sparked extensive debate whether the co-occurring conditions are separate or somehow etiologically related. In a condition such as ASD involving many aspects of everyday life, it may not be surprising that youth with ASD would exhibit behaviors that fall under various diagnostic categories. Whether the patterns of co-occurring psychiatric disorders in children with ASD observed in this study are distinct conditions or variable phenotypic manifestations of ASD cannot be resolved here. The aim of this study was to describe the patterns of concomitant disorders in children with ASD and to evaluate similarities and differences of identified subgroups. Further work on identifying subgroups of children with ASD using categorical diagnoses, dimensions of symptom severity or biological markers could lead to refinements in the psychopharmacological and behavioral interventions in ASD.

Our findings should be interpreted in light of several limitations. The children described in this report were participants in RCTs focused on either hyperactivity or disruptive behavior such as tantrums, aggression and self-injury. The findings may not apply to all children with ASD. Indeed, RCTs are often criticized for neglecting external validity in favor of internal validity [48]. The concern is that over emphasis on internal validity leads to narrow entry criteria and limited generalizability. Despite the imposition of relatively strict entry criteria, however, the participants in these multisite studies appear to resemble the complex cases seen in clinic. In addition, study participants were enrolled from 11 cities in the US, which also supports the generalizability of the results. When this limitation on generalizability is appreciated, such a clinical

Table 5a
Demographic characteristics of children with ASD by concomitant diagnostic condition.^{a,b}

Co-occurring disorder group	Sex			Age			IQ		
	Male (N = 563)	Female (N = 94)	p-Value	≤ 6 year (N = 268)	> 6 years (N = 390)	p-Value	< 70 (N = 257)	≥ 70 (N = 376)	p-Value
ADHD	464 (82.3%)	70 (74.5%)	0.073	212 (79.1%)	322 (82.6%)	0.265	203 (79.0%)	311 (82.7%)	0.239
ODD	260 (46.2%)	39 (41.5%)	0.398	139 (51.9%)	160 (41.1%)	0.007 [*]	96 (37.4%)	195 (51.9%)	<0.001 [*]
CD	64 (11.4%)	13 (13.8%)	0.496	35 (13.1%)	42 (10.8%)	0.366	35 (13.6%)	40 (10.7%)	0.260
Any anxiety disorder	237 (42.1%)	38 (40.4%)	0.761	103 (38.4%)	172 (44.2%)	0.140	82 (31.9%)	188 (50.0%)	<0.001 [*]
Any mood disorder	42 (7.5%)	7 (7.5%)	1.00	23 (8.6%)	26 (6.7%)	0.358	10 (3.9%)	35 (9.3%)	0.009 [*]
Internalizing disorder	249 (44.2%)	41 (43.6%)	0.912	111 (41.4%)	179 (46.0%)	0.244	85 (33.1%)	197 (52.4%)	<0.001 [*]
Externalizing disorder	492 (87.4%)	76 (80.9%)	0.086	232 (86.6%)	336 (86.4%)	0.944	212 (82.5%)	336 (89.4%)	0.013 [*]
≥ 2 additional disorders [*]	373 (66.1%)	62 (66.0%)	0.973	180 (67.2%)	255 (65.4%)	0.636	148 (57.6%)	276 (73.4%)	<0.001 [*]

^{*} $p < 0.01$.

^a Groups are not mutually exclusive.

^b Percents are percent of the column with the indicated diagnosis.

Table 5b
Clinical characteristics of children with ASD by concomitant condition.^{a,b}

Co-occurring disorder group	CGI-severity				ASD score			CGI-improvement (N = 478)		
	Moderate (N = 199)	Marked (N = 327)	Severe (N = 129)	p-Value ^c	≤20 (N = 333)	>20 (N = 321)	p-Value	Non response (N = 189)	Positive responder (N = 289)	p-Value
ADHD	161 (80.9%)	262 (80.1%)	109 (83.9%)	0.573	255 (76.6%)	277 (86.3%)	0.001 [*]	157 (83.1%)	232 (80.3%)	0.443
ODD	84 (42.2%)	144 (44.0%)	69 (53.5%)	0.060	146 (43.8%)	153 (47.7%)	0.327	71 (37.6%)	148 (51.2%)	0.003 [*]
CD	20 (10.1%)	33 (10.1%)	24 (18.6%)	0.035	30 (9.0%)	47 (14.7%)	0.025	24 (12.8%)	31 (10.7%)	0.496
Any anxiety disorder	80 (40.2%)	140 (42.8%)	55 (42.6%)	0.619	124 (37.2%)	150 (46.7%)	0.014	80 (42.3%)	120 (41.5%)	0.861
Any mood disorder	20 (10.1%)	24 (7.3%)	5 (3.9%)	0.037	19 (5.7%)	30 (9.4%)	0.077	9 (4.8%)	28 (9.7%)	0.049
Internalizing disorder	84 (42.4%)	149 (45.6%)	57 (44.2%)	0.654	132 (39.6%)	157 (48.9%)	0.017	85 (45.0%)	126 (43.6%)	0.767
Externalizing disorder	173 (86.9%)	277 (84.7%)	116 (89.9%)	0.570	276 (82.9%)	290 (90.3%)	0.005 [*]	165 (87.3%)	252 (87.2%)	0.973
At least 2 additional dx [*]	127 (63.8%)	217 (66.4%)	89 (68.5%)	0.375	206 (61.9%)	228 (71.0%)	0.013	126 (66.7%)	198 (68.5%)	0.673

^{*} $p < 0.01$.

^a Groups are not mutually exclusive.

^b Percents are percent of the column with the indicated diagnosis.

^c Test for trend; Treating CGI as an ordinal outcome.

sample can be very informative if the target group we wish to generalize to is similar.

Another limitation is the high reliance on parents as informants. Parental biases in reporting may have contributed to the blurring of boundaries between disorders and enhanced the identification of concomitant disorders. There might also be misinterpretation by raters of core features of ASD as psychiatric symptoms. Relatedly, diagnoses were based solely on caregiver-completed CASI/ECI symptom count cutoff scores, which do not include consideration of impairment, differential diagnosis, or multiple sources of information. Therefore, rates may differ to estimates of “caseness” based on alternative evaluative strategies. Finally, our analysis focused on DSM categories. We did not delve into transdiagnostic approaches or research domain criteria, both of which warrant further research in children with ASD. Of course, clinical and research realities necessitate both categorical and dimensional approaches. Categories have dimensions, and dimensions become categories when cutoffs are used.

4.1. Conclusions and clinical implications

These data on treatment-seeking children with ASD show that psychiatric problems often occur in multiples. It is further evidence of heterogeneity of clinical presentation in ASD and the need to individualize treatment based on specific pattern of clinical manifestations. Diagnostic assessments of children with suspected ASD also need to be broad-based and include careful screening for internalizing disorders given their substantial presence in ASD. As treatments for the core deficits of ASD are examined, their effects on co-morbid symptomatology should also be carefully assessed. Lastly, comprehensive early intervention programs should be aware of the importance of future psychiatric comorbidity, and consider preventative interventions attempting to reduce the emergence of later psychopathology.

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