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Psychiatric Comorbidity and Functioning in a Clinically Referred Population of Adults with Autism Spectrum Disorders: A Comparative Study

Gagan Joshi · Janet Wozniak · Carter Petty · Mary Kate Martelon · Ronna Fried · Anela Bolfek · Amelia Kotte · Jonathan Stevens · Stephannie L. Furtak · Michelle Bourgeois · Janet Caruso · Ashley Caron · Joseph Biederman

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Abstract To systematically examine the patterns of psychiatric comorbidity and functioning in clinically referred adults with autism spectrum disorders (ASD). Psychiatrically referred adults with and without ASD were compared on measures assessing for psychiatric comorbidity and psychosocial functioning. Sixty-three adults with ASD participated in the study (mean age: 29 ± 11 years). Adults with ASD in their lifetime suffered from a higher burden of psychiatric disorders (6 ± 3.4 vs. 3.5 ± 2.7; $p < 0.001$) including major depressive disorder and multiple anxiety disorders, and were functionally more impaired with a significant proportion having received both counseling and pharmacotherapy. Adults with ASD have high levels of psychiatric comorbidity and dysfunction comparable to a clinically referred population of adults without ASD.

G. Joshi (✉) · J. Wozniak · C. Petty · M. K. Martelon · R. Fried · A. Bolfek · A. Kotte · J. Stevens · S. L. Furtak · M. Bourgeois · J. Caruso · A. Caron · J. Biederman
Clinical and Research Program in Pediatric Psychopharmacology, Massachusetts General Hospital, YAW 6900, 55 Fruit Street, Boston, MA 02114, USA
e-mail: joshi.gagan@mgh.harvard.edu

G. Joshi · J. Wozniak · R. Fried · A. Bolfek · A. Kotte · J. Stevens · J. Biederman
Harvard Medical School, Boston, MA, USA

Present Address:
C. Petty
Boston Children's Hospital, Boston, MA, USA

Present Address:
J. Stevens
Department of Child Psychiatry, North Shore Medical Center, Salem, MA, USA

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Introduction

Autism spectrum disorders (ASD) are characterized by a variable presentation of problems with socialization, communication, and behavior, and are estimated to affect more than 1 % of children and adolescents in the general population (*Diagnostic and Statistical Manual of Mental Disorders* 1994; Kogan et al. 2009). Although ASD is well characterized in pediatric populations (Joshi et al. 2010; de Bruin et al. 2007; Wozniak et al. 1997; Simonoff et al. 2008), the prevalence and clinical characteristics of this lifelong disorder remain understudied in adult populations. Moreover, despite the fact that youth with ASD suffer from high rates of various psychiatric disorders (Joshi et al. 2010; de Bruin et al. 2007; Wozniak et al. 1997; Leyfer et al. 2006), there is a lack of empirical evidence on the prevalence of psychiatric conditions in adult populations with ASD.

Adults with ASD seek psychiatric referral and are often prescribed psychotropic medications (Tsakanikos et al. 2006) for disabling psychiatric symptoms (Kobayashi and Murata 1998; Russell et al. 2005; Blacher and McIntyre 2006; Kanne et al. 2009) that are highly suggestive of psychiatric disorders. The presence of psychiatric comorbidity further worsens the morbidity of the already compromised course of ASD (Wozniak et al. 1997; Billstedt et al. 2005) and is more likely to interfere with critical efforts at psychosocial rehabilitation. Moreover, while there is no established pharmacological treatment for ASD per se, there are well-known evidence-based pharmacotherapies for many of the psychiatric disorders afflicting adults with ASD. Subjects with ASD are generally excluded from drug trials for the

treatment of major psychiatric disorders despite evidence that their psychopharmacological responses may be atypical (Handen et al. 2000; McCracken et al. 2002; Research Units on Pediatric Psychopharmacology (RUPP) AutismNetwork 2005; Posey et al. 2006). The under-recognition of psychiatric comorbidity in ASD populations further limits research initiatives assessing interventions for comorbid psychiatric disorders. Delineating the psychiatric conditions can lead to an improved understanding of the range and magnitude of comorbid psychiatric disorders associated with ASD and will thus facilitate disorder-specific therapeutic interventions in this highly compromised population.

An emerging literature on this topic suggests the presence of various psychiatric disorders in adults with ASD who seek treatment in specialty clinics for ASD (Russell et al. 2005; Ghaziuddin and Zafar 2008; Ghaziuddin et al. 1998; Lugnegard et al. 2011). However, the available literature on psychiatrically referred populations is limited to two studies that describe major mood, anxiety, and psychotic spectrum disorders among adults with ASD on unstandardized diagnostic assessments (Ryden and Bejerot 2008; Tsakanikos et al. 2006).

Thus, in order to further clarify the frequency and scope of psychiatric comorbidity and functioning in a referred population of adults with ASD, this study examined the prevalence of comorbid psychiatric disorders assessed with structured diagnostic interviews in a consecutively referred population of adults attending a specialty clinic for ASD. Based on the literature, we hypothesized that the scope and magnitude of psychiatric comorbidity in adults with ASD would be substantial, clinically relevant, and comparable to that seen in clinically referred adults without ASD. To the best of our knowledge, this is the first comparative study evaluating psychiatric comorbidity and functioning in adults with and without ASD.

Methods

Subjects

Autism spectrum disorders participants were derived from consecutive referrals to a specialized ambulatory program for autism spectrum disorders at a university hospital from October 2007 to March 2012. Individuals of all ages with either a presumptive or established diagnosis of ASD were referred to this ASD clinic for the management of behavioral and emotional difficulties. Source of referral was either self or clinics and agencies that provide services for ASD. Age- and sex-matched psychiatric comparison subjects were derived from consecutive referrals to a general psychopharmacology program at a major academic center from 1992 to 1998. All adults were referred for psychiatric care. This psychiatric control sample is ''unselected,'' as adults were referred for psychiatric evaluation and psychopharmacological intervention for behavioral and emotional difficulties and not for evaluation of any specific disorder. In both the ASD and psychiatric control samples, there was no selection bias based on social class or insurance restrictions. This study received institutional review board approval to review, analyze, and report anonymously on these subjects.

Assessment Measures

All ASD participants, derived from the ASD clinic, received a neuropsychological assessment, a structured diagnostic interview, and a psychiatric interview. A primary caretaker (if available) also completed a structured diagnostic interview. The diagnosis of ASD was established by a board-certified psychiatrist experienced in evaluating ASD and comorbid psychiatric disorders (GJ). The detailed psychiatric diagnostic interview was conducted in two sessions of an hour each with the subject and significant other or caretaker (usually a parent), if available, and also incorporated information from multiple sources when available (e.g., psychiatric records, schools, social services). The entire assessment procedure took 8–10 h to complete, and was carried out over multiple sessions for each patient.

Diagnostic assessment of ASD required a lifelong severe and pervasive deficit in the development of reciprocal social interaction and social communication, and development of restricted patterns of behavior. ASD diagnosis was clinically established (based on all available information) when DSM-IV diagnostic criteria were met for autistic disorder, Asperger's disorder, or pervasive developmental disorders not otherwise specified (PDD-NOS). A diagnosis of PDD-NOS was considered when DSM-IV diagnostic criteria for autistic disorder and Asperger's disorder were not met and the participant had either: (1) more than one deficit in social interaction that included impaired non-verbal communication or (2) a deficit in social interaction and either ritualistic behaviors or a deficit in social communication.

All adults with ASD were evaluated by administering the Structured Clinical Interview for DSM-IV (SCID) (supplemented with modules of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version to assess childhood diagnoses) (First et al. 1996; Orvaschel 1994). Although there are no established instruments for the assessment of psychiatric comorbidity in individuals with ASD, the authors chose this instrument based on their extensive experience in the clinic and with research referred psychiatric populations including ASD. The SCID was administered to the patients themselves as well as to a parent/guardian when available, usually the subject's mother. The structured diagnostic interviews provided the clinician

with a comprehensive and systematic anamnesis of current and lifetime pathology according to the DSM-IV criteria (*Diagnostic and Statistical Manual of Mental Disorders* 1994), which served as a diagnostic screen and a clinical aid for psychiatric evaluation. We combined data from both the direct and indirect structured diagnostic interviews by considering a diagnostic criterion positive if it was endorsed in either interview.

The adult psychiatric control population was screened for ASD by the DSM-III-R diagnostic criteria-based structured interview, which was added as an ASD diagnostic module to the SCID. Using this interview, ASD was defined as subjects meeting DSM-III-R criteria for autistic disorder or PDD-NOS. To be given the diagnosis of autistic disorder, the participant had to meet DSM-III-R diagnostic criteria of eight out of sixteen symptoms, with at least two symptoms from each of the three aforementioned domains of PDD. A diagnosis of PDD-NOS was received if more than two of the required symptoms were met with symptom(s) present from each of the three domains of PDD.

The inter-rater reliability of this ASD module was established by having an independent rater with expertise in the diagnosis of PDD listen to audiotapes of 20 randomly selected modules with or without a diagnosis of PDD (GJ). Based on these audiotapes, the reliability with the rater was kappa = 0.90. The reliability between our independent rater and the final diagnostic rating made by a clinician–reviewer was kappa = 0.88. The psychometric validity of the PDD module was examined by comparing the PDD module interview-generated diagnoses with the clinical diagnoses of ASD and the Social Responsiveness Scale (SRS) scores. Excellent sensitivity of the PDD module was observed for the clinical diagnosis of ASD (94 %) and for the SRS positive screen (t score $\geq$ 60; 96 %).

All assessments were conducted by highly trained and closely supervised psychometricians with bachelor's or master's degrees in psychology or a related field. We computed kappa coefficients of agreement for diagnostic coding by having board certified child and adult psychiatrists and licensed clinical psychologists diagnose subjects from audiotaped interviews. Based on 500 assessments from interviews drawn from a large sample of psychiatry clinic-based children and adults, the median kappa coefficient was 0.98.

The interviewers were blind to the a priori information regarding the participant's specific complaints, clinical diagnosis, or referral status. Diagnoses were considered positive by the interviewers if, on the basis of interview results, full DSM-IV criteria (including clinical impairment) were met unequivocally. To resolve diagnostic uncertainties, all interviews were reviewed by a committee of board-certified child and adult psychiatrists who were blind to the subject's referral source, diagnostic status, and all other non-diagnostic data (e.g., socioeconomic status, family and social functioning). The items endorsed during the interview along with detailed notes taken by the interviewer were reviewed to yield a best estimate diagnosis (Leckman et al. 1982). Diagnoses presented for review were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered *clinically meaningful*. By "clinically meaningful," we mean that the data collected from the structured interview indicated that the diagnosis should be a clinical concern due to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture. A key point is that these diagnoses were made as part of the clinical assessment procedures for our clinic; they were not simply research diagnoses computed by counting symptoms endorsed and applying an algorithm. We estimated the reliability of the diagnostic review process by computing kappa coefficients of agreement for clinician reviewers. The median reliability between individual clinician diagnoses and the review committee diagnoses was 0.87.

Although per DSM-IV criteria, certain disorders are exclusionary in the presence of PDD [e.g., attention-deficit hyperactivity disorder (ADHD), separation anxiety disorder, social phobia, overanxious disorder/generalized anxiety disorder (GAD)], we opted for a nonhierarchical approach for diagnostic endorsements which required meeting full DSM-IV symptom and impairment criteria as the basis for diagnosis. The rationale for this was to allow empirical examination of all disorders in an effort to fully characterize the clinical picture of the subjects. Furthermore, since anxiety disorders comprise many syndromes with a wide range of severity, we used two or more anxiety disorders to indicate the presence of a clinically meaningful anxiety syndrome and refer to this as "multiple anxiety disorders."

Interviewers also rated overall adaptive functioning using the DSM-IV global assessment of functioning scale (GAF; 0 = worst to 100 = best) (Endicott et al. 1976). To evaluate school functioning, three indices of school difficulties were used: placement in special classes, extra tutoring, and repeated grades. Treatment histories included rates of counseling, pharmacotherapy, and hospitalization. Socioeconomic status was established by using categories delineated by Hollingshead (1975).

Full-scale intelligence quotient (IQ) of the study participants was assessed with the Vocabulary and Matrix subsets of Wechsler Abbreviated Scale of Intelligence (Wechsler 1999).

Statistical Analysis

We excluded our analysis to adult patients that consented to participating, completed psychiatric clinical and structured

diagnostic interviews, and had an available IQ. Therefore, from the pool of 479 clinic subjects with the diagnosis of ASD referred during the index period (October 2007–March 2012), 163 (34 %) were adults (≥18 years of age), 102 gave consent, 89 completed the clinical and structured diagnostic interviews, and among those, 63 had an available IQ.

Each ASD subject (N = 63) was paired with an age- and sex-matched non-ASD subject from a pool of 491 adult clinic subjects without ASD. In the event of multiple qualifying matches, a non-ASD subject whose interview was in close temporal proximity to the interview of the ASD subject was chosen as a match, as determined by the sequential identification numbers assigned in the consecutive referrals. Analyses were conducted using Stata Version 12.0 (StataCorp 2011). Comparisons were made using McNemar's Chi-squared test, paired *t* tests, and Wilcoxon's matched-pairs signed-ranks test depending on the distribution of the outcome variable. We compared ASD to non-ASD subjects using Holm's sequential Bonferroni method for each set of analyses (excluding demographic information) to correct for multiple testing (Holm 1979).

Results

Demographics

Among the pool of 670 individuals referred to the ASD clinic, diagnosis of ASD was clinically established in 479 subjects, of whom 163 (34 %) were adults (18 years and older). Information on the structured diagnostic interview was available for 89/102 adults who provided consent. IQ information was available for 63/89 (71 %) adults with the following ASD diagnoses: autistic disorder (41/63; 65 %), Asperger's disorder (16/63; 25 %), or PDD-NOS (6/63; 10 %). Ninety-seven percent of these ASD adults (61/63) had IQ > 70 and 84 % (53/63) had intact intellectual capacity (IQ > 85). At referral, 84 % of the adults with ASD were single and 49 % were unemployed (Table 1, Fig. 1).

Psychiatric Comorbidities

The ASD group had a significantly higher number of lifetime comorbidities (6 ± 3.4 vs. 3.5 ± 2.7; $p < 0.001$) and current comorbidities (3 ± 2.3 vs. 1.5 ± 1.6; $p < 0.001$) compared to the non-ASD group. Overall the specific rates of current and lifetime psychiatric conditions were consistent between ASD and non-ASD groups. The ASD group had higher rates of lifetime comorbidity with major depressive disorder (MDD) and multiple (≥2) anxiety disorders [≥ 2ADs; agoraphobia, obsessive–compulsive disorder (OCD), and social phobia] (Table 2, Fig. 2).

Psychosocial Functioning and Treatment History

The ASD group had significantly more impaired lifetime and current GAF scores compared to the non-ASD group (Table 1). The ASD group was also significantly more likely to have been in a special class and required extra tutoring compared to the non-ASD group. The ASD group was significantly more likely to have received combined counseling and pharmacotherapy compared to the non-ASD group.

Discussion

This study attempts to document the clinical correlates of psychiatric comorbidity and functioning in ASD adults who were clinically referred to a specialty program for ASD at a university hospital. A substantial minority of the referred population with ASD were adults who suffered from high rates of psychiatric comorbidity at a frequency comparable to the psychiatrically referred non-ASD adults. Global functioning prior to and at referral was more impaired in adults with ASD. Adults with ASD were also more likely to utilize additional educational services in their childhood in the form of extra tutoring and placement in special classes, and were more likely to be in need of mental health interventions including a combination of pharmacotherapy and counseling. These results further confirm and add to the scant literature indicating that adults with ASD are afflicted with a high burden of psychiatric comorbidity and morbidity (Ghaziuddin and Zafar 2008; Ryden and Bejerot 2008; Tsakanikos et al. 2006).

At referral, the majority of this predominantly high-functioning sample of adults with ASD was single (84 %) and unemployed (49 %). Although ASD is an early childhood onset, pervasive, and lifelong disorder, it was not recognized in more than one-third (34 %) of the referred sample of adults with ASD. The most common psychiatric diagnoses prior to clinic referral in adults with ASD were mood and anxiety disorders (57 and 50 % respectively), followed by ADHD (39 %). Consistent with the most frequent prior diagnosis of mood and anxiety disorders, adults with ASD noted impairing mood dysregulation (54 %) and anxiety (52 %) as the most common reasons for referral to the clinic. At the time of referral, more than a quarter (27 %) of the adults with ASD were not receiving any psychopharmacological treatment.

In this study, the majority of adults were suffering from a more classic form of ASD (autistic disorder or Asperger's disorder), in contrast to our recent report on a pediatric population of ASD where a majority of the psychiatrically referred population endorsed a milder form of illness (i.e., PDD-NOS) (Joshi et al. 2010). This difference could be

Table 1 Demographics, psychosocial functioning, and treatment history of psychiatrically referred adults with and without ASD

	ASD (N = 63)	Non-ASD (N = 63)	Test statistic	*p* value	Holm's adjusted alpha
Demographics					
Age (years)					
Mean	29.2 ± 11.0	29.3 ± 10.9	N/A	N/A	
Range	18–63	18–65	N/A	N/A	
Gender (male)	41 (65)	41 (65)	N/A	N/A	
Race (Caucasian)	55 (95)				
Full scale IQ					
Mean	104.4 ± 17.3	106.8 ± 13.1	t = 0.9	0.37	
Range	55–136	77.5–133			
>70	61 (97)	63 (100)	$\chi^2_{(1)} = 2.0$	0.15	
>85	53 (84)	59 (94)	$\chi^2_{(1)} = 2.9$	0.09	
Socioeconomic status (FFISS)	2.1 ± 0.9[N=36]				
Single*	53 (84)	NA			
Unemployed**	31 (49)	NA			
Highest grade achieved[N=41]		NA			
<High school	0 (0)				
High school	18 (44)				
College	18 (44)				
≥Graduate school	5 (12)				
ASD diagnosis (DSM-IV)		N/A			
Autistic disorder	41 (65)				
Asperger's disorder	16 (25)				
PDD-NOS	6 (10)				
Psychosocial functioning					
GAF					
Lifetime	43.0 ± 6.0	51.8 ± 9.2	t = −4.9	<0.0001	**0.006**
Current	50.5 ± 5.3	57.8 ± 8.5	t = −5.2	<0.0001	**0.0056**
School functioning					
Repeated grade	19 (31)	16 (25)	$\chi^2_{(1)} = 0.82$	0.39	0.025
Extra tutoring	44 (71)	27 (43)	$\chi^2_{(1)} = 3.8$	0.0002	**0.008**
Special class	31 (50)	11 (17)	$\chi^2_{(1)} = 14.3$	0.0002	**0.007**
Treatment history					
Only counseling	2 (3)	9 (14)	$\chi^2_{(1)} = 5.4$	0.02	0.013
Only Pharmacotherapy	7 (11)	6 (10)	$\chi^2_{(1)} = 0.09$	0.76	0.05
Counseling + pharmacotherapy	38 (60)	21 (33)	$\chi^2_{(1)} = 7.1$	0.008	**0.01**
Hospitalization	11 (17)	5 (8)	$\chi^2_{(1)} = 3.00$	0.08	0.017

Values expressed as N (%) or mean ± SD

Bolded values indicate statistical significance that survives the Holm–Bonferroni correction for multiple testing

N/A Not applicable, *NA* not availablem, *FFISS* four factor index of social status, *GAF* global assessment of functioning scale, *IQ* intelligence quotient

* Including divorced subjects (N = 2/63; 3 %)

** Excluding full-time students (N = 12/63; 19 %)

indicative of the referral patterns based on the disorder of concern; individuals with more severe forms of ASD (i.e., autistic disorder) are more likely to be referred to specialized ASD programs, whereas individuals with milder forms of ASD often come to clinical attention for the management of comorbid psychiatric conditions.

It is striking that despite classic presentation of ASD (autistic disorder or Asperger's disorder), the diagnosis was

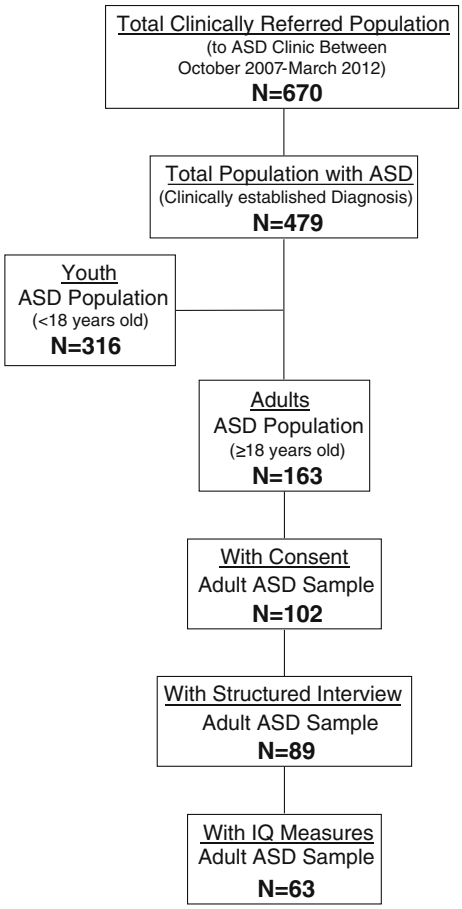

Fig. 1 Flow chart of sample ascertainment process

not previously established in over a third of the adults. The delay in ASD diagnosis could in part be attributed to the high-functioning nature of the adult population (intact language skills and intellectual functioning). This finding further highlights the under-recognition of ASD in individuals with intact intellectual function, as emphasized by a recent prevalence study that highlights unexpectedly high rates of ASD in the general population (Kim et al. 2011).

At evaluation, adults with ASD were experiencing an average of three psychiatric disorders, the most common being ADHD (42 %), followed by anxiety disorders (social phobia = 40 %; ≥2ADs = 38 %) and major depressive disorder (MDD; 31 %). They endorsed a greater burden of current and lifetime psychiatric comorbidities than the psychiatrically referred population of non-ASD adults. A wide range of psychiatric disorders identified in this ASD clinic-referred sample is consistent with previous reports of various psychiatric comorbidities observed in clinic-based populations of adults with ASD (Russell et al. 2005; Ryden and Bejerot 2008). The most prevalent lifetime comorbidities observed in more than half of the referred adult ASD population were MDD (77 %) and ADHD (68 %), followed by anxiety disorders (≥2ADs = 59 %; social phobia = 56 %), and ODD (53 %). These findings are strikingly analogous to those of previous studies that have reported ADHD and MDD to be the most common psychiatric disorders in clinically referred adults with ASD (Ryden and Bejerot 2008; Ghaziuddin and Zafar 2008). However, the rates observed in our study are somewhat higher than those in prior studies, which may be due to methodological differences in the endorsement of psychiatric comorbidity (structured diagnostic interview versus unstructured clinical assessment) and the duration of reference for assessing prevalence (lifetime vs. 1–2 years) (Ghaziuddin and Zafar 2008; Ghaziuddin et al. 1998; Ryden and Bejerot 2008).

The rate of comorbidity with ADHD observed in our adult population of ASD is similar to that observed in younger populations of psychiatrically referred youth with ASD, which suggests persistence of this childhood-onset disorder into adulthood (Joshi et al. 2010; de Bruin et al. 2007; Frazier et al. 2001; Goldstein and Schwebach 2004; Yoshida and Uchiyama 2004; Lee and Ousley 2006). Considering that ADHD is known to respond to a variety of pharmacological and non-pharmacological interventions, identifying and treating ADHD in adults with ASD can greatly facilitate psycho-educational rehabilitation efforts unique to individuals with ASD.

In the present study, lifetime comorbidity with MDD was experienced at a significantly higher rate among adults with ASD compared to those without ASD, although rates of depression at evaluation were not significantly different. These rates are strikingly similar to the prevalence of MDD documented in half of the clinically referred populations of adults and youth (ages 3–17 years) with high-functioning ASD (HF-ASD) (Joshi et al. 2010; Ghaziuddin and Zafar 2008; Ryden and Bejerot 2008). Similarly, a quarter of the ASD individuals endorsed a lifetime diagnosis of bipolar disorder (BPD), comparable to the rates observed in psychiatrically referred adults without ASD. There is wide variation in reported rates of BPD in different ASD populations, ranging from as low as 3 % in a clinically referred HF-ASD population (Ghaziuddin et al. 1998) to 4–27 % in ASD individuals attending psychiatry clinics (Ryden and Bejerot 2008; Munesue et al. 2008; Stahlberg et al. 2004). Given that there are well-established treatment options for BPD, its recognition in individuals with ASD provides an opportunity for disorder-specific treatment that may diminish the burden of morbidity in this population.

In the presence of ASD, clinically referred adults suffer from significantly higher lifetime rates of multiple anxiety disorders, including agoraphobia, social phobia, and OCD. This finding is consistent with several previous controlled and uncontrolled studies in younger ASD populations that report an equally high prevalence of anxiety disorder(s) (43–84 %) in referred populations of youth with ASD (Joshi et al. 2010;

Table 2 Psychiatric comorbidities in psychiatrically referred adults with and without ASD

	ASD (N = 63) N (%)	Non-ASD (N = 63) N (%)	Test statistic	*p* value	Holm's adjusted alpha
Tic disorder					
Tic disorder (motor or vocal)					
Lifetime	7 (11)	7 (11)	$\chi^2_{(1)} = 0.00$	1.00	0.05
Current	4 (6)	3 (5)	$\chi^2_{(1)} = 0.14$	0.71	0.006
Tourette's disorder					
Lifetime	3 (5)	0 (0)	$\chi^2_{(1)} = 3.00$	0.08	0.0016
Current	3 (5)	0 (0)	$\chi^2_{(1)} = 3.00$	0.08	0.00156
Disruptive behavior disorder					
Attention-deficit/hyperactivity disorder					
Lifetime	42 (68)	44 (70)	$\chi^2_{(1)} = 0.03$	0.86	0.008
Current	26 (42)	36 (57)	$\chi^2_{(1)} = 2.19$	0.14	0.0017
Oppositional defiant disorder					
Lifetime	33 (53)	9 (20)	$\chi^2_{(1)} = 0.89$	0.003	0.0016
Current	17 (27)	5 (11)	$\chi^2_{(1)} = 3.27$	0.07	0.0015
Conduct disorder					
Lifetime	7 (11)	8 (13)	$\chi^2_{(1)} = 0.09$	0.76	0.007
Current	1 (2)	1 (2)	$\chi^2_{(1)} = 0.00$	1.00	0.025
Antisocial personality disorder					
Lifetime	6 (10)	5 (8)	$\chi^2_{(1)} = 0.00$	1.00	0.017
Current	3 (5)	1 (2)	$\chi^2_{(1)} = 1.00$	0.32	0.0029
Major mood disorder					
Major depressive disorder					
Lifetime	48 (77)	29 (46)	$\chi^2_{(1)} = 11.1$	0.0009	**0.00104**
Current	19 (31)	14 (23)	$\chi^2_{(1)} = 1.00$	0.32	0.00278
Bipolar I disorder					
Lifetime	16 (25)	8 (13)	$\chi^2_{(1)} = 3.2$	0.07	0.00147
Current	4 (6)	3 (5)	$\chi^2_{(1)} = 0.14$	0.71	0.0056
Psychosis					
Lifetime	8 (13)	0 (0)	$\chi^2_{(1)} = 8.0$	0.005	0.00119
Current	5 (8)	0 (0)	$\chi^2_{(1)} = 5.0$	0.03	0.00135
Anxiety disorder					
Multiple anxiety disorders ($\geq$ 2)					
Lifetime	37 (59)	11 (17)	$\chi^2_{(1)} = 18.8$	<0.0001	**0.00096**
Current	24 (38)	7 (11)	$\chi^2_{(1)} = 10.7$	0.0011	0.00106
Specific phobia					
Lifetime	20 (32)	7 (11)	$\chi^2_{(1)} = 6.8$	0.01	0.00125
Current	11 (18)	6 (10)	$\chi^2_{(1)} = 1.5$	0.23	0.0021
Separation anxiety disorder					
Lifetime	13 (21)	3 (7)	$\chi^2_{(1)} = 5.3$	0.02	0.00131
Current	2 (3)	0 (0)	$\chi^2_{(1)} = 2.00$	0.50	0.0033
Agoraphobia					
Lifetime	22 (35)	4 (6)	$\chi^2_{(1)} = 14.7$	0.0001	**0.00102**
Current	15 (24)	2 (3)	$\chi^2_{(1)} = 9.9$	0.002	0.00111
Generalized anxiety disorder					
Lifetime	22 (35)	11 (17)	$\chi^2_{(1)} = 2.3$	0.13	0.00167
Current	18 (29)	9 (16)	$\chi^2_{(1)} = 2.00$	0.16	0.00185
Social phobia					

Table 2 continued

	ASD (N = 63) N (%)	Non-ASD (N = 63) N (%)	Test statistic	*p* value	Holm's adjusted alpha
Lifetime	35 (56)	12 (19)	$\chi^2_{(1)} = 16.0$	0.0001	**0.001**
Current	25 (40)	10 (16)	$\chi^2_{(1)} = 9.0$	0.003	0.001136
Obsessive–compulsive disorder					
Lifetime	15 (24)	0 (0)	$\chi^2_{(1)} = 15.0$	0.0001	**0.0098**
Current	10 (16)	0 (0)	$\chi^2_{(1)} = 10.0$	0.002	0.00108
Panic disorder					
Lifetime	5 (15)	6 (18)	$\chi^2_{(1)} = 0.82$	0.37	0.0031
Current	2 (3)	1 (2)	$\chi^2_{(1)} = 0.33$	0.56	0.0042
Post traumatic stress disorder					
Lifetime	7 (11)	1 (2)	$\chi^2_{(1)} = 1.8$	0.18	0.0019
Current	3 (5)	0 (0)	$\chi^2_{(1)} = 1.0$	0.32	0.0026
Substance use disorders					
Lifetime	21 (33)	28 (44)	$\chi^2_{(1)} = 1.7$	0.19	0.002
Current	7 (11)	5 (8)	$\chi^2_{(1)} = 0.4$	0.53	0.0036
Alcohol abuse					
Lifetime	18 (29)	5 (8)	$\chi^2_{(1)} = 7.4$	0.007	0.00121
Current	4 (6)	3 (5)	$\chi^2_{(1)} = 0.14$	0.71	0.005
Alcohol dependence					
Lifetime	8 (13)	17 (27)	$\chi^2_{(1)} = 3.5$	0.06	0.0014
Current	2 (3)	2 (3)	$\chi^2_{(1)} = 0.0$	1.00	0.013
Drug abuse					
Lifetime	9 (14)	12 (20)	$\chi^2_{(1)} = 1.00$	0.3	0.0022
Current	2 (3)	0 (0)	$\chi^2_{(1)} = 1.00$	0.32	0.0025
Drug dependence					
Lifetime	3 (5)	11 (18)	$\chi^2_{(1)} = 5.3$	0.02	0.00128
Current	1 (2)	2 (3)	$\chi^2_{(1)} = 0.3$	0.56	0.0038
Cigarette smoking					
Lifetime	7 (11)	4 (6)$^{N=20}$	$\chi^2_{(1)} = 0.00$	1.00	0.01
Current	0 (0)	1 (2)	$\chi^2_{(1)} = 1.00$	0.32	0.0024
Elimination disorders					
Enuresis					
Lifetime	16 (26)	13 (21)$^{N=43}$	$\chi^2_{(1)} = 0.3$	0.6	0.0045
Current	1 (2)	1 (2)	$\chi^2_{(1)} = 1.00$	0.32	0.0023
Encopresis					
Lifetime	6 (10)	1 (2)$^{N=43}$	$\chi^2_{(1)} = 3.6$	0.06	0.00139
Current	2 (3)	0 (0)	$\chi^2_{(1)} = 2.0$	0.16	0.00179

Bolded values indicate statistical significance that survives the Holm–Bonferroni correction for multiple testing

de Bruin et al. 2007; Leyfer et al. 2006; Muris et al. 1998; Sukhodolsky et al. 2008). In the present study, social phobia was the most common anxiety disorder (experienced by more than half of the ASD population), followed by agoraphobia, GAD, and specific phobia (each experienced by ≥one-third of the ASD population). Panic disorder was the least common anxiety disorder, experienced by 15 % of the ASD population. Similar patterns are observed in referred pediatric populations that report specific phobia as one of the most common (37–63 %) and panic disorder as the least frequent (0–9 %) of the anxiety disorders associated with ASD (Joshi et al. 2010; de Bruin et al. 2007; Leyfer et al. 2006; Muris et al. 1998).

At the time of evaluation, a substantial majority (71 %) of the ASD adults with a history of social phobia were experiencing social anxiety. In contrast, relatively lower prevalence of social phobia (7.5–20.5 %) is observed in referred populations of children with ASD (de Bruin et al.

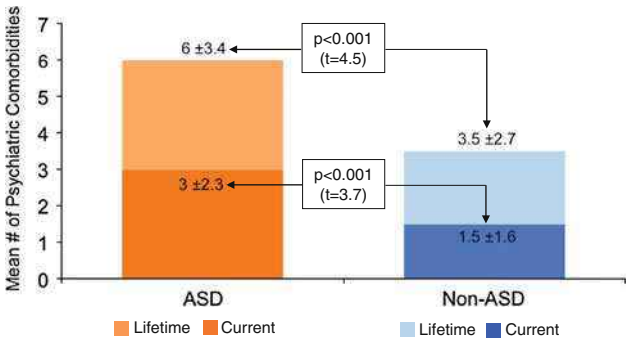

Fig. 2 Mean number of psychiatric comorbidities in psychiatrically referred adult populations with and without ASD

2007; Wozniak et al. 1997; Allen et al. 2006; Leyfer et al. 2006; Muris et al. 1998). One plausible explanation for the higher risk for social phobia in adults with ASD could be related to the increasing number of social challenges and associated anxiety experienced by ASD individuals as they struggle to respond appropriately to social complexities that intensify with age. In this study, ASD adults with social phobia report a fearful response to social situations, which is in contrast to the social indifference and detachment observed in those adults with ASD who show a lack of interest in their surroundings and in social interactions. Anxiety conditions are known to be more common in HF-ASD populations, and in this study, all of the adults with a lifetime history of social phobia were HF-ASD (IQ > 70) (Muris et al. 1998; Sukhodolsky et al. 2008; Weisbrot et al. 2005; Lecavalier 2006). Presumably, these HF-ASD individuals who are interested in socializing but fail to do so due to deficits in social interactions may be more prone to developing impairing social anxiety, as opposed to those who inherently lack interest in social interactions and thus do not exhibit anxiety or fear response in social situations. More than two-thirds of the ASD adults with social phobia also reported one other form of anxiety disorder (lifetime: N = 27/35; current: N = 20/25), including lifetime history of GAD (N = 16), agoraphobia (N = 15), specific phobia (N = 12), OCD (N = 11), separation anxiety disorder (N = 9), and panic disorder (N = 7). Furthermore, nearly half of the ASD adults with social phobia also suffered from two or more other anxiety disorders (lifetime: N = 17/35; current: N = 12/25). Thus, anxiety in this population is not limited to social phobia, as it also expresses in other forms of anxiety disorders.

In this study, nearly half of the ASD adults with a lifetime history of specific phobia were not experiencing phobic features at the time of referral, which suggests a decrease in the prevalence of this disorder with increasing age (a trend similar to what is noted in typically developing populations) (Green and Benzeval 2010). Consistent with the frequent phenotypic comorbidity of ASD and anxiety, there is emerging evidence suggesting that these disorders may also share common neural correlates. The amygdala, which regulates social and emotional processes (LeDoux 2000), has been documented to be pathological in ASD (Baron-Cohen et al. 2000; Nacewicz et al. 2006; Schultz 2005; Schumann et al. 2004) and implicated in co-occurring ASD and anxiety (Amaral and Corbett 2003). A recent study revealed a significant association between anxiety and increased total and right amygdala volumes in children with ASD (Juranek et al. 2006). Additionally, abnormalities of serotonin neurotransmission (Chugani et al. 1999) could represent a shared causal factor in ASD and anxiety and suggest paths for intervention, as the presence of anxiety in this population may adversely affect already compromised social functioning and worsen deficits in adaptive (J. Kim et al. 2000) and disruptive (Canitano 2006) behaviors.

Although repetitive behaviors are considered core features of ASD, there is a clinically significant overlap of ASD with OCD. In this study, a quarter of the adults with ASD also reported experiencing OCD at evaluation. Similar rates of OCD are documented in up to one quarter (23–25 %) of the clinically referred samples of adults with HF-ASD (Russell et al. 2005; Ryden and Bejerot 2008). In pediatric populations, an equally high prevalence of OCD (11–37 %) is reported in referred samples of youth with ASD (Joshi et al. 2010; Leyfer et al. 2006; Muris et al. 1998; Szatmari et al. 1989; Green et al. 2000). Consistent with this comorbidity, there seems to be a significant overlap in the neural underpinnings of the repetitive behaviors associated with ASD and OCD; both share neuropathological abnormalities in the anterior cingulate cortex and caudate nucleus region of the brain (Langen et al. 2007; Sears et al. 1999; Scarone et al. 1992; Levitt et al. 2003; Rojas et al. 2006; Rosenberg et al. 2000), though they differ in the neurochemical profile of the prefrontal region (Murphy et al. 2002; Ebert et al. 1997).

In this study, a somewhat high rate of lifetime and current psychosis is noted with ASD (13 and 8 % respectively). Psychosis was endorsed by the presence of delusions or hallucinations on direct or indirect structured diagnostic interview. ASD adults with psychosis reported delusions of reference, mind being read, and thought control and hallucinations involving auditory, visual, and somatic modalities. Consistent with the present study, a similar prevalence of lifetime psychosis (14 and 16.4 %) on structured and clinical diagnostic interview are reported in two larger sample size studies of psychiatric comorbidity in psychiatrically referred populations of adults with ASD (Tsakanikos et al. 2006; Stahlberg et al. 2004). The rates of psychosis with ASD in this study are in contrast to relatively low rates of psychosis reported in adult populations

referred to ASD clinics (0–7.5 %) (Russell et al. 2005; Ghaziuddin and Zafar 2008; Ghaziuddin et al. 1998). The manner of assessment of psychiatric comorbidities in these studies, including unstructured clinical interview (Russell et al. 2005; Ghaziuddin and Zafar 2008; Ghaziuddin et al. 1998), interviewing patient only (Ghaziuddin et al. 1998), and limiting lifetime comorbidity to previous 1–2 years (Ghaziuddin and Zafar 2008; Ghaziuddin et al. 1998), may have contributed to lower rates of psychosis.

It is noteworthy that up to one-third of the ASD population in this study reported substance use disorders (SUD), consistent with the rates observed in the non-ASD psychiatrically referred population. Of the ASD adults with a history of drug abuse, two were actively using drugs at evaluation (2/9). Most of the ASD adults with drug use reported using more than one drug (6/9). Cannabis was used by all of subjects with a history of drug use, with hallucinogen (5/9), benzodiazepine (4/9), and cocaine (3/9) use also common. There is a lack of information on the prevalence of SUD in previous studies that assessed for psychiatric comorbidities in ASD populations (Simonoff et al. 2008; Leyfer et al. 2006; Ghaziuddin and Zafar 2008; Ghaziuddin et al. 1998; Ryden and Bejerot 2008). Thus, equally high rates of SUD reported in clinically referred adults with and without ASD highlight the importance of assessing for SUD in adults with ASD.

Our findings should be evaluated in light of certain limitations. Given that we examined specialty clinic referred adults with ASD, these findings may not generalize to community or psychiatry clinic referred samples of adults with ASD. In this study, the diagnosis of ASD was not additionally confirmed by administering the Autism Diagnostic Interview-Revised (ADI-R; (Lord et al. 1994), as the validity of the ADI-R in adult populations is not established, and the feasibility of administering the ADI-R in studies with large samples is challenging and questionable. Additionally, in the comparison sample, the diagnosis of ASD was ruled out by DSM-III-R criteria based structured diagnostic interview for ASD. Though one strength of this study was the use of a well-established structured interview (SCID), the inter-rater reliability of our diagnostic instrument (SCID) was assessed using a separate clinic sample. Although the SCID is not normed for diagnosing psychiatric disorders in ASD populations, based on the equally high levels of psychiatric comorbidity observed in these psychiatrically referred populations of adults with and without ASD, we would argue that when structured diagnostic interviews are administered unbiased by the status of the ASD diagnoses, we observe equally high prevalence of comorbid psychiatric disorders in adults with and without ASD. As it is possible that this instrument is differentially reliable among adults with ASD, future methodological studies should establish the psychometric properties of the SCID in this population. Lastly, to avoid the underreporting of psychiatric conditions, we documented psychiatric disorders reported by either direct or indirect structured interviews, which may have contributed to overrepresentation of psychiatric comorbidity.

Despite these limitations, results of this study highlight high levels of morbidity and psychiatric comorbidity in clinically referred adults with ASD. These findings have important implications for both clinical practice and research. From a therapeutic perspective, clinicians need to consider the possibility of comorbid psychiatric disorders in ASD, rather than classifying them as core or associated features of ASD. A diagnosis of an ASD should routinely be followed by systematic assessment for other psychiatric disorders, because establishing the comorbid psychiatric diagnosis in this population is essential for implementing disorder-specific therapeutic interventions. From a research perspective, establishing the presence of comorbid psychiatric disorders in adults with ASD may lead to the identification of useful subtypes for genetic and brain imaging studies as well as for treatment trials to study therapeutic responses in this population.

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