



## REVIEW ARTICLE

## Prevalence of Comorbid Psychiatric Disorders in Children and Adolescents with Autism Spectrum Disorder

Luke Y. Tsai<sup>1, 2 \*</sup><sup>1</sup> Department of Psychiatry, University of Michigan Medical School, Ann Arbor, MI, USA<sup>2</sup> Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI, USA

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This review is based on an extensive literature search to determine the prevalence of comorbid psychiatric disorders in children and adolescents with autism spectrum disorder (ASD) and shows that case reports and clinic- and community-based studies are available with which to assess this prevalence. Attention-deficit/hyperactivity disorder, anxiety disorders, and mood disorders frequently present in children and adolescents with ASD. However, a valid and reliable prevalence of comorbid psychiatric disorders in children and adolescents with ASD has not been established as a result of the limited number and small sample sizes of the reported studies.

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## 1. Introduction

## 1.1. Evolution of definition

In 1943, Kanner<sup>1</sup> described a group of 11 children with a previously unrecognized disorder. He noted that these children had a number of characteristic features, such as an inability to develop relationships with people, extreme aloofness, a delay in speech development, and noncommunicative use of speech. Other features included repeated simple patterns of play activities and islets of ability. He adopted the term early infantile autism to describe this disorder and drew attention to the fact that its symptoms were already evident in infancy.

## 1.2. Diagnostic changes of definition of autism in DSM and ICD systems

The 1980 edition of the *International Classification of Diseases, 9th edition (ICD-9-CM)*<sup>2</sup> of the World Health Organization and the 1980 edition of the *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III)*<sup>3</sup> of the American Psychiatric Association both set definition and diagnostic criteria for infantile autism. *ICD-9-CM*

and *DSM-III* have similar definitions and diagnostic criteria for infantile autism. However, the concepts of autism are different in these two publications. In *ICD-9-CM*, infantile autism is classified as a subtype of “psychoses with origin specific to childhood,” whereas in *DSM-III*, and later in *DSM-III-R*,<sup>4</sup> infantile autism is viewed as a type of pervasive developmental disorder (PDD), which is defined as a group of severe, early developmental disorders characterized by delays and distortions in the development of social skills, cognition, and communication.

In 1994, the American Psychiatric Association published *DSM-IV*,<sup>5</sup> which continued to adopt the diagnostic term PDD. In *DSM-IV*,<sup>5</sup> these disorders include: autistic disorder (AD); Rett’s disorder; childhood disintegrative disorder; Asperger’s syndrome (AS); and PDD not otherwise specified (PDDNOS; including atypical autism). *DSM-IV*<sup>5</sup> also offers operational diagnostic criteria for all of the subtypes of PDD, except PDDNOS. This approach supports the taxonomic validity of each subtype and aims to facilitate research in the subclassification of these disorders. Since 1992, such a diagnostic subclassification has also been adopted in *ICD-10*.<sup>6</sup>

Despite the publication of the definition and diagnostic subclassification of PDD in *DSM-IV*<sup>5</sup> and *ICD-10*,<sup>6</sup> many non-medical professionals in the field of autism research prefer to use the term of autism spectrum disorder (ASD) to describe the disorders that are classified by the *DSM-IV*<sup>5</sup> and *ICD-10*<sup>6</sup> as AD, AS, and PDDNOS. One difference between the two diagnostic concepts (i.e., PDD and ASD) is that the PDD concept considers that AD, AS, and PDDNOS are three distinct clinical disorders, whereas the ASD

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\* Luke Y. Tsai, Department of Psychiatry, University of Michigan Medical School, 2385 Placid Way, Ann Arbor, MI 48105, USA.

E-mail: <[lytsai@umich.edu](mailto:lytsai@umich.edu)>.<http://dx.doi.org/10.1016/j.jecm.2014.10.005>

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concept generally considers these three disorders as a disorder on a continuum (i.e., AD as a severe form on one end, AS as a mild form on the other end, and PDDNOS as a moderate form in the middle). The recently published *DSM-5*<sup>7</sup> has adopted the ASD concept and has set up diagnostic guidelines.

### 1.3. Comorbid psychiatric conditions in ASD

Despite the changes in diagnostic terms and criteria, the field of ASD has consistently agreed that the core features are impairment in social interaction, impairment in communication, and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. Nevertheless, many patients with ASD also develop other behavioral and/or psychiatric symptoms in addition to the core features of ASD. The additional behavioral and/or psychiatric symptoms were described by many investigators prior to the early 1990s. Simons<sup>8</sup> reported in 1974 that compulsive behavior is observed in every child with a clear-cut diagnosis of autism. Ando and Yoshimura<sup>9</sup> reported in 1979 that among 47 autistic children (age range 6–14 years), 36% had hyperactivity, 68% had stereotyped behavior, 43% had self-injury, and 17% had fear. In a follow-up study of autistic adult men, Rumsey et al<sup>10</sup> reported in 1985 that 86% of these men continued to demonstrate stereotyped, compulsive behaviors, including arranging objects, and phonic tics. Le Couteur et al<sup>11</sup> in 1989 described that in 16 patients with autism (mean  $\pm$  SD age 13.26  $\pm$  3.38 years), 73% had separation anxiety, 89% had stereotyped utterances, 88% had unusual preoccupations, 55% had verbal rituals, 81% had compulsions/rituals, 69% showed hand–finger mannerisms, and 63% had unusual sensory interests. Fombonne<sup>12</sup> in 1992 observed that in 20 French patients with autism (age range 11–26 years), 74% showed separation anxiety, 50% had stereotyped utterances, 53% had unusual preoccupations, 16% had compulsions or rituals, 74% showed hand–finger mannerisms, and 42% had unusual sensory interests. In a follow-up study of 66 patients with autism in Hong Kong, Chung et al<sup>13</sup> in 1990 noted that 47% of these children were hyperactive, 64% had poor attention and concentration, 24% showed self-injurious behaviors, 23% showed fears or phobias, 9% had depressive moods, 44% showed irritability or agitation, 29% showed inappropriate affects, 11% had sleep problems, and 8% exhibited tics.

These investigators, however, did not consider that these additional symptoms might be those of comorbid disorders and they did not specifically investigate the incidence of diagnosable psychiatric disorders based on any commonly used diagnostic criteria in their samples. This approach might be influenced by the *DSM-III*, *DSM-III-R*, and *DSM-IV* diagnostic classification systems, which consider these additional symptoms as “associated features” of ASD. However, since the late 1980s there have been a number of case reports describing specific types of psychiatric disorders occurring in patients with ASD (reviewed by Tsai<sup>14</sup> in 1996). It is conceivable that some of the “associated features” may be the diagnostic features of other coexisting psychiatric disorders. The question addressed in this review is: How frequently do these comorbid psychiatric disorders exist?

## 2. Methods used to identify the relevant literature

Two approaches have been used in the published literature to address the question of whether patients with ASD have comorbid psychiatric disorders and the prevalence of these disorders. The focus of this review is to provide information on studies that have reported patients with ASD who have comorbid psychiatric disorders and the prevalence of comorbid psychiatric disorders in children and adolescents with ASD.

A systematic search of the literature was conducted to locate studies published between 1980 and 2014 that examined the comorbid psychiatric disorders of patients with ASD. The search was limited to English-language journal articles. Publications were identified by conducting searches in the major databases *PubMed*, *MEDLINE*, *PsycINFO*, and *ERIC*. Searches were conducted by entering the following terms: autism, pervasive developmental disorder, autism spectrum disorder, and comorbid psychiatric disorders. Reference lists from relevant articles (e.g., literature reviews) and recent editions of key journals (e.g., *Journal of Child Psychology and Psychiatry*, *Autism*, *Journal of Autism and Developmental Disorders*, and *Research of Autism Spectrum Disorder*) were also used to identify relevant articles. The search of the databases and reference lists was extended to the end of September 2014. Studies were included if they used the *DSM-III*, *DSM-III-R*, *DSM-IV*,<sup>5</sup> *DSM-IV-TR*, *ICD-10*,<sup>6</sup> *Autism Diagnostic Interview (ADI)*,<sup>11</sup> *ADI-Revised*, *Autism Diagnostic Observation Scale (ADOS)*<sup>15</sup> criteria to diagnose patients and to include them in the studies.

## 3. Published work on comorbid psychiatric disorders in patients with ASD

### 3.1. Case reports of comorbid psychiatric disorders

Although case reports do not give information on the prevalence of comorbid psychiatric disorders in patients with ASD, they do provide some evidence to support the proposal that there are other important psychiatric disorders that often coexist with ASD.

#### 3.1.1. Attention-deficit/hyperactivity disorder

In 2004, Goldstein and Schwabach<sup>16</sup> carried out a study to determine whether a sample of children meeting the diagnostic criteria for PDD displayed symptoms of impairment-related attention-deficit/hyperactivity disorder (ADHD) sufficient to warrant a comorbid diagnosis of ADHD. They found that of 57 children diagnosed with *DSM-IV* AD or PDDNOS, 26% also met the *DSM-IV* criteria for the combined type of ADHD and 33% met the diagnostic criteria for the inattentive type of ADHD. Yoshida and Uchiyama<sup>17</sup> found that 36 of 53 child and adolescent patients with a *DSM-IV* diagnosis of PDD also met the *DSM-IV* criteria for ADHD and that the co-occurrence rate of AS/PDDNOS (85%) was higher than for AD (57.6%).

In a retrospective study of stimulant response in children with ADHD and comorbid ASD, Santosh et al<sup>18</sup> identified 61 children who met the *DSM-IV* criteria for coexisting ADHD and ASD (7 with AD, 13 with AS and 41 with PDDNOS). In a prospective study, they found that 27 children met the *DSM-IV* criteria for coexisting ADHD and ASD.

Sinzig et al<sup>19</sup> compared the neuropsychological profiles of the attention functions of children with ASD and comorbid ADHD and identified 30 children aged from 6 years to 18 years. In a study of group differences to better understand the clinical phenotypes, Gadow et al<sup>20</sup> identified 88 children diagnosed with *DSM-IV* ASD and combined ADHD. In an assessment of the influence of psychiatric comorbidity on social skill treatment outcomes for children with ASD, Antshel et al<sup>21</sup> identified 25 children with ASD and comorbid anxiety disorder.

Clarke et al<sup>22</sup> studied electroencephalography differences to support the evidence for comorbid disorders and identified that 60 children with ADHD also had ASD diagnostic criteria of the developmental behavior checklist.<sup>23</sup> To study the efficacy and tolerability of atomoxetine in children with high-functioning ASD and combined ADHD, Zeiner et al<sup>24</sup> recruited 14 boys who qualified for the inclusion criteria. Jang et al<sup>25</sup> studied the rates of comorbid

symptoms in three different diagnostic groups and found that 38 children were diagnosed with both ASD with ADHD.

### 3.1.2. Mood disorders

Munesue et al<sup>26</sup> examined mood disorders in 44 consecutive outpatients with high-functioning ASD according to *DSM-IV*. The inclusion criteria were an IQ of  $\geq 70$  on the Wechsler Intelligence Scale and an age of  $\geq 12$  years. The investigators found that 16 patients (36.4%) were diagnosed with a mood disorder. Of these 16 patients, four were diagnosed as having major depressive disorder, two patients as bipolar I disorder, six patients as bipolar II disorder, and four patients as bipolar disorder not otherwise specified. Bipolar disorder accounted for 75% of the patients.

Siegel et al<sup>27</sup> reported that a positive response to electroconvulsive therapy was found in a severely functionally impaired adolescent with AD and classic bipolar I disorder, including an episodic pattern of decreased need for sleep, hypersexuality, expansive and agitated affect, aggression, self-injury, and property destruction. To examine the clinical and familial correlates of bipolar disorder when it occurs with and without ASD comorbidity in a well-characterized, research-referred population of young people with bipolar disorder, Joshi et al<sup>28</sup> identified 47 of 155 young people with ASD who had a comorbidity of bipolar I disorder based on the *DSM-III-R* criteria.

In an evaluation of the effectiveness of reboxetine (a norepinephrine reuptake inhibitor) treatment in pediatric patients with ASD with symptoms of depression and ADHD, Golubchik et al<sup>29</sup> reported that 11 adolescent patients with ASD (9 boys and 2 girls aged  $12.2 \pm 3.6$  years) had symptoms of depression and ADHD. Ishitobi et al<sup>30</sup> reported a positive response to quetiapine in a 17-year-old adolescent with ASD and comorbid bipolar disorder who developed symptoms of catatonia. In a preliminary investigation of treatment with lithium for mood disorder, Siegel et al<sup>31</sup> carried out a retrospective review of medical records and identified 30 children and adolescents diagnosed with ASD by the *DSM-IV-TR* criteria who also had two or more symptoms of mood disorder.

### 3.1.3. Anxiety disorders

Muris et al<sup>32</sup> examined the prevalence of comorbid anxiety symptoms in 44 children with PDD and interviewed the parents of the children using the anxiety disorders section of the Diagnostic Interview Schedule for Children. They found that severe anxiety symptoms are highly prevalent in children with PDD, with 84.1% of the children meeting the full criteria for at least one anxiety disorder. In a study that examined a family-based, cognitive behavioral treatment for anxiety, Chalfant et al<sup>33</sup> recruited 47 children who had comorbid anxiety disorders and high-functioning AS.

Lehmkuhl et al<sup>34</sup> reported a 12-year-old boy with ASD and combined obsessive-compulsive disorder (OCD) who was treated successfully with cognitive behavioral therapy with exposure and response prevention. Wood et al<sup>35</sup> tested a modular cognitive behavioral therapy program for children with ASD and combined anxiety disorders and found that 40 children (7–11 years old) were eligible to be included in the study.

Guttman-Steinmetz et al<sup>36</sup> compared symptoms of generalized anxiety disorder (GAD) and separation anxiety disorder (SAD) in five groups of boys with neurobehavioral syndromes: ADHD plus ASD; ADHD plus chronic multiple tic disorder; ASD only; ADHD only; and community controls. The investigators assessed anxiety symptoms with parent and teacher versions of a *DSM-IV*-referenced rating scale and identified 74 children with ASD plus ADHD and these children were enrolled in the study.

To assess the influence of psychiatric comorbidity on social skill treatment outcomes for children with ASDs, Antshel et al<sup>21</sup> identified 37 children with ASD plus anxiety disorder and these children

were included in their study. White et al<sup>37</sup> reported that 30 adolescents with high-functioning ASD and combined anxiety disorders were recruited to participate in a study that assessed psychometric properties and constructed the validity of measures of anxiety. To investigate anxiety problems and health-related quality of life in children with high-functioning ASD and comorbid anxiety disorders compared with children with anxiety disorders alone, van Steensel et al<sup>38</sup> reported that 115 children (90 boys and 25 girls, mean age 11.37 years) with ASD plus anxiety disorders were enrolled in their study. Ung et al<sup>39</sup> examined the clinical characteristics of 108 high-functioning children with ASD and found that 45 children had primary anxiety disorder, 17 had GAD, 13 had SAD, 13 had OCD, 28 had a social phobia, and five had a specific phobia.

van Steensel et al<sup>40</sup> carried out a meta-analysis to help to clarify the issue of which of the specific *DSM-IV* anxiety disorders occurred most in an ASD population. They identified 31 studies involving 2121 young people (aged  $< 18$  years) with ASD. Across these studies, 39.6% of the young people with ASD had at least one comorbid *DSM-IV* anxiety disorder, the most frequent being specific phobia (29.8%) followed by OCD (17.4%) and social anxiety disorder (16.6%). To assess the prevalence of autistic traits in pediatric patients with OCD and to relate these to OCD comorbidity, Ivarsson and Melin<sup>41</sup> found that nine of 109 children with OCD were identified as having comorbid ASD.

### 3.1.4. Tic disorders

Thirty-seven students attending a special school for children and adolescents with ASD were observed for the presence of motor and vocal tics by Baron-Cohen et al.<sup>42</sup> Subsequent family interviews confirmed that a diagnosis of comorbid Gilles de la Tourette's syndrome had been made in three children with ASD, giving a minimum prevalence of 8.1%. To determine the rate of tic disorders in a clinical sample ( $n = 105$ ) of children and adolescents with ASD, Canitano and Vivant<sup>43</sup> found that 24 children with ASD had comorbid tic disorders. They also reported that among the 22% of children and adolescents with tic disorders, 11% had Tourette's disorder and 11% had chronic motor tics.

### 3.1.5. Sleep disorders/disturbances

Allik et al<sup>44</sup> investigated insomnia in 32 8–12-year-old children with AS/high-functioning AD and found that 10 of these children had a diagnosis of pediatric insomnia. In a study which examined sleep patterns, sleep problems, and their correlates in children with ASD, Liu et al<sup>45</sup> reported that 167 children, including 108 with AD, 27 with AS, and 32 with other diagnoses of ASD, were identified and that their mean  $\pm$  SD age was  $8.8 \pm 4.2$  years, 86% were boys, and that about 86% had at least one sleep problem almost every day, including 54% with bedtime resistance, 56% with insomnia, 53% with parasomnias, 25% with sleep disordered breathing, 45% with morning rise problems, and 31% with daytime sleepiness.

In a study of sleep disturbance and its relation to *DSM-IV* psychiatric symptoms, DeVincent et al<sup>46</sup> found that 18% of 112 children with PDD (ASD) met the criteria for sleep disturbance. In a study of sleep disturbances in 477 children with ASD, Mayes and Calhoun<sup>47</sup> found that children were identified with sleep problems of various types: sleeps more than normal, 14%; daytime sleepiness, 21%; walks or talks in sleep, 35%; wets bed, 36%; nightmares, 39%; sleeps less than normal, 43%; wakes too early, 45%; wakes often during the night, 50%; restless during sleep, 56%; and difficulty falling asleep, 60%.

Giannotti et al<sup>48</sup> carried out a sleep study on 22 children with non-regressive autism and 18 children with regressive autism without comorbid pathologies with the parents completing the structured Children's Sleep Habits Questionnaire (CSHQ).<sup>9</sup> The

initial hypothesis, that regressed children would have more disrupted sleep, was supported by the final findings that they scored higher on the CSHQ than their non-regressed peers, particularly on the bedtime resistance, sleep onset delay, sleep duration, and night wakings CSHQ subdomains, and that both groups scored higher than typically developing controls.

### 3.1.6. Childhood-onset schizophrenia

Volkmar and Cohen<sup>49</sup> examined the detailed medical records of 163 adolescents and adults (139 male and 24 female patients) with well-documented histories of autism. They found only one patient who had been identified to have an unequivocal history of schizophrenia first developing around the age of 15 years. In a study comparing evidence for premorbid PDD as a nonspecific manifestation of the impaired neurodevelopment seen in schizophrenia, or as an independent risk factor for childhood-onset schizophrenia (COS), Sporn et al<sup>50</sup> found that 19 (25%) COS probands had a lifetime diagnosis of PDD; one met the criteria for AD, two for AS, and 16 for PDDNOS. Rapoport et al<sup>51</sup> reviewed clinical, demographic, and brain developmental data from the National Institute of Mental Health (and other) COS studies and selected family, imaging, and genetic data from studies of autism, PDD, and schizophrenia. They concluded that COS is preceded by and comorbid with PDD in 30–50% of reported cases.

### 3.1.7. Catatonia

One of the three patients reported by Realmuto and August<sup>52</sup> was found to have AD and later developed catatonia with mutism, akinesia, catalepsy plus negativism, and posturing when he was 16 years old.

## 3.2. Prevalence of comorbid psychiatric disorders in patients with ASD in defined samples

Leyfer et al<sup>53</sup> studied a combined sample consisting of 109 children (65 from Boston, 45 from Salt Lake City) ranging in age from 5 years to 17 years, all of whom met the ADI-R, ADOS, and *DSM-IV-TR* diagnosis of ASD. The investigators found that the most common *DSM-IV* lifetime diagnosis is specific phobia, which was diagnosed in 44% of the children. They found that many children with autism have phobias of more than one object or situation, that fear of needles and/or injections and crowds are the most common phobias (32%), and that over 10% of the children have a phobia of loud noises. The second most frequent *DSM-IV* disorder in this study was OCD, which was diagnosed in 37% of the children. The third most common diagnosis was ADHD, diagnosed in 31% of the children. This rate is increased to nearly 55% when subsyndromal patients were included. Sixty-five percent of the children diagnosed with ADHD had the inattentive subtype. Ten percent of the children had experienced at least one episode of major depression meeting the *DSM-IV* criteria. When subsyndromal patients were included, the rate of major depression was increased to nearly 24%. Less than 2% of the children had experienced a manic episode, meeting the criteria for bipolar I disorder. None of the children with autism had met the criteria for schizophrenia or related disorders, or for panic disorder.

Simonoff et al<sup>54</sup> studied a group of 112 10–14-year old children from a population-derived cohort. The children were assessed for other child psychiatric disorders (3 months of prevalence) through parent interviews using the Child and Adolescent Psychiatric Assessment. The investigators found that 70% of the study participants had at least one comorbid disorder and 41% had two or more comorbid disorders. The most common diagnoses were social anxiety disorder (29.2%), ADHD (28.2%), and oppositional defiant

disorder (ODD; 28.1%); of those children with ADHD, 84% received a second comorbid diagnosis.

In a combined community- and clinic-based sample of 50 9–16-year-old patients with AS/high-functioning autism using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version to identify the prevalence and types of comorbid psychiatric disorders, Mattila et al<sup>55</sup> found common (prevalence 74%) and often multiple comorbid psychiatric disorders in AS/high-functioning autism: behavioral disorders, including ODD, were shown in 44%, anxiety disorders in 42%, and tic disorders in 26% of patients. Current behavioral disorders ( $n = 22$ ) often co-occurred ( $n = 13$ ) with current anxiety disorders ( $n = 21$ ). Of the patients with current ODD ( $n = 8$ ), seven co-occurred more with current anxiety disorders ( $n = 21$ ), especially ( $n = 4$ ) with OCD ( $n = 11$ ). About half of the 19 patients with current ADHD and about half of the 21 patients with current anxiety disorder had both disorders simultaneously ( $n = 11$ ), although this was not statistically significant. The most common current anxiety disorders were specific phobias [fear of animals (dogs, bees), darkness, heights, confined spaces, bridges, and needles or injections] and OCD (22%). Two or three different current anxiety disorders were diagnosed in 14% of the participants. None of these patients met the criteria for schizophrenia or related disorders, eating disorders, or substance abuse disorders, and none had ever smoked.

Consecutive children and adolescents ( $n = 2,323$ ) referred to a pediatric psychopharmacology program were assessed by Joshi et al,<sup>56</sup> who found that 217 (9.3%) of the referred patients (age range 3–17 years) met the *DSM-III-R* criteria for ASD. They also found that young people with ASD had a high number of comorbid disorders ( $6.4 \pm 2.7$  disorders). Ninety-five percent of the young people with ASD had three or more comorbid psychiatric disorders and 74% had five or more comorbid disorders. The percentages of the comorbid psychiatric disorders of the 217 young people are: ADHD (83%), anxiety disorders including multiple anxiety disorders (61%), agoraphobia (35%), GAD (35%), OCD (25%), panic disorder (6%), SAD (37%), social phobia (28%), specific phobia (37%), disruptive behavior disorders including ODD (73%), conduct disorder (22%), elimination disorders including enuresis (37%), encopresis (22%), language disorder (48%), mood disorders including bipolar I disorder (31%), major depressive disorder (56%), post-traumatic stress disorder (2%), psychosis (20%), substance use disorders including cigarette smoking (5%), substance use disorders (1%), tic disorders including tic disorder (motor or vocal) (23%), and Tourette's disorder (18%).

To investigate and compare the rate and type of psychiatric comorbidity in patients with a diagnosis of high-functioning autism and AS, Mukaddes et al<sup>57</sup> studied 30 children and adolescents with a diagnosis of high-functioning autism and 30 children with a diagnosis of AS. Diagnoses of high-functioning autism and AS were made using strict *DSM-IV* criteria. Psychiatric comorbidity was assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version. They found that 93.3% of the high-functioning autism and 100% of the AS groups had comorbid psychiatric disorders and that the most common disorder in both groups was ADHD.

Gjeverik et al<sup>58</sup> assessed the prevalence of current comorbid *DSM-IV* psychiatric disorders in a special school population of children and adolescents with ASD ( $n = 71$ , age 6.0–17.9 years), representing all cognitive levels and the main ASD subgroups. The symptoms were assessed through parent interview and the association with the characteristics of the child were explored. The investigators found that 72% of the children and adolescents were diagnosed with at least one comorbid disorder and that anxiety disorders (41%) and ADHD (31%) were the most prevalent; OCD was more

common in older children and ODD/conduct disorder was more prevalent in patients with PDDNOS. The percentages of the comorbid psychiatric disorders were: any psychiatric disorder (72%); any anxiety disorder (42%); specific phobia (31%); social phobia (7%); OCD (10%); SAD (0%); GAD (0%); any ADHD (31%); ADHD, inattentive type (21%); ADHD, combined type (4%); ADHD, hyperactive type (6%); any mood disorder (10%); depressive disorder not otherwise specified (7%); major depressive disorder (1%); dysthymic disorder (1%); manic episode/bipolar disorder (0%); any tic disorder (11%); ODD (4%); conduct disorder (2%); any psychotic disorder (1%); and anorexia nervosa/bulimia (0%).

Rosenberg et al<sup>59</sup> used a national online registry to examine variations in the cumulative prevalence of a community diagnosis of psychiatric comorbidity in 4343 children with ASD. The researchers noted that the participants were more likely to have a single psychiatric comorbidity (26.9%) than two (14.4%), three (6.3%), or four (1.5%) comorbidities (data not shown). Of those patients with at least one comorbidity, 45.2% were found to have two or more. The most common comorbid diagnosis is ADHD or ADD (38.1%), followed by anxiety disorders (26.2%), depression (11.0%), and bipolar disorder (5.2%); only 23/4343 (0.5%) were reported to have a diagnosis of schizophrenia.

To examine patterns of comorbid psychiatric problems in children with ASD and their parents compared with IQ-matched controls and their parents, Skokauskas and Gallagher<sup>60</sup> recruited 59 (88%) boys and eight (12%) girls with ASD group (a diagnosis of ASD was given if they met the criteria for ASD on both the ADI-R and ADOS). The investigators found that the majority of parents reported their child with ASD as having either internalizing (clinical range 47.8%, borderline range 16.4%) or externalizing problems (clinical range 10.4%, borderline range 20.9%) and that patients in the ASD group meet Child Behavior Check List DSM criteria for clinically significant ADHD (44.78%) and anxiety problems.

To determine the possibility of comorbid psychiatric conditions in ASD, Memari et al<sup>61</sup> used a school-based health survey related to children diagnosed with ASD in Tehran, Iran. Ninety-one children and adolescents with ASD between the ages of 6 years and 14 years were included in the study, all were from five schools of different districts of the city, using stratified random sampling. All the patients had received a clinical diagnosis of ASD (AD, AS, and PDDNOS) by a child neurologist or psychiatrist. The researchers found that 27.5% of patients with ASD had at least one comorbid psychiatric disorder. There was a trend of higher severity in autism symptoms in patients with a comorbid disorder. The results showed that eating disorders ( $n = 11$ ) and ADHD ( $n = 8$ ) were the leading comorbid disorders. Other comorbid psychiatric disorders included bipolar disorder ( $n = 1$ ), depression ( $n = 1$ ), sleep disorders ( $n = 2$ ), and disruptive behavior disorder ( $n = 2$ ).

To identify comorbid psychiatric disorders in children with ASD and to compare those comorbidity rates with those in children with ADHD, van Steensel et al<sup>62</sup> included 40 clinically referred children aged 7–18 years. *DSM-IV* classifications were used for the primary diagnosis (ASD/ADHD), whereas comorbid psychiatric disorders were assessed using a structured diagnostic interview, the structured clinical interview for *DSM-IV*, and childhood diagnoses (KID-SCID). The investigators found that 23 children with ASD (57.5%) had at least one comorbid disorder and that comorbid internalizing disorders were noted in 35% of the children with ASD (anxiety disorders, 27.5%; SAD, 2.5%; social anxiety disorder, 10.0%; specific phobia, 12.5%; GAD, 5.0%; OCD, 7.5%; panic disorder, 2.5%; agoraphobia, 0.0%; anxiety disorder not otherwise specified, 0.0%; post-traumatic stress disorder, 0.0%; mood disorders, 12.5%; major depressive disorder, 2.5%; and dysthymic disorder, 10.0%). Comorbid externalizing disorders were identified in 22.5% of the children with ASD (ODD, 22.5%; conduct disorder, 2.5%; and ADHD, 22.5%).

In a study that analyzed subclinical psychopathology in children and adolescents with ASD without mental retardation and comorbid psychiatric disorders, Caamaño et al<sup>63</sup> recruited 25 patients (mean  $\pm$  SD age  $12.8 \pm 2.86$  years) through the Spanish Asperger Syndrome Family Association (via advertisements) and from the ASD Program at the Hospital General Universitario Gregorio Marañón in Madrid, Spain. All participants had IQs within the normal range ( $> 85$ ) as per the inclusion criteria. All the diagnoses of ASD were made by psychiatrists at baseline based on the developmental history of each participant and on previous medical, psychoeducational, and specialized diagnostic private services reports using the *DSM-IV-TR* and Gillberg criteria.<sup>64</sup> When the presence of at least one symptom at threshold or subthreshold levels was placed within the different domains of the K-SADS-PL, they found that the study children had depressive disorder (56%), psychosis (12%), panic disorder (20%), SAD (28%), social phobia (40%), agoraphobia and specific phobia (36%), GAD (32%), OCD (48%), enuresis (16%), encopresis (12%), anorexia nervosa (8%), bulimia nervosa (0%), ADHD (68%), ODD (48%), conduct disorder (16%), or tic disorder (20%).<sup>64</sup> This set of data does not directly give information on the prevalence of comorbid psychiatric disorders, but it does provide evidence to support the strong potential for ASD to be comorbid with some psychiatric disorders.

To explore how a questionnaire, the CBCL, agreed with a *DSM-IV*-based semi-structured interview, the Kiddie-SADS, Gjevick et al<sup>65</sup> recruited 55 children and adolescents (aged 6–18 years) with ASD, including the main ASD subgroups and a broad range of cognitive and language functioning. They found high rates of psychopathology in this group of participants, showing that 40 children and adolescents (73%) were diagnosed with at least one comorbid *DSM-IV* disorder and that the most prevalent diagnostic groups were anxiety disorders (24 children, 44%) and ADHD (17 children, 31%). The prevalence of comorbid *DSM-IV* disorders are: any anxiety disorder (44%); specific phobia (31%); social phobia (9%); OCD (9%); any ADHD (31%); ADHD, inattentive type (20%); ADHD, combined type (5%); ADHD, hyperactive type (5%); any depressive disorder (11%); depressive disorder not otherwise specified (9%); major depressive disorder (2%); any tic disorder (15%); and ODD (7%).<sup>65</sup>

### 3.3. Summary of prevalence studies

In this review, 11 studies were identified in which a clinically defined population was used to assess the prevalence or rates of comorbid psychiatric disorders of ASD. Table 1 shows<sup>53–63</sup> the data for 5,207 children and adolescents who participated in the studies. However, seven of the 11 studies had a sample size  $< 100$ . One study<sup>59</sup> included 4,343 participants, which inflated the total number of participating children and adolescents. Only three studies reported a more extensive list of comorbid psychiatric disorders. Nevertheless, there are wide ranges of prevalence of all the major comorbid psychiatric disorders of ASD (Table 1). For example, the prevalence of “any comorbid psychiatric disorder” ranged from 27% (Rosenberg et al<sup>59</sup>) to 95% (Joshi et al<sup>56</sup>). At present, it is too early to give any scientifically acceptable prevalence of comorbid psychiatric disorders of ASD.

## 4. Conclusion

This extensive review of the literature found many studies that have presented data to support the belief that ASD has many comorbid psychiatric disorders. This review also found some evidence indicating high rates of certain comorbid psychiatric disorders such as ADHD and anxiety disorders in children and adolescents with ASD. However, as a result of the limited number of studies and the lack of a unified research approach, it is too early to

**Table 1** Percentages of comorbid psychiatric disorders

Study	Leyfer et al. (2006) <sup>53</sup>	Simonoff et al. (2008) <sup>54</sup>	Mattila et al. (2010) <sup>55</sup>	Joshi et al. (2010) <sup>56</sup>	Mukaddes et al. (2010) <sup>57</sup>	Gjevnik et al. (2011) <sup>58</sup>	Rosenberg et al. (2011) <sup>59</sup>	Skokauskas and Gallagher (2012) <sup>60</sup>	Memari et al. (2012) <sup>61</sup>	van Steensel et al. (2013) <sup>62</sup>	Gjevnik et al. (2014) <sup>63</sup>
Sample size (n)	100	112	50	217	60	71	4,343	59	91	40	55
Age range (y)	5–17	10–14	9–16	3–17	Unspecified	6.0–17.9	5–18	12.73 (2.9)	6–14	7–18	6–18
Nature of sample	Population	Population	Community	Clinic	Clinic	Special school	Community	Community	School	Clinic	Community
Any comorbid disorder		70		95	93(HFA) 100(AS)	72	27		28	58	
Any anxiety disorder			42	61		42	26	42		28	44
Generalized anxiety disorder				35		0				5	
Social anxiety		29				7				10	
Separation anxiety				37		0				3	
Specific phobia	44		22	37		31				13	31
Social phobia				28			9				
Agoraphobia				35						0	
Obsessive-compulsive disorder	37					10					9
Panic disorder				6						3	
Any ADHD	31	28		83		31	38	45	9	23	31
Any mood disorder						10				13	
Any depressive disorder							11		1		11
Depressive disorder NOS						7					9
Major depressive disorder	10			56		1				3	2
Dysthymic disorder										10	
Bipolar I or II disorder				31		0	5		1		
PTSD				2						0	
Any tic disorder			26			11					15
Motor or vocal tic disorder				23							
Tourette's disorder				18							
ODD		28	44	73		4			2	23	7
Conduct disorder				22						3	
Schizophrenia	0		0			0.5					
Psychosis				20		1					
Sleep disorder		2									
Eating disorder			0		0				10		
Enuresis				37							
Encopresis				22							
Substance use disorder			0	1							

ADHD = attention-deficit/hyperactivity disorder; AS = Asperger's syndrome; HFA = high-functioning autism; NOS = not otherwise specified; ODD = oppositional defiant disorder; PTSD = post-traumatic stress disorder.

determine the rates of comorbid psychiatric disorders in patients with ASD. In particular, no study has been carried out based on the newly published *DSM-5* definition of ASD, which would most likely exclude patients with *DSM-IV* mild ASD.<sup>66</sup> It is likely that patients with a diagnosis based on *DSM-5* ASD would most likely be the severe type of ASD, which may have a higher prevalence of comorbid psychiatric disorders. Clinicians are usually reluctant to make additional psychiatric diagnosis in lower functioning and/or non-verbal patients with ASD who are unable to, or are incapable of, providing diagnostic information via diagnostic interviewing. The current problem, the lack of a reliable and valid alternative diagnostic method to be applied to lower functioning and/or non-verbal autistic patients, is another contributory factor to the uncertainty of obtaining the true prevalence of comorbid psychiatric disorders in patients with ASD. At present, there is no data based on *DSM-5* ASD to show the area of ASD with the highest prevalence of comorbid psychiatric disorders.

Nonetheless, accepting that ASD does have comorbid psychiatric disorders has tremendous implications for the treatment of, or intervention in, patients with ASD. For example, if a patient with ASD also has a comorbid anxiety disorder and tic disorders, then the general principle of using one type of psychotropic medication will have to be replaced by applying a “polypharmacy” principle to obtain more effective treatment outcomes. Furthermore, to provide more effective treatment to people with AD, the current assessment technology must be advanced and refined. To accomplish this goal, some modifications of the contemporary diagnostic criteria of certain psychiatric disorders may be required when dealing with an autistic population. Future research should use epidemiological samples and multi-center models to obtain more valid and reliable data on the comorbid psychiatric disorders of patients with ASD.

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