

Chapter 2

Scope and Prevalence of the Problem

John F. Strang

Background Issues

Autism spectrum disorders (ASD) are often debilitating disorders, with only 9% of adults with ASD and average or above cognitive skills reaching full functional independence as adults (Farley et al. 2009). For more than 50% of individuals with co-occurring intellectual disability, outcomes are more bleak (LoVullo and Matson 2009). One of the primary complicating factors with ASD is the presence of co-occurring conditions (Matson and Goldin 2013). Depending on the study and characteristics of the groups studied, comorbid conditions are estimated to occur in about 70–80% of individuals with ASD (e.g., Leyfer et al. 2006; Mannion et al. 2013). In referred groups, the incidence of co-occurring conditions has been found to be even higher (Joshi et al. 2010).

Understanding the scope and the range of comorbidity in ASD is critical, as comorbid conditions often have a significant impact on the functioning of people with ASD (Kohane et al. 2012). Co-occurring conditions can exacerbate existing autism symptoms (Tureck et al. 2014) and make treatment less successful (Antshel et al. 2011). Co-occurring conditions can give rise to or make worse other comorbidities in an individual (Ming et al. 2008). Comorbidity makes ASD care more expensive, and families of individuals with ASD and comorbid conditions report a greater level of challenge in obtaining services for their children (Ahmedani and Hock 2011). Some studies have emphasized that apparent psychiatric and neurological comorbidities may obfuscate or delay a diagnosis of ASD, especially early on, and result in later identification of ASD as well as delayed ASD services (Gilmour et al. 2004; Mandell et al. 2007; Levy et al. 2010).

Separating out ASD symptoms versus additional diagnoses is particularly important for treatment planning, as different conditions may require different inter-

J. F. Strang (✉)

Center for Autism Spectrum Disorders, Children's National Medical Center,
Washington, D.C., USA
e-mail: jstrang@cnmc.org

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vention strategies. As important as diagnosing comorbidities is, however, the field can be challenging, with the diagnostic criteria for many co-occurring conditions overlapping with ASD symptom diagnostics (Matson and Nebel-Schwalm 2007; Mazefsky et al. 2012). Symptoms of ASD may also interfere with an individual's ability to report symptoms, and this may be particularly difficult in individuals with intellectual disability (Matson and Cervantes 2014). There have been efforts to develop new measures specifically designed for assessing comorbidity in ASD (e.g., Leyfer et al. 2006; Matson and Gonzalez 2007; Thorson and Matson 2012), as well as studies examining the performance of existing non-ASD specific measures in assessing comorbidity (Gjevik et al. 2014). Studies into comorbidities in ASD, in addition to informing clinical approaches and supports for individuals with ASD, may help to advance inquiries into the etiologies of ASD as well as specific etiological subgroups (Doshi-Velez et al. 2014).

In considering the literature to date on comorbidity in ASD, several biases have been discussed by investigators. Matson and Cervantes note the rapid increase in studies, but with a particular focus on studies of children and adolescents (Matson and Cervantes 2014). The authors also note the dearth of investigations into people with ASD and intellectual disability, with only a handful of studies available of adults with ASD and intellectual disability. This is problematic, as there is evidence of increased comorbidity among individuals with ASD and intellectual disability (LoVullo and Matson 2009). Few studies have investigated cross-cultural factors affecting diagnosis of comorbidities in ASD (e.g., Zachor et al. 2011).

Range and Rates of Comorbidities

Reported rates of comorbidities often vary significantly by study, related to factors of the study sample, such as population-based samples versus referred samples. Some disorders arise later in development, thus the age of study sample is critical in evaluating reported rates. Additionally, some disorders are particularly related to a subset of individuals with autism, such as those with intellectual disabilities.

Physical Conditions

Sleep

Sleep problems are among the most common comorbidities in children and adolescents with ASD, with approximately two-thirds of individuals experiencing at least one sleep problem in childhood (Richdale 2001; Richdale and Schreck 2009). This is in contrast to 25% of children, in general, who experience sleep problems (Sheldon et al. 2005). Having intellectual disability and autism puts a child at particular

risk for sleep problems, with up to 80% experiencing sleep disturbance (Sheldon et al. 2005; Richdale and Schreck 2009). Sleep problems in adults with ASD are less well understood, though one study found lower rates of sleep problems among young adults than in children (Kohane et al. 2012). Sleep problems are related to many other areas of functioning, including autism severity (Schreck et al. 2004), anxiety (Rzepecka et al. 2011), and other physical conditions (Ming et al. 2008), as discussed below.

Epilepsy

Rates of comorbid epilepsy vary according to a report, from 7% (Anne-Katrin et al. 2013) to 30% (Tuchman and Rapin 2002), related to characteristics of the study sample. This is in contrast to rates of 2–3% of the general population of children (Mannion and Leader 2013). A primary risk factor for epilepsy is co-occurring intellectual disability; Amiet and colleagues found that 21.4% of the children with autism and intellectual disabilities had epilepsy, as compared to only 8% of those with ASD and no intellectual disability (Amiet et al. 2008). Female sex is also related to higher rates of epilepsy in ASD, with findings that epilepsy occurred in 35% of females and 18.5% of males (Amiet et al. 2008). An epilepsy diagnosis often emerges later in childhood, which results in higher rates of epilepsy later in development (Bolton et al. 2011). In a study of 21-year olds with ASD, the average age of diagnosed epilepsy was 13 years, with most seizures beginning after the age of 10 years (Bolton et al. 2011).

Gastrointestinal Symptoms

There is a significant variability in reported rates of gastrointestinal symptoms (GI) (Mannion et al. 2013), with most common symptoms reported being abdominal pain, constipation, food refusal, diarrhea, and nausea (Mannion et al. 2013; Ibrahim et al. 2009). Reported rates of GI problems in children with ASD range from 9 to 84% (Melmed et al. 2000; Horvath et al. 2000; Black et al. 2002; Kuddo and Nelson 2003), with some studies failing to find rates significantly higher than in the general population (Black et al. 2002). Apparently, there is no evidence for atypical motility in ASD (Buie et al. 2010). Although some emphasize that overly fixed/limited diets may lead to lack of fiber and fluids, the findings are mixed. One study failed to find a relationship between atypical diet and constipation (Gorrindo et al. 2012), while another reported a relationship between food intolerance and GI dysfunction (Ming et al. 2008). Nikolov and collaborators found that children with ASD and GI symptoms were no different from other ASD children in demographics, adaptive functioning, or ASD severity (Nikolov et al. 2009).

Other Physical/Medical Comorbidities

Many other physical/medical comorbidities have been reported, particularly among individuals with autism and intellectual disability (Hass 2010; Maski et al. 2011). Isaksen and colleagues performed comprehensive medical evaluations on 79 children diagnosed with ASD. Out of them, 10% were found to have a specific medical syndrome in addition to ASD (Isaksen et al. 2013). Neurological findings, including brain nerve pathology, motor disturbances, nystagmus, cerebellar pathology, and sensory dysfunction were common, especially among the intellectual disability group (21.4%). Dysmorphic findings were also common, occurring in 20.6% of the patients.

Psychiatric Comorbidities

Attention Deficit/Hyperactivity Disorder

Recent studies of comorbid psychopathology in ASD have focused extensively on attention deficit/hyperactivity disorder (ADHD) over other psychopathologies, possibly due to apparent rates of comorbid ADHD in ASD of over 50% (Matson and Goldin 2013). The literature reports a range of comorbidity rates for ADHD, from 30 to 80% (Leyfer et al. 2006; Simonoff et al. 2008; Ames and White 2011). A study of younger children with ASD (4–6 years old) found 41% met the criteria for comorbid ADHD (Carlsson et al. 2013). Individuals with ASD and lower cognitive skills may be more likely to have comorbid ADHD than those with greater cognitive skills (Lee and Ousley 2006). Rates of ADHD in adults with ASD have been understudied, but one group found that almost 37% of the adults with ASD self-reported significant ADHD symptoms (Johnston et al. 2013). Prior to *The Diagnostic and Statistical Manual of Mental Disorders* 5th ed. (DSM-5; American Psychiatric Association 2013), ADHD symptoms were technically subsumed into the diagnosis of ASD, and a comorbid ADHD diagnosis was not permitted. Some studies have focused on the discernment of distinct symptoms of ADHD from ASD (e.g., Gadow et al. 2006). Others have emphasized the shared etiological factors of ASD and ADHD (van der Meer et al. 2012), with increased risk for both ASD and ADHD in families, with symptoms identified in the areas of executive function skills, motor speed, emotion recognition, and detail-focused processing (Corbett et al. 2009; Fine et al. 2008; Booth and Happé 2010).

Given shared etiological factors, some have considered that ADHD and ASD may be individual manifestations of a larger disorder. Analysis of symptom clusters has suggested that the two disorders are partly distinct, with three classes of symptoms identified: (1) ADHD symptoms only, (2) clinically significant ADHD and ASD symptoms, with ADHD as the most prominent symptom cluster, and (3) clinically significant ASD and ADHD symptoms, with ASD as the most prominent

symptom cluster (van der Meer et al. 2012). Notably, in van der Meer et al.'s study, no class with just ASD symptoms was found; all the children who had ASD symptoms also presented with some level of ADHD symptoms, thus the two disorders are described as “partly distinct.”

Anxiety Disorders

Anxiety disorders are reported to occur in 25–50% of individuals with ASDs (Leyfer et al. 2006; Kuusikko et al. 2008; Sukhodolsky et al. 2008; Mattila et al. 2010). A meta-analysis of anxiety studies in children and adolescents with ASD found that almost 40% of the young people with ASD met criteria for at least one anxiety disorder (Steensel et al. 2011). The most common was specific phobia (almost 30%), followed by obsessive-compulsive disorder (OCD; 17.4%) and social anxiety disorder (16.6%). Studies are mixed in their findings of correlates to anxiety in ASD, with some finding anxiety symptoms pervasive across groups, regardless of age, IQ, or autism symptoms (e.g., Strang et al. 2012). Other studies have reported specific patterns of anxiety symptoms related to individual characteristics. For example, one study found a relationship between higher functioning ASDs and increased social worries, and lower functioning ASDs and increased avoidant and obsessive-compulsive ASD symptoms (White et al. 2009.) However, somewhat contrasting findings have also been reported, with lower IQ groups experiencing higher rates of anxiety in general and social anxiety, and higher IQ groups experiencing higher prevalence of OCD and separation anxiety. Greater age has been linked to increased incidence of anxiety disorders, though curiously, studies including younger children with ASD reported higher rates of OCD than studies with older children, which is the opposite pattern found in studies of OCD in general (Steensel et al. 2011). Atypical OCD age findings in ASD may reflect the diagnostic complexity of differentiating OCD from ASD core symptoms (see below, Symptom overlap).

Mood

Depression

Reported prevalence rates of depression in ASD vary widely, from 1.1 to 52% (Levy et al. 2010; Hofvander et al. 2009). The comorbidity of ASD and depression has received significant attention, and findings have articulated a particularly complex and nuanced relationship between the disorders (Magnuson and Constantino 2011). Magnuson and Constantino summarize a case literature of presentations of depression in ASD, noting that clinicians often rely on self report of depression symptoms, which may be limited in ASD (Tager-Flusberg 1992). The authors iden-

tify several key diagnostic signs of depression in ASD, independent of self-report, based on previous studies: sadness, tearfulness, apathy, negative affect, anhedonia, changes in sleep/weight, decline in performance/skills, and preoccupation with death (Magnuson and Constantino 2011, citing Ghaziuddin et al. 2002; Stewart et al. 2006; Lainhart and Folstein 1994; Perry et al. 2001; Pollard and Predergast 2004; Janowsky and Davis 2005). In patients with ASD and intellectual disability, self-injurious behaviors are significantly related to depression (Janowsky and Davis 2005). Lower rates of depression are reported in studies of younger individuals (e.g., Levy et al. 2010), and several authors have noted greater depressive symptoms in individuals with less autism impairment, higher IQ, and greater insight into their condition (e.g., Vickerstaff et al. 2007; Sterling et al. 2008; Mazurek and Kanne 2010). However, several authors also report very high rates of mood disorders in people with autism and intellectual disability (Bradley et al. 2004; Bradley and Bolton 2006; Hill and Furniss 2006). These may be two different paths to depression, and the qualitative nature of the depression for high functioning and more insightful and intellectually disabled individuals may be very different. Rates of depression may increase into adulthood, with one study finding more than 50% of the participants with ASD meeting criteria for depression (Hofvander et al. 2009). The quality of friendship has been related to experienced loneliness in ASD, which is related to increased depression (Whitehouse et al. 2009).

Bipolar Disorder

The comorbidity of bipolar disorder and autism is understudied and controversial (Matson and Nebel-Schwalm 2007). There is some evidence of an over-representation of bipolar disorder in referred adolescents and young adults with high functioning ASD (Munesue et al. 2008), as well as among adults (Stahlberg et al. 2004). Studies have indicated high rates of bipolar disorder among relatives of ASD probands (Bolton et al. 1998) as well as ASD among bipolar disorder probands (Joshi et al. 2013). Whereas some have suggested that bipolar disorder rates may be underestimated in ASD (Raja and Azzonoi 2008), others have noted that bipolar disorder may be over-diagnosed in ASD (Mazefsky et al. 2012).

Developmental Comorbidity—Intellectual Disability

Rates of co-occurring autism and intellectual disability vary by report. The Centers for Disease Control indicate 54% of individuals with ASD in 2010 had concurrent intellectual disability (Centers for Disease Control and Prevention 2014). Former reports were often higher, with rates up to 70% (La Malfa et al. 2004). The apparent drop in rates of ASD and intellectual disability over recent years has been attributed to the increasing number of individuals with higher cognitive abilities being diagnosed with ASD, and not to a decrease in the numbers of

individuals with autism and intellectual disability (Keen and Ward 2004). Around 40 % of individuals with intellectual disability are reported to have autism (Keen and Ward 2004).

The comorbidity of autism and intellectual disability results in striking impairments, far and above those experienced by individuals with intellectual disability alone (Brereton et al. 2006; Hill and Furniss 2006). Anxiety, mood disorders, problem behaviors, feeding issues, and stereotypies are greater in people with intellectual disability who also have autism (Hill and Furniss 2006; Bradley and Bolton 2006). Matson and Shoemaker's (2009) review of co-occurring autism and intellectual disability notes the dearth of studies on comorbidities in this area, as well as the over-focus on higher functioning individuals with autism in recent years, in spite of the greater numbers with intellectual disability and their higher levels of impairment (Matson and Shoemaker 2009).

Interrelatedness and Impact of Comorbidities

Comorbidities in ASD are often interrelated, and they can exacerbate ASD symptoms, reduce overall functioning, and result in poorer clinical outcomes over time. They are, therefore, a critical target for assessment and treatment. For example, children with comorbid ADHD and ASD had higher rates and intensity of other comorbidity than children with either ASD or ADHD (Gadow et al. 2009; Jang et al. 2013). The comorbidity of mood disorders in ASD may worsen the progression of ASD, with increased impairment of core skills (social and communication) and increased repetitive behaviors (Lainhardt 1999; Perry et al. 2001). Garcia-Willamizar and Rojahn found that comorbid psychopathology mediated the relationship between autistic traits and repetitive behaviors/restricted interests in adults with ASD and intellectual disability (Garcia-Villamizar and Rojahn 2013). The authors suggested that treating comorbid psychopathology and reducing stress could reduce the frequency and intensity of repetitive behaviors. It is important to consider the comorbidities caused by comorbidity. For example, epilepsy has its own comorbidity, including mood symptoms/suicidal ideation (Hecimovic et al. 2011).

Some investigators have found that medical comorbidities tend to cluster together, as psychiatric comorbidities (Ming et al. 2008). Others have found interrelatedness between medical and psychiatric symptoms (Rzepecka et al. 2011), particularly in the area of sleep and ASD. Sleep problems have been shown to be related to GI problems (Mannion et al. 2013); the greater a child's GI symptoms, the worse their sleep ratings. Sleep difficulties have also been linked to increased mood problems (Ming et al. 2008), as well as increased anxiety in children with ASD (Rzepecka et al. 2011). Sleep problems exacerbate ASD-related symptoms. Schreck et al. (2004) found less sleep was related to increased ASD severity ratings, increased stereotypic/repetitive behavior, and social skill weaknesses. Others have also reported a link between sleep problems in ASD and poorer social interactions (Malow et al. 2006), and too little sleep can reduce the ability to read social cues

(van der Halm et al. 2010). Goldman et al. (2011) found that poor sleep in ASD was related to more behavior problems.

Comorbidities in ASD, and especially ADHD, may have significant impact on intervention. Antshel et al. (2011) examined the outcomes from social skill intervention for children with ASD, children with ASD+anxiety disorders, and children with ASD+ADHD and found that the intervention was effective for those with ASD or ASD+anxiety disorders, but not for those with ASD+ADHD. Results indicated that social skill intervention was particularly well suited for ASD+anxiety disorder; the authors note that social skill intervention is efficacious for both ASD and anxiety disorders, so the combination of both may lend itself to this type of treatment.

In a phone survey study, the presence of an ASD and a comorbid psychiatric condition related to significantly worse health outcomes as compared to having autism alone (Ahmedani et al. 2011); children with ASD and comorbid conditions were more likely to have poor overall health and “prevented in ability.” Families of individuals with ASD and comorbidity were less satisfied with provider communications, and they were less likely to be successful in having insurance cover the necessary services for their child. Comorbidity in ASD also increases ASD-related expenditures. Children with autism have been found to have average medical expenditures 3–9 times higher than children without ASD (Amendah et al. 2011), though more recent studies have indicated even higher expenditure rates (Peacock et al. 2012). Peacock et al. looked at the impact of three co-occurring conditions with ASD on expenditures, according to a review of Medicaid records. Co-occurring autism and intellectual disability resulted in the greatest expense, 2.7 times more than for children with autism alone.

Symptom Overlap

Matson and Nebel-Schwalm (2007) highlight the heterogeneity in symptoms of ASD, which can make it difficult to differentiate ASD symptoms and comorbidities, and emphasize the importance of working to identify one comorbidity as primary in order to determine priority of intervention, long-term prognosis, and allocation of services. However, early in development this may be particularly challenging. Gillberg notes the complex overlap of symptom clusters, particularly in early childhood (Gillberg 2010). Carlsson et al. (2013) emphasize the importance of diagnosing over time in young children, as co-occurring disorders can make the diagnoses less clear at first. New instruments designed to assess comorbidity in ASD are being developed, such as the Autism Spectrum Disorder-Comorbidity for Children (ASD-CC; Matson and Gonzalez 2007).

Features of emotional dysregulation in ASD may result in inaccurate psychiatric diagnoses, or make diagnosing autism more difficult. Mazefsky et al. (2012) found that nearly 60% of the prior psychiatric diagnoses given to a group of young people with ASD (age 10–17; IQ: 71–144) were not supported by a careful psychiatric interview that accounted for ASD-related impairment. Most notably, diagnoses of

bipolar disorder or OCD were not supported in any of the individuals who had previously received these diagnoses. Almost one-third had a previous ADHD diagnosis that was not supported. Concordance for depression was higher, with 57% of the prior depressive disorder diagnoses maintained. Mazefsky et al. note that impediments to correct diagnosis such as diagnosing a psychiatric diagnosis instead of ASD, may delay the diagnosis of ASD, thereby preventing a child from receiving critical early intervention for ASD. The authors also cite Mandell's (2008) study, which found that later ASD diagnosis was related to higher chance of psychiatric hospitalization. In Mazefsky's study, out of eight children who had psychiatric hospitalizations only one was diagnosed with ASD prior to the hospitalization.

Similarly, Levy et al. (2010) in a population-based cohort, found a relationship between later diagnosis of ASD and the presence of co-occurring symptoms. Co-occurring non-ASD diagnoses were related to later age of ASD diagnosis. The authors note that "the symptomatology associated with non-ASD conditions might complicate recognition of ASDs and thus result in delayed identification" (Levy et al. 2010, p. 271). Pressures for billing may also complicate diagnostics; Leslie and Martin (2007) highlight that insurance reimbursements are often not made when a clinician bills under an autism diagnosis, which may lead clinicians to add, or put as primary, comorbid diagnoses.

OCD and social anxiety disorder each provide a rich example of the potential complexities of diagnosing comorbidities in ASD. OCD is typically diagnosed later in childhood and in adolescence, but studies in ASD have found a relationship between younger age and increased rates of OCD (Steensel et al. 2011), suggesting perhaps a different course for OCD in ASD, or more likely, diagnostic challenges. The core symptoms of ASD overlap with symptoms of OCD, and authors note the difficulty detangling symptoms of the two disorders (e.g., Matson and Cervantes 2014.) Van Steensel et al. (2011) have suggested that by assessing the nature of the special interests and routines, one can better differentiate ASD versus ASD+OCD, with each having a different character. Ruta and colleagues (Ruta et al. 2010) examined differences in symptoms between children with ASD and OCD, noting some areas that distinguished the groups, including higher frequencies of contamination and aggressive obsessions, as well as checking compulsions. Although diagnostic differentiation is a primary goal, there has been some suggestion that treatments appropriate for one disorder may transfer to the other, without a need for absolute diagnostic distinction (Rooney et al. 2011).

Difficulties in differentiating social anxiety from ASD core social symptoms are also notable. Van Steensel et al. (2011) suggest an important discriminating factor may be that the behavioral symptoms seen in both disorders such as social withdrawal, preferring to be alone, gaze avoidance, and not speaking in social situations may be more variable in children with social anxiety, whereas they would probably vary less in ASD without social anxiety. Summarizing several studies (Reaven and Hepburn 2003; Leyfer 2006; Matson and Nebel-Schwalm 2007), Rieske et al. (2012) note that features central to anxiety including unrealistic fears and sympathetic nervous system triggering, should be distinguished from impairment related to symptoms of ASD, such as a lack of engagement due to communication weaknesses or an over-focused interest.

Conclusions

Mazefsky et al. (2012) have outlined several possible understandings of high comorbidity in ASD:

1. Family history studies report high rates of emotional disorders in the relatives of children with ASD (e.g., Mazefsky, Folstein and Lainhardt 2008)), which suggests a genetic link between ASD and other disorders. Autism and ADHD run together in families (van der Meer et al. 2012), as do bipolar illness and ASD (Bolton et al. 1998; Joshi et al. 2013).
2. It may be the case that what is seen as a comorbidity is really a manifestation of ASD symptoms. Studies have shown that symptoms of apparent comorbidities can obfuscate an underlying ASD diagnosis (Mazefsky et al. 2012).
3. Varying progression of symptoms in an individual over time may appear as different disorders, but may be reflective of the same underlying pathology.
4. Having one disorder can increase the risk of a second. For example, more negative feedback from peers, awareness of social difficulties, etc., may contribute to the co-occurrence of ASD and social anxiety disorder (White et al., 2012)

Most comorbidity studies have focused on a single comorbidity or cluster of comorbidities. A new direction, now available with larger datasets, is analysis of symptom clusters. Doshi-Velez and colleagues (2014) examined electronic records, 4934 individuals of age 15 years and older. Although the study could only account for a small proportion of individuals included, the study identified three discernible symptom clusters:

1. A seizure group with high rates of intellectual disability (60%) and lower rates of boys. The authors note the established diagnostic connections between the following: autism, seizures, intellectual disability, and increased rates of female gender.
2. A multisystemic disorders group with high rates (50%) of intellectual disability. Disorders in this group included gastrointestinal, auditory disorders, and infections, and the authors noted previous studies suggesting an underlying biology for such interconnections.
3. A largely higher IQ group (only 28% ID) with primarily psychiatric disorders, and especially anxiety.

Future directions in comorbidity and ASD research should further articulate symptom cluster groups, particularly in the overlap between ADHD and ASD, and the apparent emerging subgroups of individuals with components of each disorder. A particular need in the field is better tools to differentiate complex mood disorders from autism. Currently, problems diagnosing ASD in dysregulated children result in late diagnosis and poorer outcomes. As ASD treatment studies continue to develop, it will be helpful to study the impact of various comorbidities with ASD on treatment efficacy, and to tailor interventions accordingly. Finally, the interconnections

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