

Emotional Dysregulation and Comorbidity in Autism Spectrum Disorder (ASD)

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Abstract

There is growing recognition that individuals with autism spectrum disorder (ASD) struggle with anxiety, depression and anger: symptoms that are not part of the diagnostic criteria for the disorder. Psychiatric comorbidity is common, although prevalence estimates vary widely. Rates vary from 28 to 84% of individuals with ASD meeting criteria for at least one other psychiatric disorder. Results of a meta-analysis indicate that the pooled prevalence estimate of comorbidity is 68%. Individuals with ASD have more emotional and behavioural problems than the general population and other clinical groups. It is important to understand this comorbidity because of its high prevalence, impact on both current functioning and long-term outcomes, persistence of symptoms, and cost to the individual, their family and society. The recognition and assessment of emotional and behavioural problems in individuals with ASD is challenging. Comorbid psychiatric disorders should be assessed and diagnosed early to support the individual and their family better in school/work and home environments in order to improve the quality of their lives and improve longer-term outcomes.

Emotional Dysregulation and Comorbidity in Autism Spectrum Disorder (ASD)

There is growing recognition that, in addition to the difficulties with social-communication and repetitive behaviours and/or interests, with which individuals with ASD struggle, behavioural problems and emotional difficulties are an added burden and impairment (1-9). Concerns about emotional functioning are not new and were noted in Kanner's (10) original description of children with "classic" autism. Not only do individuals meet diagnostic criteria for various mental disorders but many also just fall short of meeting full diagnostic criteria and are considered subsyndromal for the disorder, suggesting that these individuals are experiencing mental health symptoms and would also be likely to benefit from treatment (5). Thus, emotional and behavioural symptoms and disorders are commonly experienced by individuals with ASD.

Importance

Given that psychiatric concerns are common in ASD, occurring in approximately 28 to 84% of individuals, it is important to understand this comorbidity because psychiatric problems cause considerable distress, interfere with daily functioning, and significantly impact long-term prognosis and outcome (11). For instance, children with comorbid anxiety and mood problems have been reported to be more aggressive and to have poorer social relationships; their parents' social activities were also more limited than in ASD individuals without such comorbidity (12). Behavioural problems have been associated with difficulties in functioning within the community (13,14), parental stress (15)

and use of psychotropic medication to stabilize behaviour (16). In addition, many individuals with ASD and with psychiatric concerns are at risk for being hospitalized (17-19). There is evidence that psychiatric concerns are present early in life (20,21), persisting from childhood to adolescence (22) and into adulthood (23-26). Furthermore, the presence of a comorbid psychiatric disorder has important implications for treatment. Recognition that problem behaviours are related to a comorbid psychiatric disorder, rather than being an isolated behaviour or secondary to the ASD, allows for more specific and targeted treatment, which is associated with greater improvement (5). Without intervention, emotional and behavioural concerns may become more impairing as children grow older, negatively impacting long-term prognosis and outcome (11). Thus, addressing mental health concerns is an important treatment focus for this population, to minimise the long-term cycle of maladaptation. There is a growing body of evidence that treatments, such as cognitive behavioural therapy (CBT), are effective in this population (27). These findings highlight the potential impact of psychiatric concerns on the lives of individuals with ASD and their families.

Comorbidity in ASD

Individuals with ASD often struggle with multiple psychiatric disorders; 28 to 84% meet criteria for one psychiatric disorder and 27 to 50% for two or more (see Table 1 (2-3, 5-7,24,25,28-33)). A meta-analysis was conducted to obtain an impression of the overall prevalence estimates across all the studies reviewed that examined psychiatric problems. Studies were included if they reported the percentage of individuals with ASD who met criteria for at least one psychiatric disorder, regardless of methodology used to calculate prevalence (i.e., interview, questionnaire, etc). The literature was reviewed using PsycLit/PsycInfo and MEDLINE, by examining the references of articles reviewed (i.e., ancestor search), and by reviewing reference lists of review articles. Prevalence was determined by calculating the number of cases who met criteria for one psychiatric disorder across all studies, divided by the pooled sample size. An estimated 68% of individuals with ASD met criteria for at least one psychiatric disorder.

Prevalence estimates are generally high, even in studies that employed population-based recruitment strategies (see Table 1). It is important to examine comorbidity in population-based samples since clinically-referred samples tend to overestimate the prevalence (34). Furthermore, anger, anxiety and depression commonly co-occur and are positively correlated with each other (5,12,14,35-39). For example, Quek et al. (38) found that feelings of distress (such as depression) commonly co-occur with anger in individuals with ASD. This is consistent with findings in the general population (40).

Types of Comorbid or Co-occurring Disorders

Studies examining psychiatric comorbidity have been conducted primarily in children and adolescents (2,5,8,9,29,31,41,42), although studies examining these issues in adults are emerging (6,32,43-46) and rates of mental health concerns are being reported in follow-up studies examining outcomes in adults (23-25), see Table 2. As can be gleaned from Table 2, psychiatric concerns are common in children, adolescents and adults with ASD, but it is notable that rates vary widely. The inconsistencies in reported prevalence findings may be accounted for by differences in sampling (e.g., clinic vs. population-based), assessment (e.g., questionnaire vs. interview) and diagnostic (e.g., symptoms vs. disorder) approaches used in different studies. For instance, rates of depression range from 1-70%. In general, rates of depression were higher in the studies where the majority of participants were adolescents/adults, as compared to children/adolescents; consistent with rates in the typically-developing population which increase from childhood to adolescence and are highest in young adulthood (47). Rates of depression were lowest in the samples that employed a population-based methodology (7,23). Lugnegard et al. (46) reported the highest rates of depression, with 70% having experienced at least one episode of major depression and 50% with recurrent depressive episodes. Some of the reported variability may be related to what information is reported, such as current vs. lifetime prevalence or single vs. recurrent episodes. In a recent study, Kaat et al. (3) found that prevalence rates varied, depending on the mental health parameter used to determine presence of the disorder. Specifically, rates based on impairment cut-offs (i.e., extent to which psychiatric symptoms impair the child's functioning) were higher than symptom cut-offs (i.e., number of

psychiatric symptoms), and lowest rates were for clinical cut-offs (i.e., met both impairment and symptom cut-offs); however, prevalence remained high, regardless of the parameter used. For example, prevalence rates for any disorder based on combined parent and teacher report using impairment cut-off was 94%, symptom cut-off was 87%, and clinical cut-off was 84%. These findings are consistent with previous work (48). Although it is difficult to draw conclusions about rates of the various comorbid mental disorders from these varying estimates, it is clear that individuals with ASD struggle with comorbid mental health concerns.

Findings in Children and Adolescents

A systematic review examining psychosis, affective disorders and anxiety in children and adolescents with ASD found that the rates of comorbidity ranged from 0-6% for schizophrenia, 5-35% for generalized anxiety disorder (GAD), 10-64% for simple phobias, 1-37% for obsessive-compulsive disorder (OCD) and 0-50% for affective disorders or symptoms (8). Simonoff et al. (7) examined psychiatric comorbidity in a subgroup of 112 children, 10-14 years of age, from a population-derived sample using a semi-structured psychiatric interview. They found that the most common diagnoses were social anxiety disorder, 29%, attention deficit/hyperactivity disorder (ADHD), 28%, oppositional defiant disorder (ODD), 28% and GAD, 13%.

More recently, Totsika et al. (41,42) examined these problems in children and adolescents with ASD, with and without the presence of intellectual disability (ID), using a population-based sample. Behavioural and emotional problems were assessed using a questionnaire, and children who scored in the borderline or clinical range were combined to identify children with concerns. In a group of 5-year-old children with ASD, they found high rates of hyperactivity (ASD+ID: 88% vs. ASD: 59%), conduct problems (ASD+ID: 58% vs. ASD: 46%), and emotional symptoms (ASD+ID: 39% vs. ASD: 38%); with hyperactivity being significantly higher in children with ASD+ID (41). In a group of 5 to 16 year olds, reported rates were generally higher than rates reported in the sample of 5-year-old children with ASD (with and without ID), and similar, regardless of the presence of ID: hyperactivity (ASD+ID: 88% vs. ASD: 85%), conduct problems (ASD+ID: 65% vs. ASD: 64%), and emotional symptoms (ASD+ID: 71% vs. ASD: 74%) (42). The rate of concerns reported in the studies by Totsika et al. (41-42) were higher than in the study by Simonoff et al. (7), which is probably accounted for by the method of assessment ('interview format' to identify DSM-IV and ICD-10 diagnoses vs. 'questionnaire format' to identify symptoms). Taken together, serious concerns about emotional and behavioural functioning are generally reported in children and adolescents.

Findings in Adults

Consistent with the literature in children, adults with ASD also present with high rates of psychiatric comorbidity. Although studies report variable prevalence rates, in general, concerns about anxiety and depression remained high, whereas psychotic and substance-related disorders were uncommon (46), see Table 2. Hofvander et al. (44) conducted the largest study (N=122) in adults (aged 16 to 60) with ASD and normal intelligence that specifically examined psychiatric and psychosocial problems. They reported that Lifetime axis I disorders were common, with mood (50%) and anxiety disorders (53%) being the most common. Regarding the rate of lifetime axis II disorders, 62% met criteria for at least one personality disorder (PD) with obsessive-compulsive PD being the most common (32%). Somewhat lower rates were reported in other studies: 12 to 22% for anxiety (6, 25) and 1 to 32% for depression (6,23-25).

Comorbidity in ASD Compared to Other Populations

Individuals with ASD experience more psychiatric symptoms than the general population (21,49,50), and rates that are comparable to or higher than other clinical groups (51,39,49,50,52-54) or individuals with other psychiatric concerns (21,50,55). With regard to the last, in a psychiatrically-referred population of youth with and without ASD, not only were the levels of psychiatric comorbidity found in those individuals with ASD higher, but the pattern of concerns differed: they were more functionally

impaired and their needs were more complex; for example, they required extra assistance in school and more therapeutic interventions (55). Mazzone et al. (56) noted the suggestion of a possible bidirectional relationship between autistic disorders and psychiatric symptoms: individuals with ASD not only have a higher prevalence rate of anxiety disorders (8), but individuals with anxiety disorders have a higher rate of autistic traits (57). However, as intimated by these authors, the concept of bidirectionality is questionable when one of the conditions is a neurodevelopmental disorder, as is the case for autism; this implies that the autism is the underlying disorder, not that the other disorder is in some way causing the autism. Traits that could be described as “autistic” arising from a condition such as depression should not be confused with underlying autism, since it would be expected that these traits would improve or resolve completely during periods when the depression has lifted.

Levels of comorbidity are higher in individuals with ASD (with and without an ID) than those with ID alone (1,41,42,58,59), although this is not a consistent finding (60). A recent population-based investigation examining behavioural and emotional problems comparing children aged 5 to 16 years who had ASD (with and without ID), ID only, or neither condition (comparison group), found that the level of problems was highest among individuals with ASD (with and without ID) (42). The presence of ASD and ID significantly and independently increased the risk for all these problems, although the contribution of ASD was larger than that of ID (42), which is consistent with other findings in younger children (41,61). Thus, ASD and ID are independent risk factors for behavioural and emotional problems, with onset at an early age.

It has also been shown that different IQ levels are associated with different profiles of behavioural problems (48,58,62). Brereton et al. (58) found that children and adolescents with ASD and moderate to severe levels of ID were more self-absorbed and had more difficulty with social relating, whereas individuals with IQ in the borderline to normal range had more problems with communication. Estes et al. (62) found that IQ predicted a different pattern of associated symptoms from early to later childhood (from age 6 to 9). Specifically, those children classified as lower functioning (IQ below a standard score of 70) presented with higher levels of attention problems, hyperactivity and irritability, whereas the children classified as higher-functioning had increased internalizing symptoms. Witwer & Lecavalier (48) found that children with ASD and ID (IQ below 70) reported fewer symptoms overall, and were less likely to meet full criteria for GAD but more likely to be subsyndromal for GAD. Therefore, it is important to consider the moderating impact of intellectual functioning on the presentation of psychiatric symptoms in individuals with ASD.

Challenges with Assessment and Differential Diagnosis

What are the challenges?

Recognizing and assessing comorbid psychiatric concerns in people with ASD can be challenging for clinicians. Individuals with ASD may have insufficient awareness and/or language to describe their internal states, symptoms, or physiological experiences, thereby leaving the clinician to gather clinical information about the individual from parents/caregivers, through direct observation in the clinic or the individual's social environment (56). Other issues arise when behavioural/emotional difficulties are associated with severe cognitive impairment; this population is particularly challenging in terms of assessment (63).

Another challenge is determining whether the psychiatric symptoms in ASD are part of the same dimension (part of the autism spectrum) or a different dimension (part of a comorbid psychiatric disorder). Thus, differential diagnosis is complicated by difficulties differentiating between comorbid psychiatric symptoms and core ASD symptoms; these symptoms may be difficult to distinguish because they are overlapping, the presentation of psychiatric concerns may be atypical, and psychiatric concerns might be masked by symptoms typical of ASD. For example, as noted in Table 2,

OCD has been reported in 6-55% of individuals with ASD; however this remains controversial given that obsessional, stereotyped and repetitive behaviours are core features of ASD and it is difficult to determine whether the obsessive and compulsive (OC) behaviours that are present are part of the core

ASD symptoms, or related to OCD.*

Recent evidence has shown that individuals with ASD report higher frequencies of compulsive saving/hoarding and ordering; whereas the individuals with OCD reported higher frequencies of contamination and aggressive obsessions and checking compulsions (64,65) and higher severity of symptoms (65,66). No differences have been found in the

level of awareness of the intrusive and distressing nature of the symptoms (egodystonicity), although an absence of insight was seen in the ASD group (65, 66). Furthermore, individuals with ASD do not tend to show distress or perform rituals to alleviate anxiety (65), although this is not a consistent finding (67). Thus, the overlap in symptoms complicates differential diagnosis. To illustrate this further, many features that are characteristic of ASD, such as social withdrawal, limited facial affect, flattened affect, are also features of depression (8). Also, resistance to change and repetitive questioning, which are characteristic of ASD, are also seen in anxiety (9). Difficulty identifying or articulating feelings of distress may present differently (e.g., overwhelmed, agitated, scared) (68) in ASD than in typically developing individuals. Moreover, it may be difficult to determine whether a change (exacerbation or improvement) in ASD symptoms represents the presence of a psychiatric disorder, or is due to other factors (56). For example, a decrease in repetitive and obsessive behaviours, that may indicate the presence of a psychiatric concern such as depression, might be mistakenly interpreted as an improvement in ASD symptoms (69). Conversely, psychiatric concerns can also exacerbate ASD symptoms, such as an increase in ritualistic behaviours and incorporation of depressive themes into obsessions (14,51,70).

Assessment Recommendations

The assessment of mental health problems in individuals with ASD is challenging. It is important to determine which symptoms are part of the autism spectrum and which are part of the mental health concern. To do this it is important to distinguish between 'competence' and 'performance' (change in behaviour) (14,71). An example of competence in a specific skill may be impaired nonverbal communication which is seen in all situations (part of core ASD); whereas, nonverbal communication difficulties that are due to a psychiatric condition may not be seen in every situation. Thus, it is important to determine whether there is a change over time in the behaviour (9,12). It is also important to establish deterioration in adaptive functioning, and whether the impairment is over and above the impairment caused by the primary diagnosis of ASD (9). Last, given that IQ and language affect endorsement rates (48), modifications may need to be applied when using DSM criteria.

Assessment Tools

In clinical practice, psychometric tools, such as questionnaires and interviews, are often used to screen or assess emotional and behavioural concerns (72). Although clinicians find these tools to be valuable, few questionnaires or interviews have been specifically validated, designed or modified to assess comorbid psychiatric symptoms in ASD. Current studies examining psychiatric comorbidity in ASD typically use DSM-IV diagnostic criteria or adapt scales that were developed for use in the general population, which has several limitations (56). Measures that are designed or modified specifically to assess comorbid psychiatric symptoms in ASD are beginning to emerge, for example, the Autism Comorbidity Interview - Parent and Lifetime Version (5); however, these types of measures are time-intensive and require highly-trained staff to administer. It is consequently also important to determine the reliability and validity of shorter screening questionnaires. A recent study examining the utility of self-report measures to screen for psychiatric comorbidity in a group of 10 to 17 year old children with ASD and without ID found a lack of concordance between self-report questionnaires and structured parent interviews, suggesting that self-report measures may provide some useful information but not sufficient for clinical diagnostic purposes (73); this is also true for typically developing children

*Editor's note. The authors correctly allude to the important distinction between the core autism symptoms of excessively-preferred thoughts or activities which the individual typically enjoys, on one hand, and obsessive-compulsive disorder which is associated with anxiety in the individual, on the other hand. Both may coexist.

(74). It is also important to be aware of the impact of different environmental factors (e.g., family, daily routines) on psychiatric comorbidities in order to develop better social supports and coping strategies (75). Given that there is often a lack of consensus between informants (child, parents, teachers) on the presence of symptoms, it is recommended that additional information be obtained, based on multiple informants and settings, and direct observation, even when a negative screen is obtained on self-report measures (73,75).

Management of Comorbidity

Determining whether an individual is suffering from a psychiatric problem, in addition to the diagnosis of ASD, has important implications for management. Studies examining the use of cognitive behavioural therapy (CBT) to treat anxiety in ASD have recently begun to receive empirical attention, and results are promising (11,27,76-84). In general, individuals with ASD and comorbid anxiety receiving CBT showed substantial improvements after delivery of the treatment, compared to treatment as usual. Treatment response rates (i.e., achieving a clinically meaningful improvement relative to baseline) ranged from 46 to 77% in individuals who received CBT, versus only 9 to 14% in the treatment-as-usual group (TAU) (79,80,82,84), with treatment gains generally being maintained at short-term follow-up (79,80,82). Remission rates (i.e., no longer meeting criteria for the anxiety diagnosis) varied from 38 to 71% for those children and youth receiving CBT, compared to 0 to 8.7% in the comparison sample (TAU or waitlist control) (76,77,82,84). Response and remission rates are close to those seen in typically-developing anxiety-disordered children and youth: response rates range from 60 to 78% (84,89) and remission rates from 64 to 70% (90-92). McNally Keehn et al. (77) reported that the Number Needed to Treat (NNT) indicated that approximately two children must participate in CBT in order for one child with ASD to return to non-clinical levels for the primary diagnosis at post-treatment (NNT = 1.72) compared to waitlist controls; which is similar to results seen in typically developing children (NNT=2.8) (89). Although the majority of studies have examined anxiety, some programs have used cognitive and behavioural strategies to target emotion regulation (85), increase understanding and expression of affectionate behaviour (86,87), and social skills (88). CBT is considered an 'emerging' treatment based on the National Autism Center's 2009 National Standards Report, and was noted by Lang et al. (27) to be a "potentially versatile and effective intervention approach".

CBT programs that have been used with ASD populations have either been existing programs produced for typically-developing anxiety-disordered individuals that have been adapted for use in ASD, e.g., Coping Cat (77), or were specifically developed for use with individuals with ASD, e.g., Facing Fears (79). A number of modifications have been recommended, such as using concrete and visual tactics, incorporating communication and social skills training into hierarchies when required, increasing affective communication, incorporating child-specific interests, and involving parents (93,94). These treatment studies do not consider the impact of other emotional or behavioural disorders on treatment outcome, nor do they examine changes in other internalizing or externalizing symptoms. Furthermore, there is little evidence regarding treatment of other disorders such as depression, conduct problems, aggressive behaviour or attentional issues, although some research is emerging (68,85,95,98). There is also an emerging literature on the use of mindfulness-based interventions for individuals with ASD (97,98).

With regard to pharmacological interventions, the majority of clinical trials have targeted specific behavioural symptoms (e.g., aggression, hyperactivity and inattention, stereotypical and repetitive behaviours, self-injurious behaviour), whereas few studies have used pharmacotherapy to target specific psychiatric disorders (56,99,100). More research is needed to determine whether medications that are effective in non-ASD individuals with psychiatric disorders will also be effective in individuals with ASD who have similar comorbidities; to date, findings are mixed (101,102). For example, Williams et al. (102) conducted a review of the use of selective serotonin reuptake inhibitors (SSRIs), a class of antidepressants that are prescribed for the treatment of conditions often comorbid with ASD, such as depression, anxiety and obsessive-compulsive behaviours. The authors reported that there is no evidence to support the use of SSRIs to treat children with ASD, and limited evidence in adults with ASD.

Clinical Implications

Despite increasing evidence that emotional and behavioural disorders are common and serious clinical problems in individuals with ASD, these comorbidities continue to be unrecognized. This, in turn, impacts care. Comorbid psychiatric disorders should be assessed and diagnosed early to improve prognosis, and addressed routinely in post-diagnostic and early-intervention services (7,41). The expression of emotional or behavioural symptoms, e.g., anger, may serve as a useful cue to consider further assessment and examination of other mental health concerns, e.g., depression (38). Furthermore, the presence of ASD or ID should alert clinicians to assess for possible emotional and behavioural problems (42). Prompt assessment of these comorbidities should help to ensure that individuals and their families gain appropriate access to the support they need.

Table 1: Rate of Psychiatric Comorbidity

Reference	Sample	Country	N	Age	Comorbidity (%)	
				Range	1	2 or more
Kaat et al., 2013 (3)	Clinic	USA	104	6-12	81	--
Memari et al., 2012 (28)	School-based health survey	Tehran	91	6-14	28	--
Amr et al., 2012 (29)	Clinic	Egypt, Jordan, Saudi Arabia	60	6-11	63	--
Gjevik et al., 2011 (2)	School ASD population	Norway	71	6-17	72	30
Abdallah et al., 2011* (30)	Nation-wide health registry	Denmark	414	11-21	73	--
Moseley et al., 2011 (6)	Community clinic	Australia	84	11-30	42	--
Matilla et al., 2010 (31)	Community & clinic	Finland	50	9-16	84	--
Farley et al., 2009 (25)	Statewide survey	USA	41	3-25	59	27
Simonoff et al., 2008 (7)	Population-based	U.K.	112	10-14	70	41
Eaves & Ho, 2008 (24)	Clinic	Canada	48	19-31	77	--
Ghaziuddin & Zafar, 2008 (32)	Clinic	USA	28	18-57	75	--
de Bruin et al., 2007 (33)	Clinic	Netherlands	94	6-12	81	--
Leyfer et al., 2006 (5)	Community	USA	109	5-17	72	50

*Actual age range is not provided, but approximate ranges reported in table are based on the mean age ($X=16.28\pm4.55$)

Table 2: Types and Rates (%) of Comorbidity in Children, Adolescents and Adults

Reference	Age Range	Anxiety	OCD	ADHD	Depression	Manic / Bipolar	Behavioral Disorder	Oppositional Defiant Disorder	Conduct Disorder	Psychotic / Schizophrenia	Substance Related
Amr et al., 2012 (29)	6-11	58	55	32	13	--	--	--	23	--	--
Kaat et al., 2013* (3)	6-12	47	--	67	20	21	--	35	2	3	--
Memari et al., 2012 (28)	6-14	--	--	9	1	1	2	--	--	--	--
Leyfer et al., 2006 (5)	5-17	--	37	31	10	--	--	7	--	--	--
Gjevik et al., 2011 (2)	6-17	42	10	31	1	0	--	4	3	1	--
de Bruin et al., 2007 (33)	6-12	1-38	6	21	11	3	--	37	10	0	--
Simonoff et al., 2008 (7)	10-14	42	8	28	0.9	--	--	28	--	--	--
Matilla et al., 2010** (31)	12-13	42	22	38	6	--	44	16	2	--	--
Moseley et al., 2011 (6)	11-30	12	--	1	11	1	10	--	--	--	--
Lugnegard et al., 2011*** (46)	23-31	56	7	30	50-70	9	--	--	--	--	7
Hofvander et al., 2009 (44)	16-60	50	24	43	53	--	--	--	--	12	16
Billstedt et al., 2005 (23)	17-40	--	--	33	1	--	42	--	--	7	--
Ghaziuddin & Zafar, 2008 (32)	18-57	21	--	18	50	--	--	--	--	--	--
Eaves & Ho, 2008 (24)	19-31	50	50	--	21	6	63	--	--	--	--
Farley et al., 2009 (25)	22-46	22	7	15	32	2	--	--	--	2	--

*reported parent reported impairment ratings

**reported combined data for community and clinic sample for current ratings

***Actual age range is not provided, but approximate ranges reported in table are based on the mean age ($X=27\pm3.9$)

GP Comment.

What have I learned from this paper?

1. Many individuals with Autism Spectrum Disorder (ASD) experience significant emotional and behavioural problems. Psychiatric disorders commonly coexist with ASD in children, adolescents and also adults. However, they are often not recognised.
2. The rate of prevalence varies widely from 28% to 84% for one psychiatric disorder and 27% to 50% for two or more disorders in people with ASD.
3. The coexistent psychiatric disorders include ADHD, oppositional defiant disorder, anxiety, OCD, depression, manic/bipolar disorder, and psychosis/schizophrenia.
4. Having other psychiatric problems can impact the individual enormously, resulting in aggression, poor social relationships, restrictions on family's social activities and also negatively affecting long-term outcomes.
5. It remains a challenge for clinicians to assess mental health problems and to distinguish them from ASD features when both coexist. In individuals with ASD or intellectual disability, symptoms such as anger and aggression should alert the clinician to look out for other mental health concerns.
6. Although self-report questionnaires may be helpful to identify psychiatric problems, they need to be supplemented with direct observations and additional information from multiple informants and settings.
7. Cognitive Behaviour Therapy is found to be effective in treating coexistent anxiety and whilst medications can be helpful for managing symptoms such as aggression and hyperactivity, there is no evidence for using antidepressants (SSRIs) in children with ASD.

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References

1. Bradley EA, Summers JA, Wood HL, Bryson SE. Comparing rates of psychiatric and behavior disorders in adolescents and young adults with severe intellectual disability with and without autism. *J Autism Dev Disord* 2004; 34: 151-161.
2. Gjevik E, Eldevik S, Fjaeran-Granum T, Sponheim E. Kiddie-SADS reveals high rates of DSM-IV disorders in children and adolescents with autism spectrum disorders. *J Autism Dev Disord* 2011; 41: 761-769.
3. Kaat AJ, Gadow KD, Lecavalier L. Psychiatric symptom impairment in children with autism spectrum disorders. *J Abnorm Child Psychol* 2013; 41: 959-969. doi:10.1007/s10802-013-9739-7.
4. Lecavalier L. Behavioral and emotional problems in young people with pervasive developmental disorders: Relative prevalence, effects of subject characteristics, and empirical classification. *J Autism Dev Disord* 2006; 36: 1101-1114.
5. Leyfer OT, Folstein SE, Bacalman S, Davis NO, Dinh E, Morgan J, et al. Comorbid psychiatric disorders in children with autism: Interview development and rates of disorders. *J Autism Dev Disord* 2006; 36: 849-861.
6. Moseley DS, Tonge BJ, Brereton AV, Einfeld SL. Psychiatric comorbidity in adolescents and young adults with autism. *J Ment Health Res Intell Dis* 2011; 4: 229-243.
7. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. *J Am Acad Child Adolesc Psychiatry* 2008; 47: 921-929.

8. Skokauskas N, Gallagher L. Psychosis, affective disorders, and anxiety in autistic spectrum disorder: prevalence and nosological considerations. *Psychopathology* 2010; 43: 8-16.
9. Szatmari P, McConnell B. Anxiety and mood disorders in individuals with autism spectrum disorder. In: Amaral DG, Dawson G, Geschwind DH, editors. *Autism Spectrum Disorders* (pp. 330-338). New York, NY: Oxford University Press Inc.; 2011.
10. Kanner L. Autistic disturbances of affective contact. *Nervous Child* 1943; 2: 217-250.
11. White S, Oswald D, Ollendick T, Scahill L. Anxiety in children and adolescents with ASD. *Clin Psychol Rev* 2009; 29: 216-229.
12. Kim J, Szatmari P, Bryson SE, Wilson FJ. Prevalence of anxiety and mood problems among children with autism and Asperger syndrome. *Autism* 2000; 4: 117-132.
13. Ghaziuddin M, Ghaziuddin N, Greden J. Depression in persons with autism: implications for research and clinical care. *J Autism Dev Disord* 2002; 32(4): 299-306. doi:0162-3257/02/0800-0299/0.
14. Tantum D. Psychological disorders in adolescents and adults with Asperger's syndrome. *Autism* 2000; 4(1): 47-62. doi:10.1177/1362361300004001004.
15. Lecavalier L, Leone S, Wiltz J. The impact of behavior problems on caregiver stress in young people with autism spectrum disorders. *J Intellectual Disabil Res* 2006; 50: 172-183. doi:10.1111/j.1365-2788.2005.00732.x.
16. Witwer AN, Lecavalier L. Treatment incidence and patterns in children and adolescents with autism spectrum disorders. *J Child Adolesc Psychopharmacol* 2005; 15: 671-681. doi:10.1089/cap.2005.15.671.
17. Bryson SA, Corrigan SK, McDonald TP, Holmes C. Characteristics of children with autism spectrum disorders who received services through community mental health centers. *Autism* 2008; 12: 65-82.
18. Mandell D. Psychiatric hospitalization among children with autism spectrum disorders. *J Autism Dev Disord* 2008; 38: 1059-1065.
19. Mouridsen SE, Rich B, Isager T, Nedergaard NJ. Psychiatric disorders in individuals diagnosed with infantile autism as children: a case control study. *J Psychiatr Pract* 2008; 14: 5-12.
20. Davis TE, Fodstad JC, Jenkins WS, Hess JA, Moree BN, Dempsey T, Matson JL. Anxiety and avoidance and toddlers with autism spectrum disorders: Evidence for differing symptom severity presentation. *Res Autism Spec Disord* 2010; 4: 305-313.
21. Gadow KD, DeVincent CJ, Pomeroy J, Azizian A. Psychiatric symptoms in preschool children with PDD and clinic and comparison samples. *J Autism Dev Disord* 2004; 34(4): 379-393.
22. Simonoff E, Jones CRG, Baird G, Pickles A, Happe F, Charman T. The persistence and stability of psychiatric problems in adolescents with autism spectrum disorders. *J Child Psychol Psychiatry* 2013; 54(2): 186-194.
23. Billstedt E, Gillberg C, Gillberg C. Autism after adolescence: population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *J Autism Dev Disord* 2005; 35(3): 351-360.
24. Eaves LC, Ho HH. Young adult outcomes of autism spectrum disorders. *J Autism Dev Disord* 2008; 38: 739-747.
25. Farley MA, McMahon WM, Fombonne E, Jenson WR, Miller J, Gardner M, et al. Twenty-year outcome for individuals with autism and average or near-average cognitive abilities. *Autism Res* 2009; 2: 109-118.
26. Gray K, Keating C, Taffe J, Brereton A, Einfeld S, Tonge B. Trajectory of behavior and emotional problems in autism. *Amer J Intellect Dev Disabil* 2012; 117(2): 121-133.
27. Lang R, Regeister A, Lauderdale S, Ashbaugh K, Haring A. Treatment of anxiety in autism spectrum disorders using cognitive behavioral therapy: a systematic review. *Dev Neurorehabilitation* 2010; 13: 53-63.
28. Memari AH, Ziaee V, Mirfazeli FS, Kordi R. Investigation of autism comorbidities and associations in a school-based community sample. *J Child Adolesc Nurs* 2012; 25: 84-90. doi:10.1111/j.1744-6171.2012.00325.x.
29. Amr M, Raddad D, El-Mehesh F, Bakr A, Sallam K, Amin T. Comorbid psychiatric disorders in Arab children with autism spectrum disorders. *Res Autism Spec Disord* 2012; 6: 240-248. doi:10.1016/j.rasd.2011.05.005.
30. Abdallah MW, Greaves-Lord K, Grove J, Norgaard-Pedersen B, Hougaard DM, Mortensen EL.

- Psychiatric comorbidities in autism spectrum disorders: findings from a Danish Historic Birth Cohort. *Eur Child Adolesc Psychiatry* 2011; 20: 599-601. Doi: 10.1007/s00787-011-0220-2.
31. Mattila M-L, Hurtig T, Haapsamo H, Jussila K, Kuusikko-Gauffin S, Kielinen M, et al. Comorbid psychiatric disorders associated with Asperger syndrome/high functioning autism: a community and clinic-based study. *J Autism Dev Disord* 2010; 40: 1080-1093.
 32. Ghaziuddin M, Zafar S. Psychiatric comorbidity in adults with autism spectrum disorders. *Clin Neuropsychiatry* 2008; 5: 9-12.
 33. de Bruin EI, Ferdinand RF, Meester S, de Nijs PFA, Verheij F. High rates of psychiatric comorbidity in PDD-NOS. *J Autism Dev Disord* 2007; 37: 877-886. doi:10.1007/s10803-006-0215-x.
 34. Newman DL, Moffitt TE, Caspi A, Silva PA Comorbid mental disorders: Implications for treatment and sample selection. *J Abnorm Psychol* 1998; 107: 305-311.
 35. Gadow KD, DeVincent CJ, Pomeroy J. ADHD symptom subtypes in children with pervasive developmental disorder. *J Autism Dev Disord* 2006; 36: 271-283. doi:10.1007/s10803-005-0060-3.
 36. Lecavalier L, Gadow K, DeVincent CJ, Edwards MC. Validation of DSM-IV model of psychiatric syndromes in children with autism spectrum disorders. *J Autism Dev Disord* 2008; 39: 278-289.
 37. Matson JL, Nebel-Schwalm MS. Comorbid psychopathology with autism spectrum disorder in children: An overview. *Res Dev Disabil* 2007; 28(4): 341-352.
 38. Quek L-H, Sofronoff K, Sheffield J, White A, Kelly A. Co-occurring anger in young people with Asperger's syndrome. *J Clin Psychol* 2012; 68(10): 1142-1148.
 39. Weisbrot DM, Gadow KD, DeVincent CJ, Pomeroy J. The presentation of anxiety in children with Pervasive Developmental Disorders. *J Child Adolesc Psychopharmacology* 2005; 15: 477-496.
 40. Polier GG, Vloet TD, Herpertz-Dahlmann B, Laurens KR, Hodfins S. Comorbidity of conduct disorder symptoms and internalising problems in children: investigating a community and a clinic sample. *Eur Child Adolesc Psychiatry* 2012; 21: 31-38. doi:10.1007/s00787-011-0229-6.
 41. Totsika V, Hastings RP, Emerson E, Berridge DM, Lancaster GA. Behavior problems at 5 years of age and maternal mental health in autism and intellectual disability. *J Abnorm Child Psychol* 2011(a); 39: 1137-1147. doi:10.1007/s10802-011-9534-2.
 42. Totsika V, Hastings RP, Emerson E, Lancaster GA, Berridge DM. A population-based investigation of behavioral and emotional problems and maternal mental health: associations with autism spectrum disorder and intellectual disability. *J Child Psychol Psychiatry* 2011(b); 52(1): 91-99. doi:10.1111/j.1469-7610.2010.02295.x.
 43. Cederlund M, Hagberg B, Gillberg C. Asperger syndrome in adolescent and young adult males. Interview, self and parent assessment of social, emotional, and cognitive problems. *Res Dev Disabil* 2010; 31: 287-298.
 44. Hofvander B, Delorme R, Chaste P, Nyden A, Wentz E, Stahlberg O, et al. Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. *BMC Psychiatry* 2009; 9(35): doi:10.1186/1471-244X-9-35.
 45. La Malfa G, Lass, S, Salvini R, Gigant C, Bertelli M, Albertini G. The relationship between autism and psychiatric disorders in intellectually disabled adults. *Res Autism Spec Disord* 2007; 1: 218-228.
 46. Lugnegard T, Hallerback MU, Gillberg C. Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. *Res Dev Disabil* 2011; 32: 1910-1917.
 47. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustun TB. Age of onset of mental disorders: a review of recent literature. *Curr Opin Psychiatry* 2007; 20: 359-264.
 48. Witwer AN, Lecavalier L. Validity of comorbid psychiatric disorders in youngsters with autism spectrum disorders. *J Dev Phys Disabil* 2010; 22: 367-380. doi:10.1007/s10882-010-9194-0.
 49. Farrugia S, Hudson J. Anxiety in adolescents with Asperger syndrome: Negative thoughts, behavioral problems, and life interference. *Focus Autism Other Dev Disabil* 2006; 21: 25-35.
 50. Tureck K, Matson JL, May A, Whiting SE, Davis III TE. Comorbid symptoms in children with anxiety disorders compared to children with autism spectrum disorders. *J Dev Phys Disabil* 2013. doi:10.1007/s10882-013-9342-4.
 51. Russell E, Sofronoff K. Anxiety and social worries in children with Asperger syndrome. *Aust N Z J Psychiatry* 2005; 39: 633-638.
 52. Evans DW, Canavera K, Kleinpeter FL, Maccubbin E, Taga K. The fears, phobias, and anxieties of children with autism spectrum disorders and Down syndrome: Comparisons with developmentally and chronologically aged matched children. *Child Psychiatry Hum Dev* 2005; 36: 3-26.

53. Green J, Gilchrist A, Burton D, Cox A. Social and psychiatric functioning in adolescents with Asperger syndrome compared with conduct disorder. *J Autism Dev Disord* 2000; 30: 279-293.
54. Gillot A, Furniss F, Walter A. Anxiety in high-functioning children with autism. *Autism* 2001; 5: 277-286.
55. Joshi G, Petty C, Wozniak J, Henin A, Fried R, Galdo M, et al. The heavy burden of psychiatric comorbidity in youth with autism spectrum disorders: a large comparative study of psychiatrically referred population. *J Autism Dev Disord* 2010; 40: 1361-1370.
56. Mazzone L, Ruta L, Reale L. Psychiatric comorbidities in Asperger syndrome and high functioning autism: diagnostic challenges. *Ann Gen Psychiatry* 2012; 11(16). doi:10.1186/1744-859X-11-16.
57. Pine DS, Guyer AE, Goldwin M, Towbin KA, Leibenluft E. Autism spectrum disorder scale scores in pediatric mood and anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 2008; 47(6): 652-661.
58. Brereton AV, Tonge BJ, Einfeld SL. Psychopathology in children and adolescents with autism compared to young people with intellectual disability. *J Autism Dev Disord* 2006; 36: 862-870.
59. LoVullo SV, Matson JL. Comorbid psychopathology in adults with autism spectrum disorders and intellectual disabilities. *Res Dev Disabil* 2009; 30: 1288-1296. doi:10.1016/j.ridd.2009.05.004
60. Tsakanikos E, Costello H, Holt G, Bouras N, Sturmey P, Newton T. Psychopathology in adults with autism and intellectual disability. *J Autism Dev Disord* 2006; 36: 1123-1129.
61. Georgiades S, Szatmari P, Duku E, Zwaigenbaum L, Bryson S, Roberts, W. et al. Pathways in ASD Study Team. Phenotypic overlap between core diagnostic features and emotional/behavioral problems in preschool children with autism spectrum disorders. *J Autism Dev Disord* 2011; 41: 1321-1329. doi:10.1007/s10803-010-1158-9.
62. Estes AM, Dawson G, Sterling L, Munson J. Level of intellectual functioning predicts patterns of associated symptoms in school-age children with autism spectrum disorders. *Am J Ment Retard* 2007; 112(6): 439-449.
63. Hagopian LP, Jennett HK Behavioral assessment and treatment of anxiety in individuals with intellectual disabilities and autism. *J Dev Phys Disabil* 2008; 20: 467-483. doi:10.1007/s10882-008-9114-8.
64. McDougle CJ, Kresch LE, Goodman WK, Naylor ST, Volkmar FR, Cohen DJ, Price LH. A case-controlled study of repetitive thoughts and behavior in adults with autistic disorder and obsessive compulsive disorder. *Am J Psychiatry* 1995; 152(5): 772-777.
65. Ruta L, Mugno D, D'Arrigo VG, Vitiello B, Mazzone L. Obsessive-compulsive traits in children and adolescents with Asperger syndrome. *Eur Child Adolesc Psychiatry* 2010; 19:17-24. doi:10.1007/s00787-009-0035-6.
66. Cath DC, Ran N, Smit JH, Van Balkom AJLM, Comijs HC. Symptom overlap between autism spectrum disorder, generalized social anxiety disorder and obsessive compulsive disorder in adults: a preliminary case-controlled study. *Psychopathology* 2008; 41: 101-110.
67. Russell AJ, Mataix-Cols D, Anson M, Murphy DGM. Obsessions and compulsions in Asperger syndrome and high-functioning autism. *Brit J Psychiatry* 2005; 186: 525-528. doi:10.1192/bjp.186.6.525.
68. Sofronoff K, Attwood T, Hinton S, Levin I. A randomized controlled trial of a cognitive behavioural intervention for anger management in children diagnosed with Asperger syndrome. *J Autism Dev Disord* 2007; 37(7): 1203-1214. doi:10.1007/s10803-006-0262-3.
69. Stewart ME, Barnard L, Pearson J, Hasan R, O'Brien G. Presentation of depression in autism and Asperger syndrome: a review. *Autism* 2006; 10(1): 103-116.
70. Lainhart JE. Psychiatric problems in individuals with autism, their parents and siblings. *Int Rev Psychiatry* 1999; 11(4): 278-298.
71. MacNeil BM, Lopes VA, Minnes PM. Anxiety in children and adolescents with autism spectrum disorders. *Res Autism Spec Disord* 2009; 3: 1-21. doi:10.1016/j.rasd.2008.06.001
72. Grondhuis SN, Aman MG. Assessment of anxiety in children and adolescents with autism spectrum disorders. *Res Autism Spec Disord* 2012; 6: 1345-1365. doi:http://dx.doi.org/10.1016/j.rasd.2012.04.006.
73. Mazefsky CA, Kao J, Oswald DP. Preliminary evidence suggesting caution in the use of psychiatric self-report measures with adolescents with high-functioning autism spectrum disorders. *Res Autism Spec Disord* 2011; 5: 164-174.
74. Safford SM, Kendall PC, Flannery-Schroeder E, Webb A, Sommer H. A longitudinal look at parent-child diagnostic agreement in youth treated for anxiety disorders. *J Clin Child Adolesc Psychol*

- 2005; 34(4): 747-757.
75. Kanne SM, Abbacchi AM, Constantino JN. Multi-informant ratings of psychiatric symptom severity in children with autism spectrum disorders: the importance of environmental context. *J Autism Dev Disord* 2009; 39: 856-864.
 76. Chalfant AM, Rapee R, Carroll L. Treating anxiety disorders in children with high functioning autism spectrum disorders: a controlled trial. *J Autism Dev Disord* 2007; 37: 1842-1857.
 77. McNally Keehn RH, Lincoln AJ, Brown MZ, Chavira DA. The coping cat program for children with anxiety and autism spectrum disorder: a pilot randomized controlled trial. *J Autism Dev Disord* 2013; 43: 57-67. doi:10.1007/s10803-012-1541-9.
 78. Reaven J, Blakeley-Smith A, Nichols S, Dasari M, Flanigan E, Hepburn S. Cognitive behavioral group treatment for anxiety symptoms in children with high-functioning autism spectrum disorders. *Focus Autism Other Dev Disabil* 2009; 24: 27-37.
 79. Reaven J, Blakeley-Smith A, Culhane-Shelburne K, Hepburn S. Group cognitive behavior therapy for children with high-functioning autism spectrum disorders and anxiety: a randomized trial. *J Child Psychol Psychiatry* 2012; 53(4): 410-419.
 80. Reaven J, Blakeley-Smith A, Leuthe E, Moody E, Hepburn S. Facing your fears in adolescence: cognitive-behavioral therapy for high-functioning autism spectrum disorders and anxiety. *Autism Res Treat* 2012; Article ID 423905. doi:10.1155/2012/423905.
 81. Sofronoff K, Attwood T, Hinton SA. A randomized controlled trial of a CBT intervention for anxiety in children with Asperger syndrome. *J Child Psychol Psychiatry* 2005; 46: 1152-1160.
 82. Storch EA, Arnold EB, Lewin AB, Nadeau JM, Jones AM, De Nadai AS, et al. The effect of cognitive-behavioral therapy versus treatment as usual for anxiety in children with autism spectrum disorders: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry* 2013; 52(2): 132-142.
 83. Sung M, Ooi YP, Goh TJ, Pathy P, Fung D, Ang RP, Chua A, Lam CM. Effects of cognitive-behavioral therapy on anxiety in children with autism spectrum disorders: a randomized controlled trial. *Child Psychiatry Hum Dev* 2011; 42: 634-649. doi:10.1007/s10578-011-0238-1.
 84. Wood JJ, Drahota A, Sze K, Har K, Chiu A, Langer DA. Cognitive behavioral therapy for anxiety in children with autism spectrum disorders: a randomized, controlled trial. *J Child Psychol Psychiatry* 2009; 50(3): 224-234. doi:10.1111/j.1469-7610.2008.01948.x.
 85. Scarpa A, Reyes NM. Improving emotion regulation with CBT in young children with high functioning autism spectrum disorders: a pilot study. *Behav Cogn Psychother* 2011; 39(4): 495-500. doi:10.1017/S1352465811000063
 86. Sofronoff K, Eloff J, Sheffield J, Attwood T. Increasing the understanding and demonstration of appropriate affection in children with Asperger syndrome: A pilot trial. *Autism Res Treat* 2011; Article 214317. doi:10.1155/2011/214317.
 87. Attwood T. Expressing and enjoying love and affection. A cognitive behavioral program for children and adolescents with high-functioning ASD. In Scarpa A, White SW, Attwood T, editors. *CBT for Children and Adolescents with High-Functioning Autism Spectrum Disorders* (pp. 259-277). New York, NY. The Guilford Press; 2013.
 88. Bauminger-Zviely, N. Cognitive-behavioral-ecological intervention to facilitate social-emotional understanding and social interaction in youth with high-functioning autism. In Scarpa A, White SW, Attwood T, editors. *CBT for Children and Adolescents with High-Functioning Autism Spectrum Disorders* (pp. 226-255). New York, NY. The Guilford Press; 2013.
 89. Walkup JT, Albano AM, Piacentini JC, Birmaher B, Compton SN, Sherrill JT, et al. Cognitive behavioral therapy, Sertraline, or a combination in childhood anxiety. *New Engl J Med* 2008; 359(26): 2753-2766.
 90. Barrett P, Dadds MR, Rapee RM. Family treatment of childhood anxiety: A controlled trial. *J Consult Clin Psychol* 1996; 64(2): 333-342.
 91. Kendall PC. Treating anxiety disorders in children: results of a randomized clinical trial. *J Consult Clin Psychol* 1994; 62(1), 100-110.
 92. Kendall PC, Hudson JL, Gosch E, Flannery-Schroeder E, Suveg C. Cognitive-behavioral therapy for anxiety-disordered youth: a randomized clinical trial evaluating child and family modalities. *J Consult Clin Psychol* 2008; 76(2): 282-297.
 93. Lickel A, MacLean WE, Blakeley-Smith A, Hepburn S. Assessment and prerequisite skills for cognitive behavioral therapy in children with and without autism spectrum disorders. *J Autism Dev*

- Disord 2012; 42: 992-1000. doi:10.1007/s10803-011-1330-x
94. Moree BN, Davis TE III. Cognitive behavior therapy for anxiety in children diagnosed with autism spectrum disorders: modification trends. *Res Autism Spec Disord* 2010; 4: 346-354. doi: 10.1016/j.rasd.2009.10.015.
95. Frazier TW, Youngstrom EA, Haycook T, Sinoff A, Dimitriou F, Knapp J, Sinclair L. Effectiveness of medication combined with intensive behavioral intervention for reducing aggression in youth with autism spectrum disorder. *J Child Adolesc Psychopharmacology* 2010; 20(30): 167-177. doi:10.1089=cap.2009.0048
96. Safren SA. Cognitive-behavioral approaches to ADHD treatment in adulthood. *J Clin Psychiatry* 2006; 67(suppl 8): 46-50.
97. Singh NN, Lancioni GE, Manikam R, Winton ASW, Singh ANA, Singh J, Singh ADA. A mindfulness-based strategy for self-management of aggressive behavior in adolescents with Autism. *Res Autism Spec Disord* 2011; 5(3): 1153-1158. doi:http://dx.doi.org/10.1016/j.rasd.2010.12.012
98. Spek AA, van Ham NC, Nyklíček I. Mindfulness-based therapy in adults with an autism spectrum disorder: A randomized controlled trial. *Res Dev Disabil* 2013; 34(1): 246-253. doi:10.1016/j.ridd.2012.08.009
99. Blankenship K, Erickson CA, McDougle CJ. Pharmacotherapy of autism and related disorders. *Psychiatric Ann* 2010; 40(4): 203-209.
100. Davis NO, Kollins SH. Treatment for co-occurring attention deficit/hyperactivity disorder and autism spectrum disorder. *Neurotherapeutics* 2012; 9: 518-530.
101. King BH, Hollander E, Sikich L, McCracken JT, Scahill L, Bregman JD, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. *STAART Psychopharmacology Network. Arch Gen Psychiatry* 2009; 66(6): 583-590.
102. Williams K, Brignell A, Randall M, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *Cochrane Database of Systematic Reviews* 2013; 8: CD004677. doi: 10.1002/14651858.CD004677.pub3