

# Autism spectrum disorders co-morbidities and treatment approaches

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## Abstract

Autism Spectrum Disorder (ASD) is a group of neurodevelopmental disorders, a complex clinical syndrome with different etiologies and pathogenesises, and is almost always accompanied by co-morbid conditions. In this short review, we address the most frequent neurological/psychiatric and somatic co-morbidities, and the latest evidence-based treatment options for these co-morbidities from the literature.

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders, and a complex clinical syndrome with different etiologies and pathogenesises. There is significant clinical and phenotypic heterogeneity associated with ASD, which is not a discrete condition, but rather is part of a broader spectrum of neurodevelopmental conditions, as symptoms of autism almost never occur in isolation. In addition, there are a number of psychiatric, neurologic and somatic co-morbidities, that need to be understood and addressed in order to improve clinical outcome.

## ASD and psychiatric/neurological co-morbidities

As many as 95% of individuals with autism have one or several comorbid psychiatric diagnoses, and 'pure' autism is extremely rare [1].

While the most prevalent co-morbid diagnoses are sleep disorders, anxiety, depression and Attention Deficit Hyperactivity Disorder (ADHD) [2,3] other common diagnoses include eating disorders, and auto-, hetero-aggression and self-harm [4]. Two thirds of individuals with ASD receive psychotropic medication, and 40% receive more than one psychotropic medication as the same time [5].

In addition, a recent longitudinal cohort study recently reported a 2-fold higher mortality risk through young adulthood for individuals diagnosed with autism, which seems to be mediated through shared neurologic (e.g. epilepsy) and mental/behavioral disorders [6].

There is a high prevalence of epilepsy in ASD [7-9], and studies show up to 60% of epileptiform activity in the EEG of individuals with ASD [10]. Epilepsy is affecting approximately 19% of those with ASD [11] and is more common in those who also have an intellectual disability (ID), affecting a up to 40% of individuals with ASD and ID [12].

Increased awareness and broadening of the diagnostic criteria have resulted in an increase of autism prevalence [13-15], that has been associated with a reduced prevalence of ID in ASD as defined by the DSM-5 compared to older studies. In the latest CDC report [16], 31% of children with ASD were classified in the range of ID (IQ < 70), 44% were in the borderline range, and 44% had IQ scores in the average to the above average range (IQ > 85).

## ASD and somatic co-morbidities

In addition to psychiatric and neurologic co-morbidities, patients with ASD also have significant comorbidity of somatic disorders. One of the most common co-morbid conditions affect the gastro-intestinal (GI) system, which are four times more frequent than in the general population and range from constipation to inflammatory bowel disease

[11,17,18]. In addition, children with autism have a five-time higher rate than their peers to develop feeding problems [19], including Avoidant/Restrictive Food Intake Disorder (ARFID), although precise prevalence data are still not available for this disorder. It is important to note that some behavioral problems, especially in children with ASD and ID, can be due to GI problems, including reflux, that sometimes are the primary underlying issue for these behavioral issues, including self-harm and aggression [20]. The role of dysregulations of the gut-brain-microbiome axis is an area of active investigation [21]. GI disorders are also often associated with sleep disorders [22].

Autoimmune conditions have been associated both with increasing the risk of having autism, and with ASD condition itself [23,24]. Individuals with autism have significantly more allergies, autoimmune diseases (including psoriasis and food allergies), but less asthma than controls, as assessed in a population-based case-control study [25].

All these different co-morbid conditions associated with ASD need to be considered and treated, and below we provide a sketch of the possible, available approaches.

It is important to note that to this day, there is no FDA-approved treatment for the core symptoms of autism, and that the only two psychotropic medications approved for autism treatment, risperidone and aripiprazole, are indicated to help with symptoms related to irritability. In terms of non-pharmacological approach to the treatment of core symptoms of autism, cognitive behavioral therapy interventions, such as Applied Behavior Analysis (ABA) [26], pivotal response

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treatment (PRT) [27] or the Early Start Denver Model (ESDM) [28] are considered as evidence-based practiced by several studies.

## Addressing ASD co-morbidities

### Sleep disorders

Sleep disorders are commonly reported in ASD, and 53% of children have at least one sleep problem including bedtime resistance, insomnia, parasomnias, also some report a prevalence up to 86% [29-33].

Abnormal circadian rhythms, and abnormalities in melatonin physiology, may be at the basis of sleep disorders in ASD [34], and there is emerging evidence that melatonin offers positive effects on sleep disorders in ASD [35].

### Anxiety

Anxiety disorder are among the most frequent co-occurring condition in ASD, affecting up to more than 50% of individuals, across all age groups [36]. Among anxiety disorder, the most frequent is specific phobia (~30%), followed by obsessive compulsive disorder (~17%) and social anxiety disorder (~17%), and general anxiety disorder (~15%) [37].

Anxiety treatment includes psychopharmacological and behavioral approaches. In their review, Vasa et al. [38] reported that whilst citalopram and buspirone treatment offered some improvement, fluvoxamine did not. Issues with SSRI treatment include behavioral activation (increased activity level, impulsivity, insomnia, disinhibition), and these side effects seem to be frequent in ASD [39]. In a more recent systematic review, Ameis et al. [35] insist on the fact that systematic RCT studies evaluating SSRI effect on anxiety and mood are lacking, and that SSRI fail to improve stereotypic and repetitive behaviors in ASD.

Cognitive behavioral therapy (CBT) showed moderate efficacy for anxiety disorders in youth with high functioning ASD, and neurofeedback and deep pressure provided some benefit, but the authors of the meta-analysis [38] underlined the paucity of studies with large sample sizes and long-terms RCT and their need in order to better understand what the best approach may be to help relief anxiety symptoms in ASD.

There are currently no RCT study showing reliable benefit of complementary and alternative medicine strategies to improve anxiety symptoms in ASD.

### Depression

Depression is an extremely common mental health problem experienced by individuals with autism, and it increases with age and higher IQ [40,41]. The prevalence of depression seems to be associated with somatic co-morbid disorders including seizure disorders and GI problems, and it reaches up to 70% according to some studies [36].

One of the difficulties in the diagnosis of depression is that it typically relies on subjective self-report, which may be difficult for some to provide, in particular for children with ASD, and the tools to properly evaluate depression in ASD are lacking [42]. While traditional signs and symptoms of depression may be seen, in addition individuals with ASD may express their depression by other symptoms including aggression, increased compulsiveness, and self-injurious behavior, amongst others [43].

Research evaluating the effect of treatment with medication and/or psychotherapy is lacking [44], Currently, a single-blind RCT protocol

is being studied to evaluate the effects of CBT on depressive symptoms on adults with ASD [45]. Other approaches may include mindfulness-based therapies [46].

### Attention Deficit Hyperactivity Disorder (ADHD)

Although until the DSM-5 one could not have both a diagnosis of ASD and ADHD, there has been and still is ample evidence that there is a high prevalence of ADHD in ASD, that has been estimated in the most recent study on the co-occurrence of these two conditions to be about 45% [47]. This observation underlines the importance of the evaluation and, if necessary, the treatment of ADHD in autism, e.g. with instruments such as the A-TAC [48].

The treatment of ADHD consists of both behavioral and pharmacological interventions. Non-pharmacological treatment intervention for ADHD include parenting interventions [49,50], as well as cognitive behavioral therapy [51]. Medication for ADHD includes methylphenidate, atomoxetine and guanfacine, and recent meta-analyses have shown that there is emerging evidence that these drugs have a positive effect targeting ADHD symptoms in ASD [34].

### Eating Disorders (ED)

Many children and adults with ASD manifest food selectivity or picky eating, and close to 70% of children with ASD would fall under the new diagnosis of ARFID [52].

Eating disorders can be one of the presenting symptoms of females with autism, and close to half of females with serious ED score in the ASD range on the ADOS [53]. In addition, in young girls with ASD, the prevalence of severe ED was recently estimated to be 11% [54].

Chronic eating problems put individuals at risk for medical and developmental problems, and children with ASD have abnormal values of many minerals and vitamins [55]. These disorders may be associated with gastro-intestinal disorders, and the role that these plays, along issues related to sensory sensitivity and desire for sameness needs to be further studied. Cognitive behavioral therapy may help to alleviate picky eating in ASD [56].

### Aggressive behavior

The prevalence of aggression is between 9% and 22%, and aggressive behavior is more common in individuals with ASD who also have ID [57]. Aggression is more common towards caregivers, and towards themselves (self-injurious behavior, SIB). It contributes to negative outcome, and is therefore important to address, either with cognitive behavioral therapy, or pharmacologically, with risperidone or aripiprazole. Other types of medications are sometimes used [57], but because the neurobiological mechanisms underlying aggressive behavior are not completely understood, more research is clearly needed in that topic. However, it appears that it may principally stem from difficulties communicating, together with sensory overload, anxiety, and the disruption of routines.

### Epilepsy

Studies suggest that up to 46% of individuals with autism also have epilepsy [9], although a recent meta-analysis of 16 studies reported a prevalence of about 9% in ASD individuals without ID, and of 24% in those with ID [58]. There are two peaks of epilepsy development, one in infancy and the other one at puberty [59]. Epilepsy is more common in individuals who suffer from a genetic syndrome, such as e.g. tuberous sclerosis, Cornelia de Lange syndrome, or Dravet syndrome [60]. In

children, epilepsy with ASD is associated with greater cognitive deficits, and individuals with autism and untreated epilepsy are at greater risk for overall poor health, and in extreme circumstances, premature death.

The ASD-epilepsy comorbidity is a complex one, as having ASD increases the risk of having epilepsy, but also epilepsy increases the risk of having ASD, as illustrated by the Landau-Kleffner syndrome. There may be common underlying predispositions for both conditions (genetic and environmental), but the relationship between these two conditions remains controversial [61].

The treatment of epilepsy is challenging and depends on the origin of the seizures. For example, in tuberous sclerosis, rapamycin may specifically decrease the seizures [62]. Quality of life can be greatly improved by a good management of seizures. A rather comprehensive description of current treatment options is given in the review by Brodie et al. [63].

### Psychotic disorders

Individuals with ASD are at higher risk of developing psychotic disorders in early adulthood, including schizophrenia and bipolar disorder, and some have suggested that this may be due to common underlying genetic conditions. A recent genome-wide association data study (GWAS) has indeed recently shown common variant risks for psychiatric disorders [64] and found significant positive genetic correlation between ASD and schizophrenia. In some copy number variants (CNVs) syndrome such as the 22111.2 or 16p11.2, it seems that duplication or deletion both increase the risk of developing autism or schizophrenia [65,66].

Treatment of psychotic disorders include lithium (for bipolar disorder), anti-seizure medication, as well as aripiprazole and risperidone.

### Intellectual Disability (ID)

The proportion of persons with ASD affected with ID varies according to different studies and depends on how wide or narrow the definition of ASD is, and the kind of test used to test intelligence, and there is an opposite trend between the increasing rates of ASD and those of ID in ASD [66].

The definition of ID is an intellectual quotient more than 2 standard deviations below the norm, i.e. 70 or lower. IQ test typically have a verbal and a non-verbal component, and individuals with autism sometimes get lower scores on the full-scale IQ because they have more difficulties with the verbal tests, and because they may take more time to execute some of the tests. Some researchers have suggested that non-verbal tests such as the Raven Progressive Matrices are better evaluating the actual reasoning capacities in ASD [67].

Because individuals with ASD and ID are more challenging to test in protocol of brain imaging for example, there is still a lack of information regarding issues specific to that group, and future studies will hopefully address this very important aspect of ASD.

### Gastro-intestinal (GI) system

GI problems are one of the most common somatic co-morbidity in ASD, and unfortunately, they often get overlooked in those with ASD who have communication deficits and may be mistaken for behavioral problems. There are indeed many reports indicating that aggressive behaviors, or strange behaviors inaccurately thought to be epileptic fits, are in fact due to pain in the GI system. As long as the issue of a painful

reflux, constipation, or other GI problems has not been addressed, no psychotropic medication will help. For a comprehensive review on the evaluation and treatment of GI problems in ASD [68].

A deficit in the regulation in the gut-brain-microbiome axis is the subjects of a lot of new interest [21] and the role of probiotics in helping some of the ASD GI symptoms is an active area of investigation. However, one has to note that there is insufficient evidence to support gluten-free diet in ASD [69].

### Immune system

There are many indicators of immune dysfunction in ASD, including neuroinflammation, increased response of T cells, and the presence of auto-antibodies [70]. Viral infection during the first trimester and/or bacterial infection during the second trimester of pregnancy has been associated with ASD [71], and maternal immune activation (MIA) may underlie the development of neurodevelopmental disorders.

There is a higher incidence of auto-immune diseases in the family members of children with ASD and the possibility that maternal autoantibodies against fetal brain protein impact brain development leading to ASD has been suggested by several studies [67].

### Conclusion and future perspective

In conclusion, Autism Spectrum Disorder rarely occurs as a pure, isolated condition, and is in the vast majority of cases associated with psychiatric or somatic co-morbidities. It is of utmost importance to address the possibility of the presence of each of these potential co-morbidities, as the quality of life of ASD individuals affected can significantly depend on it. Also, one has to keep in mind that what can be a priori seen as a behavioral problem may have its roots as a GI dysfunction.

There is so far no treatment available to address the core symptoms of autism but addressing the co-morbidities with the existing proven treatment may improve the symptoms and the well-being of individuals with autism.

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