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Autism Spectrum Disorder: Classification, diagnosis and therapy

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ABSTRACT

Autism Spectrum Disorder (ASD) refers to a group of neurodevelopmental disorders including autism, Asperger's syndrome (AS) and pervasive developmental disorder-not otherwise specified (PDD-NOS). The new diagnostic criteria of ASD focuses on two core domains: social communication impairment and restricted interests/repetitive behaviors. The prevalence of ASD has been steadily increasing over the past two decades, with current estimates reaching up to 1 in 36 children. Hereditary factors, parental history of psychiatric disorders, pre-term births, and fetal exposure to psychotropic drugs or insecticides have all been linked to higher risk of ASD. Several scales such as the Childhood Autism Rating Scale (CARS), The Autism Spectrum Disorder–Observation for Children (ASD-OC), The Developmental, Dimensional, and Diagnostic Interview (3di), are available to aid in better assessing the behaviors and symptoms associated with ASD. Nearly 75% of ASD patients suffer from comorbid psychiatric illnesses or conditions, which may include attention-deficit hyperactivity disorder (ADHD), anxiety, bipolar disorder, depression, Tourette syndrome, and others. Both pharmacological and non-pharmacological interventions are available for ASD. Pharmacological treatments include psychostimulants, atypical antipsychotics, antidepressants, and alpha-2 adrenergic receptor agonists. These medications provide partial symptomatic relief of core symptoms of ASD or manage the symptoms of comorbid conditions. Non-pharmacological interventions, which show promising evidence in improving social interaction and verbal communication of ASD patients, include music therapy, cognitive behavioral therapy and social behavioral therapy. Hormonal therapies with oxytocyin or vasopressin receptor antagonists have also shown some promise in improving core ASD symptoms. The use of vitamins, herbal remedies and nutritional supplements in conjunction with pharmacological and behavioral treatment appear to have some effect in symptomatic improvement in ASD, though additional studies are needed to confirm these benefits. Developing novel disease-modifying therapies may prove to be the ultimate intervention for sustained improvement of symptoms in ASD.

Contents

Abbreviations: ADHD, attention deficit hyperactivity disorder; ADI-R, Autism Diagnostic Interview-Revised; AS, Asperger's syndrome; ASD, Autism Spectrum Disorder; ASDI, Asperger Syndrome Diagnostic Interview; ASD-OC, Autism Spectrum Disorder-Observation for Children; BPD, bipolar disorder; CARS, Childhood Autism Rating Scale; CBT, cognitive behavioral therapy; COS, childhood-onset schizophrenia; DISCO, Diagnostic Interview for Social and Communication Disorders; DSM, Diagnostic and Statistical Manual of Mental Disorders; GAD, generalized anxiety disorder; MIA, maternal immune activation; OCD, obsessive–compulsive disorder; OT, oxytocin; PDD-NOS, pervasive developmental disorder-not otherwise specified; SBT, social behavioral therapy; TS, Tourette syndrome.

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1. Introduction

"Autism" is derived from the Greek word "*autós*", which means "self". Eugen Bleuler, a Swiss psychiatrist, initially coined this term in 1908 to describe withdrawal from reality in patients with schizophrenia. In 1943, Leo Kanner redefined the term to describe symptoms of social isolation and linguistic disorders in children without schizophrenia or other known psychiatric disorders. These children had difficulty communicating and interacting with others and displayed repetitive behaviors and loss of interest in social activities (Kanner, 1943). In 1944, Hans Asperger identified children with social isolation who lacked the linguistic abnormalities typical of autistic children (Asperger, 1944). This led to the diagnosis of a new autistic-like disorder, which became to be known as "Asperger's Syndrome" (Hippler & Klicpera, 2003).

In 1994, the fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) included five Pervasive Developmental Disorders (PDDs): autistic disorder, Asperger's syndrome (AS), pervasive developmental disorder-not otherwise specified (PDD-NOS), Rett's disorder and child disintegrative disorder (APA, 2000). Children diagnosed with these disorders typically showed deficits in three domains: social interaction, communication, and repetitive/restricted behaviors. The symptoms included marked impairment in non-verbal behaviors such as eye-to-eye gaze, facial expression, and body postures, as well as stereotyped repetitive behaviors and loss of interest in social functions, communications and activities. Based on these criteria, a patient diagnosed with autistic disorder would have exhibited at least six of twelve deficits in social interaction, communication or repetitive behaviors. At times, there could be rather large variations in symptom severity across different disorders, particularly in the development of spoken language; a patient with AS may have had no significant language delay whereas a patient with PDD-NOS or autism may have suffered from severe impairment in the development of spoken language (Filipek et al., 1999).

2. New classification of ASD

The wide variations in the severity of symptoms both within and across the group of disorders complicated the ability to effectively discern one disorder from the other. Seeking to eliminate some of this variability, the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM 5; www.dsm5.org) shifted from grouping the disorders as separate diagnoses under the umbrella of PDDs to conceptualizing them as all members of the broader category of known as Autism Spectrum Disorder (ASD). With this revision, the diagnostic criteria also changed. The number of core domain deficits was reduced to two (social communication and repetitive behavior). ASD would now be diagnosed when a patient demonstrated at least three symptoms in the domain of social communication and at least two symptoms of restricted interests/repetitive behaviors; including an added behavior of hyper- or hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment. In addition, a new diagnosis of social communication disorder (SCD) was created for children who do not fit the criteria of ASD because they lacked repetitive behaviors, but still suffered from verbal and nonverbal communication deficits that negatively affected their social relationships before the age of 3 (Halfon & Kuo, 2013; Mahjouri & Lord, 2012). Screening and elimination of other medical conditions such as seizures, attention deficit hyperactivity disorder (ADHD), anxiety, depression and gastrointestinal (GI) problems were also recommended to confirm diagnosis.

There were concerns that with the new classification of ASD the folding of all disorders into one might exclude many patients with other autistic disorders, such as AS and PPD-NOS. Some also contested the new conceptualization of these priorly distinct disorders as a progression of the same underlying disorder with symptom severity ranging from mild to moderate to severe rather than separate disease processes. A study by Huerta and colleagues put some of these concerns to rest. The researchers compared the different rates of sensitivity and specificity of DSM-IV vs. DSM 5 in diagnosing ASD, and reported that 91% of patients diagnosed with ASD using DSM-IV retained this diagnosis when using DSM 5 (Huerta, Bishop, Duncan, Hus, & Lord, 2012). The DSM-IV criteria for diagnosing Asperger's disorder and PDD-NOS were slightly more sensitive than DSM 5, however, only 9% of children diagnosed as having PDD by DSM-IV would not meet criteria for ASD under DSM 5 (Kulage, Smaldone, & Cohn, 2014; Tsai, 2012).

3. Prevalence and risk factors of ASD

The prevalence of ASD has been steadily increasing in the past two decades. In 2000, the Center for Disease Control's Autism and Developmental Disabilities Monitoring (ADDM) Network estimated the incidence of ASD to be 1 in 150 children. In 2006, the incidence of ASD increased to 1 in 110 children, and in 2008, it increased yet again to 1 in 88 children. In 2012, the ADDM network revised its ASD estimates to 1 in 68 children (Christensen et al., 2016). In 2016, the National Health Center for Health Statistics released its latest prevalence rate and reported a new record high, citing ASD could be found in as many as 1 in 36 children (Zablotsky, Black, & Blumberg, 2017). This ratio is thought to be the same across all racial, ethnic or socioeconomic backgrounds, however gender variations exist. The prevalence of ASD appears to be four- to five-fold higher in boys than in girls (Christensen et al., 2016). Increased ASD screening frequency in children and adults; better diagnostic criteria and more accurate behavioral and neuropsychological scales may all have also contributed to the steady rise in the prevalence of ASD.

Genetics plays a prominent role in ASD. Studies evaluating the prevalence of ASD found that in identical twins, if one twin has ASD, then the other will have 36%–95% chance of also having ASD. In non-identical twins, if one child has ASD, the chance of the other twin having the same disorder drops to 0–30% (Hallmayer et al., 2011; Rosenberg et al., 2009). Siblings of children with ASD have a 2–8% risk of also developing the disorder, and this rises to 12–20% if the inflicted child shows deficits in one to two of the three domains impaired in autism (Bolton et al., 1994). ASD symptoms tend to be expressed more frequently in patients with genetic or chromosomal conditions. About 10% of children with ASD also have Down's syndrome or fragile X syndrome (DiGuiseppi et al., 2010; Hall, Lightbody, & Reiss, 2008). Parental history of psychiatric disorders, and in particular schizophrenia and affective disorders, has been linked to an increased risk for ASD (Jokiranta et al., 2013). In addition, parental age may be another risk factor; studies suggest that children born to older parents are at a higher risk for developing ASD (Durkin et al., 2008). Children born prematurely (<33 week gestation) or with low birth weight (>2500 g) are associated with 2-fold increased risk for ASD (Schendel & Bhasin, 2008).

Fetal exposure to insecticides such as chlorpyrifos has been linked to a reduction in infant body weight and length, delayed psychomotor development, and a higher risk of ASD (Landrigan, 2010; Rauh et al., 2006). In addition, recent epidemiology studies provide evidence that exposure of pregnant mothers, especially during 1st or 2nd trimester, to viral or bacterial infections, promotes maternal immune activation (MIA) and increases the risk for neuropsychiatric diseases including ASD in their children (by 13%) compared to children of unexposed pregnant mothers (Estes & McAllister, 2016; Patterson, 2009). MIA has been linked to increases in neuroinflammatory cytokines as well as abnormalities in synaptic protein expression and aberrant developments in synaptic connectivity, all of which may underlie the pathophysiology of ASD (Pendyala et al., 2017).

Exposure of pregnant mothers to psychotropic medication, especially during the first trimester, has been considered a risk factor for ASD (Gardener, Spiegelman, & Buka, 2009). Children exposed to valproate in uteri have an 8-fold increased risk of developing ASD (Resale et al., 2005). Additional studies suggest that prescribing antidepressants to pregnant women modestly increases the risk of ASD (Andrade

et al., 2008; Croen, Grether, Yoshida, Odouli, & Hendrick, 2011; Gidaya et al., 2014), although these findings have not been confirmed in other studies (Hviid, Melbye, & Pasternak, 2013; Sørensen et al., 2013). Several limitations may have led to the current discrepancies among replicated studies, including the absence of careful adjustments for the maternal history of psychiatric illnesses, accounting for genetic predispositions to ASD, and the variable molecular and clinical effects of dissimilar antidepressants. However, a recent 12-year, register-based study, which included over 145,000 singleton full-term live birth infants born to mothers who had received anti-depressants during pregnancy, concluded that the use of antidepressants, specifically selective serotonin reuptake inhibitors, during the second and/or third trimester does increase the risk of ASD in children, even after adjusting for maternal depression and other confounding factors (Boukhris, Sheehy, Mottron, & Bérard, 2016). Nonetheless, additional clinical studies are still needed to validate whether there is definitive increased risk of ASD in children born to women diagnosed with depression who are receiving either no treatment or antidepressant treatment during pregnancy, and to also correlate this risk with medication effect, antidepressant types and dosages during pregnancy.

4. Neurobiology of ASD

Recent neurobiological findings of behavioral functioning in ASD point to altered brain connectivity as a key feature of its pathophysiology; though findings determining aberrations in specific functional tracts continue to undergo consistent revision. ASD has been generally conceptualized as a disorder in long distance cortical and subcortical underconnectivity with compensatory poorly formed shorter circuit overconnectivity, which leads to the often seen enhanced discrimination of, or attention to, simple stimuli among individuals with ASD with coterminous impairment in the successfully sensory integration of these simple stimuli into a more complex gestalt perceptual representation (Kana, Keller, Cherkassky, Minshew, & Just, 2009).

A well-known clinical vignette illustrates that children with ASD perform better than aged match peers in identifying the number of triangles in an Embedded Figure test, but struggle when asked to identify the larger figure represented by the triangles (Baum, Stevenson, & Wallace, 2015). This dichotomy is not unique to visual stimuli: absolute pitch, or "perfect pitch" is an auditory phenomena that enables one to replicate or name a single tone without any external reference and is found in individuals with ASD in significantly greater numbers than peer matched controls (Bonnel et al., 2003; Dohn, Garza-Villarreal, Heaton, & Vuust, 2012). However, when these singular pitches are linked together to form a melody, ASD individuals demonstrate poorer meter enculturation and rhythmic entrainment when compared to non ASD controls: awareness of rhythm is a more complex auditory perceptual skill, and one that is necessary for the prosodic discrimination of normal speech patterns (DePape, Hall, Tillmann, & Trainor, 2012).

More recently, Cerliani et al. (2015) discovered increased connectivity between sensory cortices, the thalamus and basal ganglia; suggesting subcortical connectivity dysfunction has a role in bottom-up behavioral deregulation with poor compensatory top down cortical control. Fishman, Keown, Lincoln, Pineda, and Müller (2014) found overconnectivity, but reduced activation and communication efficiency, both within, and between, the theory of mind (TOM) cortical networks and the mirror neuron system (MNS) in adolescents with ASD; these signal:noise ratio aberrations occur in key social cognizance networks that underscore the ability to understand, interpret, empathize and react to others, and may represent a compensatory effect by the brain to interpret social cues through different pathways when unable to effectively signal bind input from multi-sensory stimuli with the frontal circuitry generally used to form cohesive conceptual constructs and social judgments.

Baum and colleagues proposed that because sensory information forms the building blocks for higher-order social and cognitive functions, deficits in multisensory integration are a critical cornerstone for characterizing and understanding ASD, suggesting that aberrations in successfully integrating multisensory processing should not be conceptualized as merely one feature of ASD, but rather as the foundation upon which the other core symptoms develop. This inability to synthesize various sensory inputs alters the ability to form metaphors and complex cognitive representations necessary to effectively abstract, grasp language and respond to social cues, which collectively represent the core symptoms off ASD (Baum et al., 2015).

5. Diagnosis of ASD

Due to the complexity, severity and overlap of ASD symptoms with other psychiatric disorders, it is important to use appropriate instruments and scales to correctly diagnose ASD in order to improve the clinical management of ASD patients. Assessment instruments include parent/caregiver interviews, patient interviews, direct observation of patients, and detailed clinical assessments that encompass a thorough review of family history for ASD or other neurodevelopmental disorders. These scales are authoritatively reviewed by Vllasaliu et al., 2016. Among the scales that are widely used to diagnose ASD are the following.

5.1. The developmental, dimensional, and diagnostic interview

The Developmental, Dimensional, and Diagnostic Interview (3di) is a computer- and investigator-based interview with parents/caregivers. It contains 740 items; 183 items assess demographic background, 266 items evaluate ASD symptoms, and 291 items examine potential comorbidity with other disorders (Skuse et al., 2004). Answers are scored from "0" (no evidence of impaired behaviors) to "2" (definite evidence of such behavior). The 3di can be used to diagnose individuals with ASD from early childhood through to adulthood, and typically the length of assessment ranges from 1.5 to 2 h (Skuse et al., 2004).

5.2. Childhood Autism Rating Scale (CARS)

Childhood Autism Rating Scale (CARS) is a popular scale that is frequently used to assist in the diagnosis of ASD in children (Schopler, Reichler, DeVellis, & Daly, 1980). It can distinguish between children with autism and children with other developmental delay disorders such as mental retardation. Additional studies supported the utility of CARS in diagnosing ASD in adolescents and adults (Mesibov, Schopler, Schaffer, & Michal, 1989). CARS consists of 15 items that cover different symptoms of ASD, and provides reliable comparison of an affected child's behaviors and skills against expected developmental growth of a healthy child. Each item is scored from "1" (normal behavior) to "4" (severely abnormal behavior). Scores between 30 and 37 indicate mild to moderate ASD, while scores between 38 and 60 indicate severe ASD (Schopler et al., 1980).

5.3. The Autism Spectrum Disorder–Observation for Children

The Autism Spectrum Disorder-Observation for Children (ASD-OC) is an observation scale consisting of 45 items and used to observe and rate core autistic symptoms including social impairment, communication deficits and repetitive behaviors (Neal, Matson, & Hattier, 2012). The behaviors of individual with ASD are compared to children of same age group and scored as "0" (no impairment), "1" (mild impairment) or "2" (severe impairment). A recent clinical study supported the clinical validity of ASD-OC as a reliable scale to assess symptoms of ASD in children aged 3–15 years (Neal, Matson, & Hattier, 2014).

5.4. The Autism Diagnostic Interview-Revised

The Autism Diagnostic Interview-Revised (ADI-R) is an investigator-based interview for parents/caregivers of children and adults for possible autism or ASD patients (Lord, Rutter, & Le Couteur, 1994). It contains 93 items that specifically evaluate different behaviors at different ages, including reciprocal social interaction, language and communication, stereotyped repetitive behaviors or interests, and age-of-onset criteria. It is typically scored from "0" (no evidence) to "3" (extreme severity of impaired behavior), takes 2–3 hours to complete and can only be given to children with mental age 2 or higher (Lord et al., 1994).

5.5. The Asperger Syndrome Diagnostic Interview

The Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI) is a short 15–20 min investigator-based interview intended for physicians to determine if an individual patient meets the criteria for diagnosis of autism or AS (Gillberg, Gillberg, Råstam, & Wentz, 2001). It consists of 20 items divided into 6 groups, which are: (A) verbal and speech problems (5 items), (B) non-verbal communication problems (5 items), (C) impairment in social interaction (4 items), (D) restricted interests (3 items), (E) routines (2 items) and (F) motor clumsiness (1 item). To be diagnosed with AS or high-functioning autism, an individual must have definite score in 3 items in group A, 2 items in group C, and at least one item in groups B, D, E, F (Gillberg et al., 2001).

5.6. The Diagnostic Interview for Social and Communication Disorders

The Diagnostic Interview for Social and Communication Disorders (DISCO) is a semi-structured interview for parents and caregivers, and is used for the diagnosis of individuals with ASD from infancy to old age. It provides a developmental evaluation of social behavior, skills and communications of patients from early days to present age (Maljaars, Noens, Scholte, & van Berckelaer-Onnes, 2012; Wing, Leekam, Libby, Gould, & Larcombe, 2002). The DISCO, which takes 2 to 3 h to administer, uses a dimensional approach for assessment rather than cut off points, and aims to closely assess, over the course of many years, the patterns of impairments in social behaviors and communications in individuals suspected of exhibiting ASD symptoms.

5.7. Autism Spectrum Disorder–Diagnosis Scale for Intellectually Disabled Adults

The Autism Spectrum Disorder–Diagnosis Scale for Intellectually Disabled Adults (ASD-DA) is used to distinguish adults with intellectual disability (ID) and ASD from adults with ID only (Matson, Wilkins, Boisjoli, & Smith, 2008). The ASD-DA consists of 31 items that cover the three core deficits (social impairment, deficits in communication, and restricted interests), can be administered in 10 min, and typically scored as "0" (no impairment) or "1" (impairment). A cut-off score ≥19 indicates comorbid ASD while a score <19 indicates that the adult has ID without ASD (Matson et al., 2008).

6. Comorbid disorders

Nearly three-quarters of children with ASD also have another medical, psychiatric, or neurological disorder that results in additional physical and/or mental impairment; increased treatment cost, and greater caregiver demands on the patients' families. Awareness of the high rates of ASD association with comorbid disorders is necessary to guide the proper diagnosis and treatment of the syndrome and to improve the prognosis and clinical outcomes of ASD patients. There are over 16 different conditions or disorders that are frequently associated with ASD, and include attention-deficit hyperactivity disorder (ADHD), anxiety, bipolar disorder, inflammatory bowel disease, epilepsy, fragile X-syndrome, gender dysphoria, intellectual disability, neuroinflammation and immune disorders, non-verbal learning disorder, obsessive-compulsive disorder (OCD), schizophrenia, sensory problems, sleep disorders, Tuberous sclerosis, and Tourette syndrome and tic disorders (Bauman, 2010; Erickson et al., 2005; Glidden, Bouman, Jones, & Arcelus, 2016; Pardo, Vargas, & Zimmerman, 2005; Smalley, 1998; Zafeiriou, Ververi, & Vargiami, 2007). In this review, we will focus on the disorders with the highest degree of comorbidity with ASD, including ADHD, depression, anxiety, Tourette's syndrome and tic disorders, bipolar disorder, and schizophrenia.

6.1. ADHD

There is a high degree of co-morbidity between ASD and ADHD. Studies show between 30 and 50% of patients with ASD also display ADHD symptoms, and 66% of ADHD patients also show features of ASD (Davis & Kollins, 2012; Leitner, 2014). Both disorders often include difficulties in attention, impulsivity, and various degrees of hyperactivity. Both disorders have a genetic predisposition; are more prevalent in boys than in girls; are typically diagnosed during preschool years, and can cause significant behavioral, academic, emotional and psychosocial disturbances that often impair daily functional activities (Rao & Landa, 2014). Findings from the Autism Treatment Network (ATN) database suggest that individuals with comorbid ASD/ADHD have a lower quality of life and higher degree of daily functional impairment than individuals who have either of these conditions separately (Sikora, Vora, Coury, & Rosenberg, 2012).

The DSM-5, with its revised ADHD diagnostic criteria, has recognized the frequency of ASD and ADHD co-occurrences and includes a dual comorbid diagnosis of ASD/ADHD (www.dsm5.org; Leitner, 2014). This should create an opportunity for improved recognition of patients who have both of these disorders and thereby allow for more tailored clinical management. Further studies on these comorbid disorders should provide new insights into common biological substrates and brain pathways shared by both disorders and pave the way for the development of novel and improved drug therapies for ASD, ADHD and ASD/ADHD populations.

6.2. Depression

Depression occurs frequently in ASD, though in many cases the proper diagnosis of depression in ASD is challenging and can be left untreated due to the masking of depressive symptoms by features of ASD (Chandrasekhar, 2015). Prevalence rates of depression among young ASD patients range from 10%–50% (Simonoff et al., 2008). Findings from Interactive Autism Network database indicate that 11% of ASD children have also been diagnosed with depression (Rosenberg, Kaufmann, Law, & Law, 2011). The depressive episodes in ASD children tend to be more severe in symptoms and last for longer periods than in children with either non-ASD neuropsychiatric disorders or healthy development (Mayes, Calhoun, Murray, Ahuja, & Smith, 2011). Consistent with these studies, adults with ASD seem more vulnerable to depression those with other developmental disorders or healthy individuals (Lugnegard, Hallerbäck, & Gillberg, 2011).

6.3. Anxiety disorders

Up to 80% of children with ASD also suffer from one or more anxiety disorders (Muris, Steerneman, Merckelbach, Holdrinet, & Meesters, 1998; Simonoff et al., 2008). Separation anxiety disorder (SAD) has the highest comorbidity rate with ASD (38%) followed by obsessive–compulsive disorder (OCD; 37%), generalized anxiety disorder (GAD; 35%) and social phobia (30%) (Leyfer et al., 2006; Muris et al., 1998). Presence of anxiety disorders typically compounds psychosocial functional impairment and increases severity of ASD symptoms, particularly around behaviors related to social avoidance, sleep, family and peer

interactions, and noncompliance with school activities (Davis et al., 2011; Klin et al., 2007; Montes & Halterman, 2006). Young patients with ASD often display repetitive behaviors such as counting, tapping, repeating words, facts and expressions. This is similar to the obsessions and compulsions typically seen in OCD patients (Russell, Mataix-Cols, Anson, & Murphy, 2005). Adolescents with AS or high functioning autism are more likely to suffer from an anxiety disorder since their higher cognitive functioning may make them more aware of their environment and their perception by their peers (van Steensel, Bögels, & Perrin, 2011).

6.4. Bipolar disorder

Bipolar disorder (BPD) is frequent and often emerges during adolescence in ASD patients (Vannucchi et al., 2014). One study found that 30% of BPD-I patients also met criteria for ASD, and this comorbidity contributed to an earlier age of onset of BPD-I symptoms (Joshi et al., 2013). Another study also found a significant minority of ASD patients suffer from bipolar disorder (Skokauskas & Frodl, 2015). A third study reported high prevalence of BPD co-morbidity in 44 young, high-functioning ASD patients (Munesue et al., 2008). Accurate detection of dual ASD/BPD diagnosis can lead to more targeted therapies and improvement of quality of life for these patients.

6.5. Tourette syndrome and tic disorders

Tourette syndrome (TS) is a neurodevelopmental disorder that affects motor neurons and is characterized by the persistence of unwanted, brief, repetitive, non-rhythmic motor movements, and one or more vocal/phonic tics (Cavanna & Termine, 2012). Although less well-documented than its associations with ADHD, depression, anxiety and bipolar disorder, there is evidence to suggest that TS co-occurs more commonly in patients with ASD than in the general population. One study reported that 4.6% of TS patients also had a comorbid pervasive developmental disorder (Burd, Li, Kerbeshian, Klug, & Freeman, 2009). Another study found that 22% of ASD patients exhibited symptoms of TS and other chronic motor tics (Canitano & Vivanti, 2007). The higher prevalence of ASD with TS compared to the general population suggests that both disorders may share common genetic traits or similar imbalance of synaptic neurotransmission (Zafeiriou et al., 2007).

6.6. Childhood-onset schizophrenia

Childhood-onset schizophrenia (COS) is a rare and severe form of schizophrenia where onset of psychosis typically happens before age of 13. COS patients can show severe impairments in social and motor development as well as significantly greater premorbid language-delays and learning disabilities than those with onset of schizophrenia in adolescence (Alaghband-Rad et al., 1995; Russell, Bott, & Sammons, 1989). Early studies suggested a relatively heavy familial-genetic predisposition to COS (Kallman & Roth, 1956; Kolvin, 1971). Several studies have since found comorbidity between ASD and COS. One study found that 39% of a sample of 33 patients had symptoms of autism years before onset of schizophrenia (Watkins, Asarnow, & Tanguay, 1988). Another study found that 28% of 101 young patients with COS had comorbid ASD (Rapoport, Chavez, Greenstein, Addington, & Gogtay, 2009). Once a dual COS/ASD diagnosis is confirmed, an aggressive pharmacotherapy treatment combined with psychological counseling and family education should be implemented.

7. Pharmacological therapies for ASD

The current treatment options for ASD include pharmacological and non-pharmacological interventions. Pharmacological interventions include different classes of drugs including psychostimulants, atypical antipsychotic drugs, antidepressants, alpha-2 adrenergic receptor agonists, cholinesterase inhibitors, NMDA receptor antagonists, and antiepileptic mood stabilizers (Aman, Farmer, Hollway, & Arnold, 2008). This section focuses on the main drug classes and the most prescribed medications used for the treatment of pediatric and adult ASD patients, and discusses their efficacy, safety and tolerability profiles as determined in double-blind, randomized, placebo-controlled trials (RCTs), in retrospective open-label clinical trials, or in pilot studies.

7.1. Psychostimulants

Since there is a high degree of co-morbidity between ASD and ADHD, treatment with traditional ADHD psychostimulant drugs such as methylphenidate and amphetamines appears to be beneficial in managing ADHD symptoms in ASD patients (Davis & Kollins, 2012). Earlier double-blind, crossover RCTs suggested that methylphenidate may be useful in the treatment of hyperactivity in ASD children (Handen, Johnson, & Lubetsky, 2000; Quintana et al., 1995), though the latter study reported an increase in adverse events such as social withdrawal and irritability. A larger crossover RCT conducted by The Research Units on Pediatric Psychopharmacology (RUPP) Autism Network reported that methylphenidate was effective at reducing hyperactivity and impulsivity in 50% of 72 children with ASD (ages 5–14 years) who also had hyperactivity. Nonetheless, this improvement remains lower than the 70%–80% improvement of symptoms after treatment with methylphenidate in children with ADHD only (RUPP Autism Network, 2005). In addition, lower doses of methylphenidate were used since ASD patients were unable to tolerate the higher doses commonly used in ADHD patients (RUPP Autism Network, 2005). Another trial in preschool-aged children also reported 50% reduction in hyperactivity and impulsivity on twice/day dosing of methylphenidate (range 2.5–10 mg or 0.14–0.58 mg/kg for both the morning and noon doses); higher doses were associated with a higher incidence of side effects including irritability and stereotypic behaviors, gastrointestinal and sleep problems (Ghuman et al., 2009). It should be noted that psychostimulants were mainly effective in improving comorbid hyperactivity and impulsivity in ASD patients with no benefits on other symptoms such as irritability, social withdrawal, repetitive behaviors, or speech impairment (RUPP Autism Network, 2005).

7.2. Atypical antipsychotic drugs

Atypical antipsychotic drugs target dopamine, serotonin, and other neurotransmitter receptor subtypes with variable affinities and have been widely used for treatment of schizophrenia and other psychotic disorders (Baldessarini & Tarazi, 2005). The atypical antipsychotic drugs commonly prescribed for ASD patients are risperidone, aripiprazole, quetiapine, ziprasidone, and to a lesser extent olanzapine (Posey, Stigler, Erickson, & McDougle, 2008).

7.2.1. Risperidone

An early 12-week, double-blind RCT found that risperidone (mean dose 2.9 mg/d) significantly reduced repetitive behavior, aggression, anxiety or nervousness, depression, and irritability in adult patients with ASD (autism and PPD NOS) compared to placebo-treated patients (McDougle et al., 1998). Risperidone was well tolerated, with no evidence of extrapyramidal effects, cardiac events, or seizures (McDougle, Holmes, et al., 1998).

A larger multicenter trial conducted by RUPP Autism Network reported that treatment of 101 ASD children and adolescents (5–17 years old) with risperidone (mean dose 1.8 mg/kg) for 8 weeks resulted in 57% reduction in irritability vs. 14% reduction in the placebo group. Risperidone treatment also significantly improved aggression, social withdrawal, repetitive behaviors, and hyperactivity (McCracken et al., 2002). A second multicenter double-blind, RCT conducted in 79 ASD children found that risperidone treatment (mean dose, 1.2 mg/d) significantly reduced irritability and hyperactivity and to lesser extent social

withdrawal when compared to placebo-treated patients (Shea et al., 2004). In the last two trials, however, risperidone treatment was associated with significant weight gain as well as fatigue, drowsiness and dizziness. Nonetheless, these trials provided enough convincing evidence when weighing the risks vs benefits of treatment to make risperidone the first FDA-approved atypical antipsychotic drug for ASD (Posey et al., 2008). Evidence also indicates that low doses of risperidone (0.5–1.5 mg/d) are effective in reducing irritability and agitation in very young ASD children (aged 2–9 years) (Luby et al., 2006; Posey, Walsh, Wilson, & McDougle, 1999).

7.2.2. Aripiprazole

Two double-blind RCTs evaluated the efficacy and safety of aripiprazole in ASD children. The first study included 218 autistic children and adolescents (aged 6–17 years) who were randomized to receive either one of three different doses of aripiprazole (5, 10 or 15 mg/d) or placebo for 8 weeks. All three doses significantly reduced irritability compared with placebo at week 8. The three most common side effects were sedation, drooling and tremor, and this contributed to a higher mean of discontinuation rate of aripiprazole-treated patients (10.3%) vs. placebo (7.7%) (Marcus et al., 2009).

The second RCT was an 8-week study with 98 children and adolescents (aged 6–17 years) diagnosed with ASD who also displayed aggressive or self-injurious behaviors. Patients received a flexible dose of aripiprazole (mean dose 8.6 mg/d) or placebo. Aripiprazole was efficacious in reducing irritability as early as week 1 and maintained its effect through the end of the trial at week 8. Discontinuation rates were 10.6% in aripiprazole group vs. 5.9% in the placebo group (Owen et al., 2009). These trials led to FDA approval of aripiprazole as the second atypical antipsychotic drug to treat irritability in children and adolescents with autistic disorder aged 6–17 years (Blankenship, Erickson, Stigler, Posey, & McDougle, 2010).

7.2.3. Quetiapine

Results of clinical trials with quetiapine to treat ASD patients were inconclusive, since the majority of these trials were non-blinded or included retrospective chart review of patients. Two open label trials in small number of ASD patients reported low response rate (<25%) and high incidence of side effects including sedation, aggression and weight gain (Fondling et al., 2004; Martin, Koenig, Scahill, & Bregman, 1999). In contrast, several case series studies found higher response rate (40%–60%) with considerable side effects after treatment of ASD children with quetiapine (Corson, Barkenbus, Posey, Stigler, & McDougle, 2004; Hardan, Jou, & Handen, 2005). These findings suggest that quetiapine is less effective than risperidone in managing the symptoms of ASD, and point to the need for conducting additional double-blind RCT to more accurately evaluate the efficacy, safety and tolerability of quetiapine in ASD.

7.2.4. Ziprasidone

Two open label studies have evaluated the efficacy, safety and tolerability of ziprasidone in ASD children. One study reported significant improvement in aggression, agitation, and irritability after 14 weeks of treatment with ziprasidone (mean dose 59 mg/d). The drug was well tolerated, and a few patients even lost weight (average weight lost 5.8 lb), which may be attributable to switching from other atypical agents that are commonly associated with significant weight gain (McDougle, Kem, & Posey, 2002). Another study assessed the effects of switching 10 adult ASD patients, who had suffered excessive weight gain while on risperidone or quetiapine, to ziprasidone. All 10 patients lost significant weight (average weight lost 9.5 lb) after 6 months of treatment with ziprasidone (mean dose 128 mg/d) with no deterioration in their controlled behavioral symptoms (Cohen, Fitzgerald, Khan, & Khan, 2004). Additional double-blind RCTs are needed to validate the therapeutic benefits of ziprasidone in ASD patients.

7.2.5. Olanzapine

An 8-week double-blind RCT reported that olanzapine improved response rates in 11 young ASD patients (Hollander et al., 2006). Open-label treatment of 8 children, adolescents, and adults (age range, 5–42 years) with olanzapine (mean dose 7.8 mg/d) significantly improved many symptoms including irritability, anger, anxiety, hyperactivity, social withdrawal, and language usage (Potenza, Holmes, Kanes, & McDougle, 1999). The most prominent adverse event was increased mean body weight of the group by 8.4 kg during the course of the 12-week trial (Potenza et al., 1999). Another open-label pilot trial compared the efficacy of olanzapine (mean dose 7.9 mg/d) vs. haloperidol (mean dose 1.4 mg/kg) in 12 children with ASD. 83% of olanzapine-treated patients vs. 50% of haloperidol-treated patients were rated as responders. However, olanzapine-treated patients experienced significant weight gain (mean 4.1 kg) vs. haloperidol-treated patients (mean 1.5 kg) (Malone, Cater, Sheikh, Choudhury, & Delaney, 2001). In spite of the superior efficacy of olanzapine in managing symptoms of ASD, its clinical use has been limited due to its well-known metabolic side effects including increased appetite, excessive weight gain and impaired insulin sensitivity (Tschoner et al., 2007).

7.3. Antidepressant drugs

Antidepressant drugs, specifically SSRIs, are widely prescribed to ASD patients (Scahill & Boorin, 2011), and the use of these agents has been steadily increasing (Langworthy-Lam, Aman, & van Bourgondien, 2002), in spite of the inconclusive, and in many instances weak, evidence that supports their benefits in improving core symptoms of ASD or comorbid depression and anxiety (Williams, Wheeler, & Silove, 2010). Fluoxetine, sertraline, citalopram, escitalopram, and fluvoxamine are among the widely used SSRIs in ASD (Nadeau et al., 2011).

7.3.1. Fluoxetine

A double-blind RCT clinical study reported that 20-week treatment with liquid fluoxetine significantly reduced repetitive behaviors in ASD children compared to placebo-controlled patients without any noted safety or tolerability issues. However, no improvement was observed on other ASD symptoms (Hollander et al., 2005). Another RCT reported inconsistent improvement in anxiety symptoms and repetitive behaviors in a small number of comorbid ASD/anxiety adult patients treated with fluoxetine for 16 weeks (Buchsbaum et al., 2001). A larger RCT (158 participants) known as SOFIA (Study of Fluoxetine in Autism) failed to detect any significant improvement in repetitive behaviors in young ASD patients compared to placebo-treated group (Autism Speaks, 2009). The summation of evidence points to an inconclusive benefit in the use of fluoxetine to treat symptoms of ASD.

7.3.2. Sertraline

Few trials have evaluated the efficacy and tolerability of sertraline in ASD patients. A small open-label clinical trial found that 2–8 weeks of treatment with sertraline (25–50 mg) significantly improved anxiety and irritability in 8 out of 9 pediatric ASD patients (Steingard, Zimnitzky, DeMaso, Bauman, & Bucci, 1997). A larger open-label trial reported that 12-week treatment with higher doses of sertraline (50–200 mg) reduced aggressive and repetitive behaviors in adult ASD patients (McDougle et al., 1998). The medication was well tolerated with minimal adverse events. Double-blind RCTs are still needed to more thoroughly assess the benefits of sertraline in ASD patients.

7.3.3. Citalopram

A retrospective open-label study reported that citalopram improved anxiety and aggression in a small number of young ASD patients, but without affecting the core symptoms of the disease (Couturier & Nicholson, 2002). Another retrospective study that reviewed medical charts of 15 young ASD patients found that citalopram reduced anxiety, repetitive behaviors, and irritability with mild side effects (Namerow,

Thomas, Bostic, Prince, & Monuteaux, 2003). However, a larger multisite trial which enrolled 149 young ASD children and conducted by the Studies to Advance Autism Research and Treatment (STAART) Autism Network, casted doubt on these earlier findings. The trial failed to detect clinical benefits for citalopram over placebo, and also revealed a higher incidence of side effects including hyperactivity, insomnia, and diarrhea in citalopram-treated ASD patients, ultimately concluding that citalopram is ineffective for ASD (King et al., 2009).

7.3.4. Escitalopram

Studies evaluating escitalopram in ASD are scarce. A 10-week, open-label study reported that escitalopram improved impulsivity and overall psychosocial functioning in young ASD patients compared to placebo (Owley et al., 2005). However, a large number of patients experienced side effects such as hyperactivity, aggression or irritability leading to early treatment termination. Additional double-blind RCTs are needed to evaluate escitalopram in adult ASD patients with and without comorbid anxiety or depression.

7.3.5. Fluvoxamine

Clinical results with fluvoxamine for ASD are also inconclusive. An open-label trial found that 83% (15 out of 18) of young ASD patients with comorbid anxiety and compulsive symptoms failed to show significant improvement in their ASD or anxiety symptoms after 10 weeks of treatment with low dose of fluvoxamine (1.5 mg/kg/day) (Martin, Koenig, Anderson, & Scahill, 2003). A high incidence of adverse events such as akathisia, agitation, sleep difficulties, headaches and appetite changes were also reported in these patients (85). In contrast, a 12-week double-blind RCT suggested that fluvoxamine might have some clinical benefits in terms of reducing repetitive thoughts, behaviors and aggression in adult ASD patients compared to placebo-treated patients (McDougle et al., 1996).

7.4. Alpha-2 adrenergic receptor agonists

The use of alpha-2 adrenergic receptor agonists is associated with the treatment of aggressive behavior, sleep disturbances and anxiety, which are prominent symptoms in ASD patients. These medications inhibit norepinephrine neurotransmission in the brainstem, leading to a decrease in sympathetic outflow and peripheral resistance thereby diminishing states of hyper-arousal, anxiety, and/or motor spasms (Newcorn et al., 1998). An earlier double-blind, crossover RCT reported that 4-week treatment with the alpha-2 adrenergic receptor agonist *clonidine* reduced hyperarousal behaviors and improved social interactions in young ASD patients (Fankhauser, Karumanchi, German, Yates, & Karumanchi, 1992). Another double-blind RCT found modest improvement of irritability and hyperactivity in ASD children after treatment with clonidine (Jaselskis, Cook Jr., Fletcher, & Leventhal, 1992). A third open labeled retrospective clinical trial found that clonidine was effective in reducing sleep initiation latency and night awakening, and to a lesser degree, in also improving hyperactivity and aggressiveness in ASD children, with a fairly benign tolerability profile (Ming, Gordon, Kang, & Wagner, 2008). Further evaluation with RCTs will provide more insight into the clinical efficacy and safety of clonidine in ASD.

Guanfacine extended release (guanfacine-ER), another alpha-2 receptor agonist, has also been studied in ASD. In a RCT, symptoms of hyperactivity, impulsiveness, and distractibility were significantly improved in ASD children treated for 8 weeks with guanfacine-ER compared to placebo-treated patients. Side effects included drowsiness, fatigue and decreased appetite (Scahill et al., 2015). Another double-blind RCT also reported improvement of hyperactivity in ASD children treated with guanfacine compared to placebo controls (Handen, Sahl, & Hardan, 2008). Both trials, however, reported side effects including drowsiness, fatigue, and decreased appetite, which suggest that caution is needed when prescribing this agent to ASD patients.

8. Non-pharmacological therapies for ASD

8.1. Complementary and integrative health

Despite the growing prevalence of ASD in the United States over the past few decades, the currently available pharmacologic therapies demonstrate variable levels of efficacy and are able to only diminish the effects of the disruptive repetitive behaviors associated with the condition rather than provide modification of the underlying disease process itself (Reichow, Barton, Boyd, & Hume, 2012). Given concern of the side effect profile of atypical antipsychotics commonly used as first line pharmacotherapy in ASD, coupled with the desire to find treatments that may successfully alter the underlying neurodevelopmental abnormalities present in children with ASD, there has been increased interest in turning to complementary and integrative health (CIH), formerly defined as complementary and alternative medicine (CAM), to augment traditional treatment practices. Recent studies suggest anywhere from 30 to 72% of parents of children with ASD are also utilizing supplementary CIH (Hanson et al., 2007).

The National Center for Complementary and Integrative Health (NCCIH), a subdivision of the National Institute of Health (NIH), groups CIH interventions into two main categories: mind/body practices and natural products, emphasizing that complementary practices are often run in parallel rather than as an alternative to traditional medical practices, while integrative health reflects the coordinated combination of both traditional and complementary therapies. Brondino et al., 2015 published a systematic review to provide a comprehensive overlook of the efficacy of CIH in ASD, grouping topics into biological (i.e. NCCIH defined natural products) and non-biological based interventions (i.e. NCCIH defined mind/body practices); the latter which encompassed auditory and sensory integration practices, yoga, acupuncture and music therapy (Brondino et al., 2015). While concluding that there is cautious evidence for the use of sensory integration therapies, acupuncture and massage, the authors noted that the overall evidence for utility of CIH based treatments in ASD was sparse, pointing to variables such as the heterogeneity in clinical manifestations of ASD impacting outcomes as well as an overall paucity of well developed, methodologically sound studies.

A notable exception was the use of music therapy, for which the authors found promising evidence in the treatment of ASD, noting that this conclusion was strengthened by the existence of numerous studies on the topic, and suggesting that this may be due to music therapy being commonly classified as a behavioral, rather than a CIH, intervention and therefore enjoying greater scientific and clinical acceptance to its use (Wieland, Manheimer, & Berman, 2011). The Cochrane Collaboration in 2014, revised its 2006 review on music and autism, citing evidence that music therapy may help children with ASD to improve their skills in primary outcome areas that constitute the core of the condition including social interaction, verbal communication, initiating behavior, and social-emotional reciprocity contributing to increasing social adaptation skills and to promoting the quality of parent-child relationships. The review did recognize the need for further studies to determine the longevity of these effects and cautioned about creating music therapy protocols in clinical practice without requisite expertise.

8.2. Music therapy

Music therapy may be particularly efficacious in ASD due to its distinct ability to potentially change both the structure and functional connectivity of the cortex (Altenmüller & Schlaug, 2015), allowing for greater multisensory integration across cortical and subcortical domains in early developmental stages, the absence of which is widely postulated as the core underlying neurophysiologic aberration in ASD. Patients diagnosed with ASD generally show a preserved, and even heightened, sense of musicality that extends into adulthood, with an ability to interpret and respond to the emotions conveyed in song or

music even when unable to do so in speech (Heaton, 2009). In 2014, Shard and colleagues demonstrated a neurophysiologic correlate for this in finding 22 children with ASD, with varying levels of functioning, activated bilateral temporal brain networks during sung-word perception, similarly to an age and gender-matched control group and that functional front-temporal connectivity, disrupted during spoken-word perception, was preserved during sung-word listening in ASD (Sharda, Midha, Malik, Mukerji, & Singh, 2015).

While further studies are required to determine if this same pattern of activation remains in adults with ASD, this finding provides a compelling potential mechanism for how and why music may heighten mentalization and access to emotional attunement for ASD individuals: binding what Kana and colleagues wrote in 2009: "it is not only frontal activation that is critical, but the synchronization of frontal activity with activity in posterior Theory of Mind areas, as well as other areas, which may be important in accomplishing "mentalizing" with the synchronous and sustained bilateral temporal and frontal activation invoked through song that Sharda revealed (Kana et al., 2009; Sharda et al., 2015). Music's ability to modulate emotion and mood in individuals both with and without ASD is well established: both experimentally and anecdotally. Both passive listening, and to a greater extent, active playing, have been shown to activate areas of the brain involved in cognitive, sensorimotor and perception-action mediation through increasing the oscillation synchrony between these various cortical areas and thereby promoting heightened sensory-integration (Koelsch, 2009).

8.2.1. Neuromodulatory effects of music

Both short and long term music listening and music making engage multisensory and motor networks; induce changes within these networks; and create connections between distant, but functionally related brain regions with continued music exposure (Altenmüller & Schlaug, 2015). Professional musicians demonstrate changes in the volume and density of the motor cortex, arcuate fasciculus as well as the cerebellum when compared to age matched controls (Halwani, Loui, Rüber, & Schlaug, 2011). In addition, children who engage in long-term instrumental practice have larger corpus callosum as well as frontal, temporal and motor areas relative to controls (Schlaug, Marchina, & Norton, 2009). In a 2009 study utilizing music-based intervention (e.g. auditory motor mapping training "AMMT"), Schlaug et al. reported on two cases where previously nonverbal children with autism were able to speak after undergoing AMMT. The researchers postulated that due to its ability to strengthen the synaptic connections between various somatosensory cortical areas, music might improve deficits in the mirror neuron system (MNS) found in children with autism (Dapretto et al., 2006), priming them to speak. In particular, the researchers pointed to previous evidence demonstrating a change in the volume and fiber density of the arcuate fasciculus in not only professional musicians but also in adult patients with Boca's aphasia who demonstrated both clinical improvement and structural changes in this front-temporal tract following an intensive course of music based speech therapy (Schlaug et al., 2009). They suggested that this may also underlie the communication deficits in individuals with autism with a role for music based therapies to supersede these deficits.

Further studies to investigate the efficacy of music based interventions in facilitating speech output as well as correlative changes in language areas of the brain must be conducted, however early evidence suggests a strong improvement across clinical domains in ASD and a large body of evidence demonstrates structure and functional changes in the brain following a period of active musicality in key areas, including the MNS, that may serve as the mechanism through which clinical improvements for ASD patients engaged in musical training occur.

8.3. Cognitive-behavioral therapy

Cognitive behavioral therapy (CBT) is a psychotherapeutic intervention that has previously been shown to be effective across a range of psychiatric disorders, including anxiety, depression and OCD. In general, the highly structured and highly predictable nature of CBT makes it especially appropriate for ASD patients both for targeting core symptoms as well as for comorbid anxiety and depression (Hesselmark, Plenty, & Bejerot, 2014). Generally, these programs always include a core element of psychoeducation, as well as social coaching to enhance development of social skills, instruction on self-care skills, and highly structured worksheets and visual aids (Ung, Selles, Small, & Storch, 2015). Modified CBT techniques and protocols have been developed for ASD patients to address those symptoms and difficulties arising from their disorder which would also interfere with application of standard CBT such as their problems in recognizing and understanding both their own and others' thoughts and feelings (Danial & Wood, 2013).

CBT in high functioning young ASD patients can be administered individually, can involve the presence of family members and/or can be done in a larger group setting. While individual treatment may be more effective due to its increased flexibility and personalization to specific skills and needs of the individual patient (White, Ollendick, Scahill, Oswald, & Albano, 2009; White, Oswald, Ollendick, & Scahill, 2009), there are also certain distinct advantages to utilizing group CBT for ASD patients. Group CBT allows for increased social interaction; sharing of experiences, promotion of self-acceptance and improved insights of both strengths and impairments related to ASD (Hesselmark et al., 2014). In highly functioning ASD children, CBT is a commonly used intervention to treat comorbid anxiety and depressive symptoms, disruptive behavior and core symptoms of ASD (Danial & Wood, 2013). While there are adapted CBT protocols for ASD children and young adolescents there are generally few studies on adult CBT (Kerns, Roux, Connell, & Shattuck, 2016).

One of the most common uses of CBT in ASD is treatment of anxiety; this co-occurring disorder often leads to several other problems including increased irritability, disruptive behaviors, inattention, and decreased functionality (Ung et al., 2015). Several studies and meta-analyses and a recent systematic review reported that CBT was effective in reducing anxiety in ASD children (Ho, Stephenson, & Carter, 2018; Kreslins, Robertson, & Melville, 2015; Spain & Blainey, 2015; Sukhodolsky, Bloch, Panza, & Reichow, 2013; Ung et al., 2015). A recent systematic review evaluating 48 studies found that CBT significantly improved affective communication, social skills, cognition and facial emotion perception in ASD children and adolescents (Weston, Hodgekins, & Langdon, 2016). These findings are in agreement with the results of previous meta-analyses of clinical trials conducted on young ASD patients (Kreslins et al., 2015; Sukhodolsky et al., 2013). However, no significant benefits were found when using CBT on affective disorders in adult ASD patients (Weston et al., 2016).

One main goal of using CBT on children with ASD is to build the cognitive capacities to understand other people's cognitive and mental states as well as to build the social skills required for reciprocal interactions. Very few studies have investigated the efficacy of CBT on core ASD symptoms, and have thus far mostly employed varied methodology while targeting only one or a few skills. This makes it difficult to pinpoint which components of the intervention were effective. The systematic review of Weston et al. (2016) concluded that the effect was not significant on patient reported measures, however, a significant small to medium effect size was found in caregiver and task based measures and a medium effect size for clinician based measures (Weston et al., 2016). From this, the researchers concluded that CBT might be an evidence-based and valid intervention method in ASD that can contribute to detectable improvements in core symptoms (Danial & Wood, 2013; Weston et al., 2016).

8.4. Social behavioral therapy

Social behavioral therapy (SBT) in ASD focuses on functional independence and quality of life by targeting development of emotional regulation, social skills and communication. Different types of SBT

interventions include both specific targeted approaches focusing on each symptom domain, as well as more complex and comprehensive approaches (Lai, Lombardo, & Baron-Cohen, 2014).

Comprehensive early intensive behavioral interventions are based on Applied Behavioral Analysis (ABA), an experimental approach that evaluates the impact of environmental events on behavior and employs structured specific teaching methods focusing on language, cognitive, sensorimotor skills, social interactions, everyday living skills and specific problem behaviors (Lai et al., 2014; Vismara & Rogers, 2010). Such comprehensive ABA programs include early intensive behavioral intervention (EIBI) in children under 5 years old. EIBI, which works by decomposing complex skills into more elementary subskills and teaching them individually, increased intellectual functioning in 50% of young ASD children (Cohen, Amerine-Dickens, & Smith, 2006; Sallows & Graupner, 2005). Other ABA programs include the Learning Experiences: An Alternative Program for Preschoolers and Parents (LEAP), which focuses on integrated teaching with non ASD peers, and emphasizes individual-based curricula (Vismara & Rogers, 2010).

SBT also include developmental intervention models, which conduct a comprehensive evaluation based on developmental history, assessment of functioning, and clinical observations of interactions to yield a developmental profile for every patient, establish affected domains and design targeted interventions (Vismara & Rogers, 2010). Such models include the Denver Model and the Early Start Denver Model (for toddlers) (ESDM) (Dawson et al., 2010); Responsive Teaching (Mahoney & Perales, 2005); and the Developmental Individual-Difference Relationship-based model (DIR/Floortime) (Greenspan & Wieder, 1997).

Besides comprehensive programs, there are also targeted interventions focusing on specific cognitive skills and domains tailored individually to the existing level of functioning, skills and needs. Such interventions include enhancement of functional communication, emotion recognition, social skills, and promoting independence (Lai et al., 2014). Such targeted programs include the Picture Exchange Communication System (PECS) (Liddle, 2001), the use of speech generating devices, self-management (Koegel, Park, & Koegel, 2014) or Reciprocal Imitation Training (RIT) (Ingersoll & Schreibman, 2006).

8.5. Oxytocin and vasopressin

Oxytocin (OT) and vasopressin are closely related neurohypophyseal nine-amino acid peptide hormones differing in only 2 amino acids, synthesized in the hypothalamus and stored in the neurohypophysis. OT and V receptors are highly expressed in the amygdala, hippocampus, and nucleus accumbens, and play a role in social behaviors, bonding, and parental care (Alvares, Quintana, & Whitehouse, 2017; Landgraf & Neumann, 2004). Several studies detected lower OT plasma levels paralleled by higher levels of its precursors in ASD patients (Green et al., 2001; Modahl et al., 1998) as well as associations between ASD and genetic variation in OT receptors (LoParo & Waldman, 2015). These findings lead to the formulation of "Oxytocin Deficit" hypothesis of social impairments characterizing ASD and consequently pointed to OT as a promising therapeutic option in ASD targeting social and communication (Alvares et al., 2017; Lacivita, Perrone, Margari, & Leopoldo, 2017).

Several randomized clinical trials or open label studies have evaluated the effects of OT in ASD using various dosing regimens and behavioral and cognitive outcome measures. One trial reported that acute intravenous administration of OT decreased repetitive behaviors and enhanced social cognition in ASD patients (Hollander et al., 2007), while another trial found that acute intranasal OT administration improved social cognition (Guastella et al., 2010). Functional neuroimaging studies reported increased activation in brain regions involved in processing of social information and reward processing in ASD patients after OT administration (Alvares et al., 2017; Aoki et al., 2015; Domes et al., 2013).

Repeated administration of OT over several weeks has also been noted to benefit ASD patients. One study reported significant improvements in core social symptoms in high functioning ASD adults after 6-week intranasal OT administration (Watanabe et al., 2015). Another study found that 5-week administration of intranasal OT administration significantly improved social communication behaviors in young ASD children (Yatawara, Einfeld, Hickie, Davenport, & Guastella, 2016). Nonetheless, several other clinical trials failed to establish significant benefits of long-term OT administration on clinically meaningful endpoints in ASD patients (Dadds et al., 2014; Guastella et al., 2015). An important limitation of OT treatment is its intranasal vs. intravenous administration routes by which only a small fraction reaches the brain, and therefore the majority of the administered agent can trigger peripheral side effects (Leng & Ludwig, 2016). A recent systematic review found that ASD patients receiving OT treatment experienced side effects including nasal discomfort (14.3%), skin irritation (4.5%), diarrhea (4.5%), irritability (9.0%) and fatigue (7.2%). However, these adverse events were not significantly different from placebo-treated patients, indicating that intranasal OT is both safe and well tolerated (Cai, Feng, & Yap, in press).

Vasopressin enhanced responses to social communications and interactions combined with evidence from preclinical studies suggest that vasopressin V1a receptor antagonists may exert pro-social benefits for disorders where social and emotional functions are core deficits, as well as antidepressant and anxiolytic effects (Lacivita et al., 2017; Ratni et al., 2015). A limited number of clinical trials have evaluated the efficacy and safety of V1a antagonist in ASD. One trial suggested that intravenous administration of V1a antagonist RG7713 might improve social communication in adults with high functioning ASD (Umbricht et al., 2017). Another V1a antagonist Balovaptan (RG7314) has shown the potential to improve social interaction and communication in ASD patients. The Food and Drug Administration (FDA) in USA has recently granted this compound "Breakthrough Therapy Designation", raising the hope for approval of the first pharmacotherapy to improve core social and communication deficits in ASD (Roche Press Release, 2018).

8.6. Omega-3, vitamins and herbal medicine

8.6.1. Omega-3 fatty acids

Omega-3 fatty acids have recently become the focus of attention in the treatment of various neuropsychiatric and somatic disorders. Essential omega-3 long chain polyunsaturated fatty acids (n-3 LCPUFAs) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) appear to play a central role in neurodevelopment including both structural and functional effects on neurotransmission, oxidative stress, inflammation and immunity (Mazahery et al., in press).

The therapeutic benefits of omega-3 fatty acid supplementation in ASD patients are still debated. Few open label trials have provided evidence that oral supplementation of Omega-3 fatty acids improved social, behavioral and attention deficits in young ASD patients (Meiri, Bichovsky, & Belmaker, 2009; Ooi et al., 2015). In contrast, RCTs have found no evidence for the efficacy of omega-3 fatty acid supplementation on improvement of ASD symptoms (Horvath, Lukasik, & Szajewska, 2017). In addition, while generally safe and well-tolerated, these supplements are associated with significantly higher gastrointestinal side effects compared to placebo, which are known to be associated with behavioral symptoms including irritability, hyperactivity, stereotypy and social withdrawal (Chaidez, Hansen, & Hertz-Picciotto, 2014), which may further limit the utility of omega-3 fatty acids as a therapeutic intervention in ASD.

8.6.2. Herbal medicine

Several herbal remedies such as Gingko biloba, Zingiber officinale (ginger), Astralagus Membranecaeus, *Centella asiatica* (gotu cola), and Acorus Calamus (Calamus) may have therapeutic benefits in ASD

patients based on their somatic effects including increasing cerebral circulation, enhancing cognitive functions, exertion of a calming or sedative effect, and enhancing immune response (Bahmani, Sarrafchi, Shirzad, & Rafieian-Kopaei, 2016). One recent systematic review concluded that while being safe, herbal medicines, when used in combination with conventional therapy, showed promising results in improving abnormal behaviors and inattention in ASD patients. Such findings, however, should be considered with caution due to problems with the methodological quality of the included studies (Bang et al., 2017). Potential interactions of herbs with other medications, as well as the dangers related to unsafe sources have constituted additional limitations for the use of these remedies. Additional RCTs are needed to further validate potential therapeutic benefits of herbal remedies in ASD.

8.6.3. Nutritional supplements, dietary interventions

ASD patients are at an increased risk of malnutrition due to lowered energy intake, gastrointestinal dysfunction, indigestion, and mal-absorption of nutrients. Therefore, nutritional status should always be assessed in ASD patients to rule out any nutrient deficiencies. Studies examining dietary and nutritional status of ASD patients reported that all studied children were underweight and that their food included insufficient amounts of vitamin D, calcium, potassium, iron and fiber (Kawicka & Regulska-Ilow, 2013).

There have been several interventions attempted in treating ASD using nutritional supplements, in part to correct for nutritional deficiencies and in part due to their putative role in biochemical processes involved in the pathophysiology of ASD symptoms. These supplements include vitamins A, C, D, E, B6 and B12, folic acid, mineral microelements, and robotics (Kawicka & Regulska-Ilow, 2013). Nevertheless, a recent systematic review of clinical trials assessing effects of nutritional supplements failed to provide convincing evidence for the therapeutic benefits of these agents on ASD-related symptoms (Sathe, Andrews, McPheeters, & Warren, in press). While no improvement in ASD core symptoms can be expected, supplementation of nutritional deficiencies may be necessary to overcome any malnutrition side effects in ASD patients.

Several dietary treatment approaches have also been proposed for ASD children based on the observed peculiar gastrointestinal functional alterations and related behavioral patterns in these populations. Elimination diets aimed at omitting foods with negative effects on ASD symptoms due to allergic reactions or inadequate tolerance such as the gluten- and casein-free diet (GF-CF diet) provided no or marginal beneficial effects (Sathe et al., in press; Sung et al. 2007; Whiteley et al., 2010). The ketogenic diet with up to 90% of energy coming from fats has showed some effect on improving social and communication skills in ASD children (Evangeliou et al., 2003). The specific carbohydrate diet aiming at restoring intestinal function by prevention of pathogenic intestinal microflora was specifically designed to treat ASD symptoms (Gottschall, 2004) with mainly anecdotal reports concerning its use and efficacy. While dietary approaches on their own do not appear to offer treatment for core symptoms of ASD, they could be beneficial for normalizing symptoms arising from related gastrointestinal dysfunction or dietary deficiencies and therefore may be important contributors to the increased overall well-being of ASD patients (Kawicka & Regulska-Ilow, 2013).

9. Summary and conclusions

ASD refers to a group of developmental disorders including autism, Asperger's syndrome and PPD-NOS. The new diagnostic criteria of ASD, as revised in DSM 5, focuses on two main domains: social communication impairment and restricted interests/repetitive behaviors, with at least three deficits in social communication and at least two symptoms of restricted interests/repetitive behaviors required for ASD diagnosis. A high percentage (up to 75%) of ASD patients have other comorbid neurological or psychiatric conditions, which may complicate the accurate diagnosis of ASD. ADHD, depressive disorders, anxiety disorders and bipolar disorder are among the most commonly co-occurring conditions with ASD. Elimination or appropriate identification of these co-occurring neuropsychiatric conditions is important to confirm diagnosis.

The prevalence of ASD has been steadily increasing over the past 20 years, with the latest estimates reaching as high as 1 in 36 children, with boys having 4-fold higher risk than girls for developing ASD. Twin studies indicate that hereditary factors contribute to the development of ASD, with high convergence rates in monozygotic twins. Siblings of ASD children also carry a higher risk of developing ASD, and these disorders are more frequently expressed in patients with chromosomal abnormalities such as Down's syndrome and fragile X syndrome. Parental history of psychiatric disorders, premature birth and fetal exposure to psychotropic drugs (including antidepressants) or insecticides have both been linked to a higher risk of developing ASD. Diagnosis of ASD remains, to a large extent, clinically subjective, though the availability of different scales has refined the assessment process and aided in diagnostic clarification. Scales may be used at several developmental stages to diagnose individuals with ASD from early childhood through to adulthood, and may also be helpful in differentiating between ASD and other developmental delay disorders.

Therapies for ASD encompass pharmacological and non-pharmacological interventions. Pharmacological treatments include psychostimulants drugs such as methylphenidate and amphetamines, which are beneficial in improving comorbid hyperactivity and impulsivity in ASD patients, but provide little benefit on ASD core symptoms. Atypical antipsychotic drugs (risperidone, aripiprazole, quetiapine, ziprasidone, and olanzapine) are effective in reducing irritability and agitation in ASD patients. Caution is needed when prescribing these medications, especially for young ASD patients, because of their adverse side effects including metabolic deficits and sedation. Antidepressant drugs (fluoxetine, sertraline, citalopram, escitalopram, and fluvoxamine) are also prescribed to ASD patients to reduce repetitive behaviors and improve anxiety and aggression, though the overall therapeutic benefits of these agents remain unclear. Other pharmacological agents such as the alpha-2 adrenergic receptor agonists clonidine and guanfacine extended release have shown benefits in treating aggressive behaviors and anxiety disorders, as well as improving sleep disturbances in ASD patients.

Complementary and integrative health has been garnering increased interest as supplementary non-pharmacological interventions for ASD. Music therapy has shown promising evidence improving social interaction and verbal communication for children with ASD. Music exposure may allow for the modulation of the underlying neuroanatomical and neurophysiologic abnormalities in ASD thereby promoting greater multisensory integration across cortical and subcortical domains and allow for better compensation for the postulated deficits in these pathways in ASD. CBT, with its structured educational and coaching nature, has shown benefits in improving core symptoms of ASD as well as comorbid anxiety, depression and disruptive behaviors. SBT, with its interventions designed to promote functional communication, emotion recognition, social and cognitive skills, has also demonstrated efficacy in improving core ASD symptoms in young patients.

The neurohypophyseal peptide hormones OT and vasopressin have emerged as promising therapeutic options for ASD. Intranasal administration of OT appears to decrease repetitive behaviors and enhance social cognition in ASD patients, though these findings are still debated. More recent data suggest that Balovaptan, a vasopressin V1a receptor antagonist, may improve social interaction and communication in ASD patients which may lead to it becoming the first FDA-approved drug to treat core social and communication deficits in ASD. Finally, supplementation of treatment with vitamins, herbal remedies and nutritional supplements including omega-3 fatty acids, Gingko biloba, vitamins A, C, D, E, B6 and B12, folic acid, mineral microelements, and probiotics appear to have some beneficial effects in improving some of the symptoms

of ASD, though additional evidence to confirm these findings is still needed.

In conclusion, the rapid rise in the incidence of ASD among children may stem from the improved diagnosis of the disorder due to improvement in the precision of widely used scales, though objective tests to confirm the diagnosis have yet to be developed. The availability of these tests, or the discovery and validation of selective biomarkers for ASD, will more accurately confirm the diagnosis of the disorder, and may either further increase its incidence beyond the current 1 in 36 children or provide greater clarity in determining clinical presentation and prognosis. The available pharmacological and non-pharmacological therapies appear to alleviate some of the core symptoms of the disease and allow for better management of the comorbid conditions that are highly expressed in ASD patients. While strides have been made in understanding the developmental pathophysiology of the disease, true disease modifying agents remain yet to be discovered. Novel and much-needed disease-modifying therapies that can delve deeper into the core deficits of the disorder and normalize its pathophysiology or prevent its expression may prove to be the ultimate intervention for the improved treatment of ASD.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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