Pharmacology & Therapeutics 190 (2018) 91–104

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Autism Spectrum Disorder: Classification, diagnosis and therapy

Samata R. Sharma [a], Xenia Gonda [b], Frank I. Tarazi [c,*]

[a] Department of Psychiatry, Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02115, USA
[b] Department of Psychiatry and Psychotherapy, Kutvolgyi Clinical Centre, Semmelweis University, Kutvolgyi ut 4, 1125 Budapest, Hungary
[c] Department of Psychiatry and Neuroscience Program, , Harvard Medical School, McLean Hospital, Belmont, MA 02478, USA

ARTICLE INFO

Available online 12 May 2018

Keywords:
Asperger's syndrome
Autism
Cognitive behavioral therapy
Comorbid disorders
Music therapy
Pervasive developmental disorder

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.

* Corresponding author at: Harvard Medical School and McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA.
E-mail address: ftarazi@hms.harvard.edu (F.I. Tarazi).

https://doi.org/10.1016/j.pharmthera.2018.05.007
0163-7258/

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