PSYCHOPHARMACOLOGY IN ASD – A CHALLENGE THROUGHOUT LIFETIME

IOANA MORARU
Resident Doctor in Child and Adolescent Psychiatry,
Child and Adolescent Department, Prof.Dr. Alexandru Obregia Psychiatry Hospital, Bucharest, Romania

Corresponding author email: ioana.joy.moraru@gmail.com

ABSTRACT:
Background: Autism spectrum disorder is a neurodevelopmental disorder that appears in early childhood and is present throughout lifetime. The most recent epidemiological data published by the CDC in 2018 reports a prevalence of 1 in 59 children aged 8 years. The aetiology of ASD involves numerous genetic and environmental factors and no certain cause can be established now. The literature suggests the involvement of several brain circuits such as the serotonergic system, GABA system and glutamatergic system. The heterogeneity of core symptoms and the common co-occurring conditions – ADHD, anxiety, depression, sleep disorders, epilepsy and irritability – highly affect the individual's functionality and represent a treatment challenge for physicians. Currently there is no standard psychopharmacological treatment for the core symptoms of ASD in children, adolescents and adults. The psychotropic medications are used to alleviate co-occurring health problems and their efficacy varies according to the developmental stage.
Aims: To provide an updated information about psychopharmacological agents used in treatment of core symptoms and co-occurring conditions in ASD, using a modern classification of psychotropic agents that takes in consideration the underlying mechanism of action and the brain circuits involved in the pathophysiology of ASD.
Methods: We performed a literature search using Google Scholar database of articles published in English from 2010 until 2018 pertaining to the use of psychotropic agents in ASD.
Conclusion: In the pediatric population we identified the frequently used pharmacological treatments: methylphenidate and atomoxetine for co-occurring ADHD, risperidone and aripiprazole for irritability, aggression and self-injurious behavior. For sleep disorders a few small studies support the use of melatonin. There is a small number of psychopharmacological studies in the adult ASD population regarding treatment of core symptoms and co-occurring conditions. The currently used treatments are based on extrapolations from studies in children with ASD or neurotypicals with similar symptoms or other conditions frequently found in ASD.

Key words: Autism, psychopharmacology, neuroscience-based nomenclature, pharmacological nomenclature, neurodevelopmental disorders.

INTRODUCTION

Autism Spectrum Disorder is a group of Neurodevelopmental Disorders in DSM V (Diagnostic and Statistical Manual of Mental Disorders) alongside Intellectual Disabilities, Communication Disorders, ADHD, Specific Learning Disorder and Motor Disorders [1]. The concept of a spectrum emerged in 2013 with the publication of the DSM V. In DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders Forth Edition Text Revision) autism could be found in Pervasive Developmental Disorder Chapter, as: autistic disorder, Asperger's Disorder or PDD

-NOS (Pervasive Developmental Disorder, Not Otherwise Specified) along with Rett's Disorder and Childhood Disintegrative Disorder [2]. Although reunited under the same name since 2013, the heterogeneity of the symptoms is a reality and effective targeted treatments for core symptoms is still a goal to be achieved. The prevalence of ASD reported by CDC in 2018 was 1 in 58 children aged 8 years, a marked increase from previous years [3]. The core symptoms of ASD are social communication deficits and restrictive and repetitive pattern of behavior, interests, activities and sensory anomalies [1]. The management of ASD is a complex task due to its still unclear aetiology, persistence throughout the individual's lifetime and co-occuring mental and physical disorders: ADHD, anxiety, OCD, depression, sleep disorders, epilepsy and irritability [9].

METHODS AND RESULTS

I performed a literature search using the Google Scholar database of articles published in English from 2010 until 2018 pertaining to the use of psychotropic agents in ASD. The search terms included autism spectrum disorder, ASD, psychopharmacology, guidelines, classes of medication such as SSRI, antipsychotics, mood stabilizers and individual agent names such as Risperidone or Aripiprazole. Special attention was paid to randomized control trials, literature reviews and and open label studies of new pharmacological agents that are in clinical trials at the time this article was published. Case reports where not included.

Throughout this article, the treatment of ASD is classified in two main developmental stages: Childhood &Adolescence and Adults. For each developmental stage, we will discuss the pharmacological and non-pharmacological treatment of core symptoms and of co-occurring symptoms and mental disorders [9]. The pharmacological treatment is described using the Neuroscience-based Nomenclature Project and Neuroscience -based Nomenclature Child & Adolescent, that proposes the classification of psychotropic medication according to Pharmacological Domain and Mode of Action. We chose this new classification because it is up to date with the advances in neuroscience and is better related to the brain circuits thought to be involved in ASD pathogenesis [10]. Non-pharmacological treatments are mentioned for their evidence-based usage in treatment of ASD, however they are not the scope of this review.

The main co-occurring conditions discussed are depression, anxiety, sleep problems, irritability, ADHD, problematic sexual behaviors associated with ASD.

Howes et al. suggests the following classification of treatment [9].

A. Children and Adolescents with ASD

1. Treatment for *core symptoms:*

(1) Non-pharmacological treatment - includes behavioral therapy, language and communication training, occupational therapy, special education, vocational training, social skills training [15]

(2) Pharmacological treatment: serotonergic agents, glutamatergic agents, GABAergic agents, Dopamine agents, other agents [9]

2. Treatment *of co-occurring symptoms and mental disorders*

(1) Non-pharmacological treatment: behavioral therapy such as CBT in anxiety and depression [9]

(2) Pharmacological treatment: serotonergic agents, glutamatergic agents, GABAergic agents, Dopamine agents, other agents [9]

B. Adults with ASD

Treatment of *co-occurring symptoms and mental disorders:*

(1) Non-pharmacological treatment: Cognitive Behavioral interventions [9]

(2) Pharmacological treatment: serotonergic agents, glutamatergic agents, GABAergic agents, Dopamine agents, other agents [9]

A. Children and Adolescents

Pharmacological Treatment *of core symptoms*

In this section we discuss the pharmacological treatment of core symptoms of ASD, the most recent molecules that showed promise in clinical trials and are currently not in routine clinical use. Also, molecules that clinicians use often in their practice for the treatment of other symptoms. Some studies have shown some improvement in core symptoms as well.

The core symptoms of ASD are defined as deficits in social communication and interaction and repetitive and restrictive interests and behaviors [1].

Serotonergic Agents

Fluoxetine liquid form

Fluoxetine is a serotonin reuptake inhibitor (SERT). Hollander et al conducted a study in 2005 of the effects of fluoxetine on repetitive behaviors in ASD. A double-blind placebo- controlled crossover study of 5 children and adolescents with ASD was conducted, over two acute 8-week phases. The authors used CY-BOCS as a measure of outcome. Results showed that a low dose of liquid fluoxetine (mean final dose: 9.9 ±4.35 mg/day) was superior to placebo regarding repetitive behaviors, measured using CY-BOCS compulsion scale, and the overall reduction was less than 10%. Also, side effects did not significantly differ from the placebo group [8].

According to Politte et al., there are age-related differences in serotonin functioning in people diagnosed with ASD, and this may contribute to the low efficacy of serotonergic agents and the higher vulnerability to adverse effects [15] [5].

Glutamatergic Agents

Memantine

Memantine is a NMDA receptor antagonist [13]. Preclinical studies showed that this molecule can modulate the action of NMDA receptor according to the level of glutamate available in the synapse: if the synapse has a high level of glutamate, memantine blocks the NMDA receptor; if glutamate levels are low, memantine has the opposite effect. Studies in adults diagnosed with Alzheimer's Disease showed that memantine improves functional communication.

Aman et al. conducted a large randomized (1:1) control trial of safety, tolerability and efficacy of memantine in children diagnosed with ASD. One hundred twenty-one children 6-12 years old where randomized to memantine ER of placebo group for 12 weeks. The investigators used SRS (Social Responsiveness Scale) total raw score as a measure of efficacy, CATS-I (Core autism Treatment Scale-Improvement) and CCC-2 (Children's Communication Checklist-2). The results showed no statically significant between-group difference of efficacy of memantine on core symptoms of autism. However, the treatment was shown to be safe and well tolerated at the dosages examined by this study [11].

Two other studies, one retrospective review of 18 children and one open-label trial of 151 individuals with ASD showed improvement in social behavior, language function improvements and self-stimulatory behavior [19].

D-cycloserine

D-cycloserine is a partial agonist at the glycine$_b$ site of the NMDA receptor. There are several studies that showed some beneficial effects in treatment of negative symptoms in schizophrenia. Posey et al. conducted a small study of the effects of D-cycloserine on social impairment in children with PDD (Pervasive Developmental Disorder), based on

the overlap between negative symptoms in schizophrenia and social withdrawal in ASD. The study was a prospective single-blind for 8 weeks and involved 12 individuals 5 years and older. D-cycloserine was administered in ascending doses of 0.7, 1.4, 2.8 mg/kg/day each for 2 weeks. Effectiveness was measured using CGI (Clinical Global Impression), the SRS (Social Responsiveness Scale), CY-BOCS and ABC (Aberrant Behavior Checklist). Results showed reduced social withdrawal and increased social responsiveness and in 40% of subjects the improvement was clinically meaningful as reported by parents and clinicians [16].

Two additional studies showed that d-Cycloserine and social skills training where superior to placebo in reducing SRS scores at 22 weeks, but not at 11 weeks. Although this molecule is showing some promising results, there is no routine use of d-Cycloserine in clinical settings [9].

GABAergic Agents

Arbaclofen

Arbaclofen is a $GABA_b$ agonist that in preclinical trials showed the ability to inhibit glutamate release, and theoretically restore the balance of E/I neurotransmission in ASD. Two studies have been conducted with Arbaclofen in children and young people with ASD.

Erickson et al. conducted a safety, tolerability and efficacy study in non-syndromic ASD using an 8-week, open label trail of 32 children and adolescents. Improvements where seen on several outcome measures, including Lethargy/Withdrawal subscales, SRS, Cy-BOCS and ABC-Irritability. The most common adverse events where agitation, irritability – resolved without dose changes [6].

Veenstra-VanderWeele et al. conducted a RCT phase 2 trial on 150 participants aged 5-21 years with ASD. No difference from placebo was found on the primary outcome measure, the Withdrawal/Lethargy subscale on ABC (Aberrant Behavior Checklist), parent reported [18].

There is still insufficient data to recommend the routine use of this molecule in a clinical setting [9].

Dopaminergic Agents

Risperidone

Risperidone is a D2, 5-HT2, NE and alpha-2 receptor antagonist that blocks central dopamine D2 receptors in the human brain [13]. It is approved by European Medicine Agency and Food and Drug Administration for the treatment of irritability in ASD. There are trials that performed a secondary analysis of the participants selected for irritability, and measured outcomes on core symptoms. The RUPP study (Research Units on Pediatric Psychopharmacology) and RUPP 2 showed a significantly decrease in ABC Lethargy/Withdrawal and Hyperactivity subscales [9].

Aripiprazole

Aripiprazole is a D2, 5-HT1A receptor partial agonist and 5-HT2A receptor antagonist, so it has a dual action on dopamine and serotonin [13]. It is approved by the FDA for the treatment of irritability in ASD, but secondary analysis has been made to investigate its effects on core symptoms. Significant improvements have been observed on stereotypic behavior, especially on hand, body and head movements

Because these results were obtained through secondary analyses of subjects with ASD chosen primary for their irritability and not for their level of stereotypical behavior, their use is not recommended for targeting repetitive behaviors, the risk of adverse effects can overcome the clinical benefit and further research is needed [9].

Methylphenidate

Methylphenidate is a Dopamine and Norepinephrine releaser via DAT and NET

reuptake inhibition [13]. A sub-analysis of data from a larger ASD trial in children that exhibited ADHD symptoms, part of the RUPP, reported improvements in joint attention and self-regulation that where dose dependent. The effects where moderate versus placebo. However, it is unclear if these effects where due to improvements in ADHD symptoms. No studies have been conducted on ASD children without ADHD [9].

Other agents

Oxytocin is a neuropeptide produced by the paraventricular nucleus of the hypothalamus and released by the posterior pituitary gland. It is approved as a drug in obstetrics since 1980. Animal studies have shown an important role on social behavior such as affiliation, attachment and social cognition [15]. In 2015 Gaustella et al. conducted a study in male adolescents with ASD and results did not show any significantly improvements on SRS (Social Responsiveness Scale). Yatawara et al. conducted a trial in 2016 on small children and reported significant improvement on the primary outcome, the caregiver-rated social responsiveness. Many studies have been conducted on the effect of oxytocin on ASD social interaction and stereotyped behavior, most of them in adult population. Results show some promise, and there are currently 12 active studies in progress [9].

Vasopressin and IGF-1 (Insulin Growth Factor-1) are currently being studied for the treatment of core symptoms [9].

Pharmacological treatment of co-occuring symptoms and mental disorders

Depression

In children with ASD there are no rigorous studies that investigate the role of serotonergic agents, such as SSRIs for the treatment of mood disorders. The use of these medications for the treatment of depression is based on trials in patients without ASD. There is increased evidence of sensitivity to adverse effects when SSRIs are administered to children with ASD [9].

Anxiety

There are no studies that specifically investigate the treatment of anxiety disorders in children with ASD. Several trials have investigated the pharmacological treatment of anxiety and symptoms of OCD (Obsessive-compulsive Disorder).

Risperidone has shown improvement of OCD symptoms if given in high doses, and one study showed significant improvement in anxiety symptoms measured by parent reported insecure/anxious scale of N-CBRF (Nisonger Child Behavior Rating Form). However, a 16-week trial of risperidone reported increased anxiety as an adverse effect of treatment with risperidone [9]. The risperidone studies where not conducted with OCD and anxiety symptoms as primary targets, children were selected according to the level of irritability.

Clomipramine is a serotonin, norepinephrine reuptake inhibitor – SERT, NET. It is approved by the FDA for the treatment of OCD in children older than 10 years. [14]. One study investigated the effect of this agent in 12 children with ASD and OCD compared with placebo and desipramine (norepinephrine reuptake inhibitor). Clomipramine was superior to placebo and desipramine regarding stereotypies, anger, compulsions and ritualized behaviors [7]. Cardiovascular and treatment induced seizures have been reported [9].

Sleep disturbances

Melatonin

Melatonin is a Mel1 and Mel2 receptor agonist [13]. Rossignol et al. conducted a meta-analysis melatonin use in ASD. Five RCT trials of children with ASD reported statistically significant improvements in sleep duration and sleep onset latency, compared with placebo. No improvement

was found on night-time awakenings. No adverse effects were reported [17].

Irritability

In children with ASD the most common irritability symptoms are severe tantrums, aggression or self-injurious behaviors. Irritability is more common in ASD co-occurring with mood or anxiety disorders [9].

Risperidone

It is approved by European Medicine Agency and Food and Drug Administration for the treatment of irritability in ASD. There are 10 RCT reporting its efficacy in treating irritability in children with ASD. All studies reported large effect sizes. The most common reported adverse effects where: weight gain, increased appetite, fatigue, drowsiness and drooling. Long term administration -six months- is associated with persistent side effects and hyperprolactinemia [9]

Aripiprazole

It is also approved by the FDA for the treatment of irritability in ASD. Several RCT reported that aripiprazole was more effective in reducing irritability compared to place after 8 weeks. The most common adverse effects reported where sedation, weight gain with a decrease in serum prolactin level [4].

ADHD

Methylphenidate

Methylphenidate is a Dopamine and Norepinephrine releaser via DAT and NET reuptake inhibition [13]. Four studies reported that it is an effective treatment of ADHD in people with ASD, however the response level was lower than for people with ADHD without ASD; one study reported a 50% response rate in ASD subjects with co-occurring ADHD compared to 70-80% response rates in subjects with ADHD an no ASD. The severity of adverse effects may also be greater in people with ASD, with higher discontinuation rates 18% ASD and ADHD compared to 1.4% ADHD without ASD [9].

Atomoxetine

Atomoxetine is a Norepinephrine reuptake inhibitor [13]. Two studies show improvement in hyperactivity but not inattention. Atomoxetine can be an alternative to methylphenidate [9]

Other agents

Treatment with Clonidine showed improvements on hyperactivity symptoms. Guanfacine was reported as effective in two studies, and a 50% reduction in symptoms. Some preliminary evidence for lofexidine (Norepinephrine alpha-2 receptor agonist) – a small non-randomized study-reported significant improvement in ADHD symptoms, hyperactivity in particular [9].

Problematic sexual behaviors

Mirtazapine is a Norepinephrine and Serotonin receptor antagonist [13]. A few case reports have shown promise in treating problematic sexual behaviors (excessive masturbation) in children with ASD aged 5 and 13 years. An open label study of 10 children and adolescents with ASD reported an 80% response rate in masturbation frequency. The dosage ranged from 5 mg/day to 30 mg/day with adverse effects such as increased appetite, weight gain and sedation [5].

B. Adults with ASD

Treatment of co-occurring symptoms and mental disorders

Depression

In adults with ASD and mood disorder, only fluoxetine has been studied in a small sample of 6 adults. The study focused on the cerebral regional metabolism and its ability to predict SSRI response [9] [12].

Anxiety and OCD

There are no studies focusing solely on anxiety treatment in adults with ASD. There are a few studies on OCD symptoms. Fluoxetine, fluvoxamine and risperidone where reported to reduce symptoms of compulsions, obsessions and anxiety [9].

Sleep Disturbances

Although there is some evidence of melatonin effectiveness in children with ASD, there are no clinical trials available for adults. There is one small retrospective study on 6 adults with ASD that reported reduced sleep onset latency and reduced nocturnal awakenings with melatonin [9].

Irritability

Risperidone and fluvoxamine where reported to significantly reduce irritability in adults with ASD. However, irritability was not the primary outcome of these studies [9].

CONCLUSIONS

In the pediatric population we identified the frequently used pharmacological treatments for co-occurring conditions: methylphenidate and atomoxetine for co-occurring ADHD. For irritability, aggression and self-injurious behavior risperidone and aripiprazole are approved by the FDA and EMA based on 10 RCT. For sleep disorders a few small studies support the use of melatonin in children.

Currently there are no approved medications for the core symptoms of autism. Arbaclofen, Memantine and D-cycloserine show promising results, improving social interaction or repetitive and restrictive behaviors, but further randomized control trials are needed.

There is a small number of psychopharmacological studies in the adult ASD population regarding treatment of core symptoms and co-occurring conditions. And most of them are case reports and retrospective studies. The currently used treatments are based on extrapolations from studies in children with ASD or neurotypicals with similar symptoms or other conditions frequently found in ASD.

There is a need for randomized double-blind placebo-control trials especially in the ASD adult population. The high incidence among children predicts a high number of adults in need of psychiatric follow-up and efficient treatment options for co-occurring conditions and core symptoms as well.

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