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Pharmacobiological Treatments in Autism Spectrum Disorders

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ABSTRACT

Autism spectrum disorders (ASD) refer to a group of neuro-developmental disorders affecting young children and adults. Currently, the treatment options for ASD are mostly restricted to treating its symptoms. Among the various approaches for treating ASD, pharmacobiology-based treatments are numerous. Our objective is to review the up-to-date information on different types of medications and briefly discuss the evidence-based potential of these treatments in ASD therapy. PubMed searches for reports and reviews on clinical data from the last 15 years, between 2002-2017, using search terms of each category of treatment along with the terms “autism”, “mechanism”, and/or “side effects” were conducted. Several pharmacobiological interventions have been prescribed for ASD, including antipsychotics, stimulants, antidepressants, supplements, and special diets. However, none of these methods is an effective ASD treatment, and only few show much promise. We provide a brief overview of the current pharmacobiological treatments for ASD, their mechanisms of action, and clinical research-based evidence on their effectiveness. Based on our review, we recommend that caution should be exercised when choosing a pharmacobiological treatment method for ASD as majority of existing evidence is not from large-scale long-term high quality studies.Future research should focus on rigorous investigative design, long-term implementation, and meaningful uniform outcome measurements.

Key Words: Antidepressants, Antipsychotics, Special diet, Vitamins

INTRODUCTION

Autism spectrum disorders (ASD) in young children and adults are characterized by impaired socialization, communication, emotion processing, and stereotyped/repetitive behaviors, along with sensory processing dysfunction, speech and language impediments, seizures, gastrointestinal issues, irritability, aggression, hyperactivity, and sleep disorders [1, 2]. According to recent statistics by Centers of Disease Control and Prevention (CDC), 1 in every 68 children in the US is affected by ASD [3]. This could be due to true increase in prevalence or increased awareness and diagnosis. ASD also shows higher prevalence in boys[3], familial patterns and sibling learning issues [4, 5], and high monozygotic twin concordance [6]. Numerous underlying causes for ASD have been indicated such as genetic mutations, neurotoxicity and inflammation, impaired immune response, dysbiosis, nutrient imbalance, and oxidative stress [2].

Several treatment strategies have been undertaken in patients with ASD including behavioral and physiological interventions. Here, we review some of the physiology- and pharmacology-based interventions for ASD along with recent-advances in ASD treatment and their effectiveness in treating ASD. These include selective serotonin receptor-uptake inhibitors (SSRIs), antidepressants, antipsychotic drugs, stimulants, dietary supplements, and special diets[7, 8]. Very limited data are currently available regarding the long-term effectiveness and side-effects of these treatments for ASD. So far, no medication has shown a consistent positive effect on patients with ASD.

Apart from the above mentioned treatments, therapeutic approaches such as stem cell therapy, hyperbaric oxygen therapy, transcranial magnetic stimulation, and early intervention therapies involving speech and language therapy, music therapy, and sensory therapy are also undertaken for patients with ASD[9, 10].Among all the different approaches for ASD treatment, the early intervention method has been shown to be most effective till date [11, 12]. However, a review of these targeted approaches are beyond the objective of this review.

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Selective serotonin-uptake inhibitors (SSRIs) and Tricyclic antidepressants

Serotonin (5-hydroxytryptamine) is a neurotransmitter derived from tryptophan, and mainly sourced from the raphe nuclei in the brain. The serotonergic system plays an important role in attention, arousal, and feeding [13]. Studies have shown that children with autism have elevated levels of blood serotonin [14].

SSRIs used in the treatment of ASD in various randomized controlled trials (RCTs) include fluoxetine, fluvoxamine, fenfluramine, and citalopram. SSRIs block the re-uptake of serotonin at the synapse, thus increasing the availability of serotonin and the activation of serotonin receptors [15]. In children and adults, SSRIs have shown limited positive outcome, although all the studies have been with small sample sizes, with potential risk of bias [16, 17]. In addition, SSRIs such as olanzapine, and fluvoxamine, have been shown to have undesirable side effects including irritability and weight gain [16, 18]. A large multi-center, double-blinded, randomized controlled trial has been recently started known as Fluoxetine for Autistic Behaviors (FAB trial) to determine the efficacy of low-dose fluoxetine for treating ASD symptoms in children and adolescents [19].

On the other hand, prenatal exposure to SSRIs have been linked to ASD risk in epidemiological studies [20, 21]. However, two very recent studies have concluded that there is no significant relationship between prenatal exposure to SSRIs and ASD risk and suggest that the previously observed association may be due to other factors [22, 23].

Tricyclic antidepressants (TCAs) have the same effect as SSRIs in increasing the serotonin levels [24]. A short-term treatment of tianeptine showed a modest effect on irritability in 12 children with ASD [25]. Low-dose amitriptyline has also shown promise in youth with ASD for hyperactivity and impulsivity [26]. However, no large randomized clinical trials have been conducted till date with TCAs for treatment of ASD.

Antipsychotics

Old antipsychotics or neuroleptics are D2 dopamine receptor antagonists, although they are also effective against acetylcholine receptors, serotonin receptors, and adrenergic receptors. The old antipsychotics are less preferable due to their tight, long-lasting binding with the receptors. On the other hand, the second generation or atypical antipsychotics such as risperidone and aripiprazole, dissociate more rapidly from the receptors due to hit-and-run binding properties. Risperidone and aripiprazole have shown positive effects in several different clinical trials especially for ASD-related irritability[27, 28]. However, the major drawback of atypical antipsychotics are side effects such as weight gain, metabolic changes, sleep disturbances, higher risk of sedation and tremor, drooling, increased appetite, fatigue, dizziness, and withdrawal dyskinesias [29, 30]. Another atypical antipsychotic drug, clozapine, has been shown to be effective against hyperactivity and aggression in children with ASD [31].Therefore, based on limited evidence with small sample sizes and short follow-ups, atypical antipsychotics may be more effective as short-term interventions for certain behavioral symptoms in patients with ASD.

Stimulants and Non-stimulants

Stimulants such as methylphenidate are shown to improve the hyperactivity-impulsive symptoms in children with ASD that are regulated by multiple monoaminergic gene variants and has been shown to be well-tolerated and efficacious in several studies [32, 33]. However, some studies have shown severe adverse effects with methylphenidate including social withdrawal, irritability, insomnia, and anorexia in children with ASD [34].

Among non-stimulants, atomoxetine has been commonly used for treating the hyperactivity-attention deficit symptoms of ASD. In a recent double-blind placebo-controlled trial in children with ASD, the atomoxetine group showed an improvement in hyperactivity symptoms, with side effects of only fatigue and reduced appetite [35].

Supplements

Based on the Pauling theory that suggests that deficiencies of vitamins and minerals may lead to mental disorders, many doctors have recommended the use of supplements in children with ASD, including omega-3-fatty acids, various vitamins, magnesium, iron, zinc and copper. An insufficiency in omega-3-fatty acids has been linked to abnormal development of the nervous system and to various psychiatric disorders [36]. In ASD studies, although omega-3-fatty acid supplementation had no significant beneficial effects in adult patients [37], another study on children have shown significant improvements in social and communication responses[38]. Among vitamins, vitamin B6 and magnesium [39], and vitamin D [40], have shown beneficial effects in few studies, while others such as vitamin A, and vitamin B12 and folic acid have been proposed as potential treatment options for ASD. Minerals such as magnesium [39], iron[41], and zinc [42], have also been recommended for nutritional therapies in ASD. However, large-scale high-quality randomized-controlled studies are required to conclusively determine if nutritional supplements are an effective therapeutic approach for ASD.

Special diets

Although special diets such as gluten-free casein-free (GFCF) diet have been reported to have beneficial outcomes in children with ASD, most of these reports are anecdotal and do not have sufficient clinical evidence. The hypothesis

behind the proposal of GFCF diet for ASD treatment is that the overload of high peptides such as gluten and casein may produce an opioid-like effect that could manifest as common behavioral symptoms of ASD. In addition, inflammation of the gastro-intestinal tract as well as unbalanced gut microbial, both of which are implicated in ASD, could get aggravated with casein and gluten, causing discomfort and pain in children with ASD leading to behavioral issues. However, intervention studies with GFCF diet show mixed results. Two of the most recent reviews on this topic suggest that there is very little evidence to suggest any beneficial outcome with GFCF diet on ASD symptoms [43, 44]. GFCF diet may be beneficial for ASD individuals with specific gut-related issues, or as a short-term relief.

The ketogenic diet, which is usually used for treating children with refractive epilepsy, is a high-fat, low-protein, low-carbohydrate diet. One study that investigated the effect of ketogenic diet on 30 children with ASD showed significant improvements in social and communication functions [45].

A low-oxalate diet has been recommended for children with ASD (40-50 mg per day) based on one study in patients with ASD showing higher plasma oxalate and urine oxalate levels [46].

CONCLUSION

Apart from the various treatments reviewed here, other approaches such as acupuncture, music therapy, various early behavior interventions, and social skill groups have been implemented for treatment of ASD with varying results. The review of recent literature from the last 15 years shows no large-scale, high-quality studies for any ASD treatments that have investigated their long-term effectiveness and/or side effects. Moreover, the evidence is contradictory between studies for several treatments. For treatments that show promise, for example, atypical antipsychotic drugs, the side effects are significant. Hence, well-designed long-term RCTs with sufficient sample size are required to conclusively link the potential efficacy and/or the side effects of these treatments with ASD. Based on the existing quality of evidence, we recommend caution before choosing these modes of treatment for ASD. Currently, early intervention-based approaches that integrates both developmental and behavioral models seem to be the most effective treatment paradigm for ASD.

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Conflict of Interest

The authors have no conflict of interest to declare

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