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Review

Drug therapy in autism: a present and future perspective

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Abstract:
Autism is a neurodevelopmental disorder, with a multifactorial etiology, characterized by severe abnormalities in communications, social awareness and skills, and the presence of restrictive and stereotyped patterns of behaviors. It is traditionally considered a "static" encephalopathic disorder without any specific cure and few effective biomedical interventions. There are various factors which are involved in the etiopathogenesis of autism or autism spectrum disorder (ASD) such as impaired immune responses, neuroinflammation, abnormal neurotransmission, oxidative stress, mitochondrial dysfunction, environmental toxins and stressors. The autism is often associated with a number of genetic disorders such as fragile X syndrome, tuberous sclerosis, epilepsy and Down syndrome. The recent approaches to autism treatment included various non-pharmacological and pharmacological therapy such as food supplementation, detoxification, treatment of neuroinflammation, immunologic treatments and psychotropic medications, which are found to be effective in treating various behavioral symptoms of autism. In current practice, there is no curative treatment for autism but the recommended treatment for autism involves educational therapies: speech therapy, sensory integration therapy, auditory therapy. There are classes of different pharmacological agents which are found to be effective in improving behavioral symptoms of ASD such as neurotransmitter reuptake inhibitors (fluoxetine), tricyclic antidepressants (imipramine), anticonvulsants (lamotrigine), atypical antipsychotics (clozapine), acetylcholinesterase inhibitors (rivastigmine), etc. New classes of drugs with novel mechanisms of action should be there so that this disorder will become less prevalent in the future.

Key words:
autism, ASD, behavior, clinical studies, drugs

Abbreviations: ASD – autistic spectrum disorder, CAM – complementary and alternative medicine, CNS – central nervous system, DHA – docosahexaenoic acid, DNA – deoxyribonucleic acid, DSM IV-TR – Diagnostic and Statistical Manual of Mental Disorders (4th edn., text revision), EPS – extrapyramidal side effects, FXS – fragile X syndrome, GABA – γ-aminobutyric acid, GI – gastrointestinal, GSH – reduced glutathione, GSSG – oxidized glutathione, MRI – magnetic resonance imaging, NMDA – N-methyl-D-aspartate, PDD – pervasive developmental disorder, SAH – S-adenosylhomocysteine, SAM – S-adenosylmethionine, SSRI – selective serotonin reuptake inhibitors

Introduction

Autism spectrum disorders (ASDs) comprise a complex and heterogeneous group of pathological conditions including autism, Rett and Asperger syndromes, and pervasive developmental disorder, characterized by severe abnormalities in communications, social awareness and skills, and the presence of restrictive and stereotyped patterns of behaviors, interests, and

activities [23]. In addition to these core symptoms, there are few other behavior disturbances which are commonly seen in the autistic individuals, such as anxiety, depression, sleeping and eating disturbances, attention issues, temper tantrums, and aggression or self-injury [131]. There is increasing evidence that autism is a complex, multifactorial disorder involving various genetic vulnerabilities interacting with environmental factors which affects the brain as well as the body [68].

ASD is used to describe a group of childhood neurodevelopmental disorders whose onset is usually before 3 years of age [23]. Autism is a behaviorally defined syndrome diagnosed on the basis of clinical history of the patient [4] as there is no specific biomarker for this disorder. While there are no definitive medical tests to indicate the presence of any form of ASD, diagnosis can be made by three years of age based on the presence or absence of specific behaviors that are used as diagnostic criteria [97]. The diagnostic criteria include the presence of language impairment, restrictive behaviors, social reciprocity deficits and a tendency to engage in repetitive or ritualistic behavior, to manifest a desire for similarity before the age of three years [4]. It is considered as a brain-based, highly genetic disorder, and has often been presumed to be based upon abnormal brain developmental events. It is known that the autism syndrome is commonly found in a number of biologically distinct genetic syndromes such as Fragile X and tuberous sclerosis, and it is presumed that ''idiopathic'' autism (comprising 85–95% of autism cases) is substantially heterogeneous as well [58].

Incidence and Prevalence

Epidemiological studies of autism are revealing much higher rates in recent years than those reported prior to 1990. Several decades ago, autism was considered a rare disorder occurring in 3–4/10,000 individuals, while current rate estimates that 10 to 15 of every 10,000 children are autistic, which shows the increasing incidence of autism in the children [5, 97] but possibly greater than 20 of every 10,000 children have dysfunction [11, 92]. The number of children diagnosed with ASD has substantially increased over the last decade and this disorder currently affects about 1 out of 91 individuals in the United States [16, 73]. However, since autistic syndrome occurs four times more frequently in males than females, reporting the prevalence of ASD in all children significantly underestimates the number of affected males [49]. If we look at the overall data, it has been found that 1 in 58 of males are likely affected with ASD [73] and the prevalence of affected males approaches two percent of the general population [20]. Autism is traditionally considered a "static" encephalopathic disorder without any specific cure and few effective biomedical interventions [91].

Etiopathogenesis

In an important neuroimmunopathogenic study, it has been suggested that innate, rather than adaptive, neuroimmune responses are among the various immunopathogenic mechanisms associated with autism; however, this does not exclude other cellular or humoral responses at early stages of the disease [103]. Neuroglial cells such as astrocytes and microglia, along with macrophages, play an important role in neuronal function and contribute to the regulation of immune responses in the CNS [118]. On the basis of neuropathologic analyses of postmortem brain tissue from 11 autistic patients, the authors demonstrated the presence of an active neuroinflammatory process in the cerebral cortex and white matter and showed marked activation of astroglia and microglia in the brain [103].

Several studies have suggested that abnormalities in GABAergic and glutamatergic transmission contribute to the development of autism spectrum disorders [29, 90]. GABA-mediated calcium signaling regulates a variety of different developmental processes from cell proliferation migration, differentiation, synapse maturation, and cell death [98]. Impaired GABAergic signaling mediate autism like stereotypes in the majority of experimental animal models of autism [21, 41]. It has also been found that GABAergic dysfunction accounts for the hyper excitability observed in an animal model of fragile X syndrome (FXS) [37].

Various classic mitochondrial diseases are also seen in children affected with autism and are usually caused by genetic anomalies (abnormalities). However, in many cases of autism, there is an evidence of

mitochondrial dysfunction without the classic features, which shows less severity [118]. This dysfunction might also be contributing to many symptoms of autism, such as cognitive impairment, language deficits, increased oxidative stress, and others [114]. The inability to neutralize reactive oxygen species and free radicals during mitochondrial respiration lead to increased oxidative stress. Oxidative stress is also known to be involved in various neurodegenerative diseases in humans. Increasing evidence suggests a role of oxidative stress in the development and clinical manifestation of autism [25]. It is suggested that autism may result from an interaction between genetic, environmental, and immunological factors, with oxidative stress as a mechanism linking these risk factors [24]. Mitochondrial dysfunction could further lead to oxidative stress and lower glutathione levels. Impaired energy production and oxidative stress induced release of glutamate leads to excitoxicity. Many industrial toxins, including pesticides, can inhibit mitochondrial function. Again, a diet high in antioxidants, organic raw, fresh fruits and vegetables seems appropriate for reducing oxidative stress in autistic patients [118].

Herbert [59] states that environmental toxins and stressors might cause or trigger autism, implying that we have to look at the whole person and whole body affected by these stressors. This involves shifting from autism as a genetically determined brain disorder to a newer and more inclusive model that considers autistic behavior one of many effects of genetic and environmental impacts on the whole body, including the brain. A recent report suggested that close relatives of children with autism (who themselves do not meet criteria of autism) can have autism-related symptoms, milder social and communication deficits and stereotyped behaviors [35].

The autism syndrome is often associated with a number of genetic disorders such as FXS, tuberous sclerosis, Rett syndrome, epilepsy, Asperger syndrome and Down syndrome [12, 33, 43, 121]. FXS is the most common chromosomal abnormality associated with autism and about 2–5% of autistic children also has this syndrome. At least 15% of males with FXS fulfill the criteria for infantile autism. Autism and FXS are neurodevelopmental disorders that sometimes manifest shared neurocognitive and behavioral phenotypes [10, 30]. In several studies, it has been reported that about 30% of autistic children have epilepsy and other genetic disorders such as Smith-Lemli-Opitz syndrome [122], FG syndrome [101] and reduced adenosine deaminase activity [106].

Genomic and mutational studies have identified a number of known genes which are supposed to be involved in the pathogenesis of autism and that are also implicated in excitatory and inhibitory neurotransmission [1]. For example, GABA has been linked to chromosome 15 which is implicated in autism [91]. This inhibitory neurotransmitter is involved in early brain development; impairments in this neurotransmitter are likely to have a negative effect on the maturation of local circuits which are involved in information processing as well as complex cognitive behavior [10]. Atypical GABAergic signaling have also been found in different brain regions of persons with autism, which indicates that this disorder is widespread in their brains and may be implicated in the cognitive deficits present in these patients [46]. There are more than ten genes that contribute to the underlying genetic risk of developing autism [91]. Autism-associated mutations of neuroligins (NLGN3, NLGN4) cell-adhesion molecules are also proposed as candidate genes implicated in neural alteration affecting information processing in autism [10].

Although autism has been considered as neurodevelopmental disorder caused by various structural and genetically based neurochemical alterations, different markers of chronic inflammation and oxidative stress has also been found in autistic patients [58, 61]. Recent studies suggested that many autistic children have also been accompanied with many other medical problems (Tab. 1) such as increased oxidative stress [67], mitochondrial dysfunction [114], increased metal toxicity burden [2], immune dysregulation with gastrointestinal disturbances and immune activation of glial cells in the brain [69, 125], combined with central nervous system (CNS) hypoperfusion or ab-

Tab. 1. Various biomedical problems observed in ASD [15]

Biomedical problem	Autistic spectrum disorder (ASD)
Oxidative stress	Yes
Mitochondrial dysfunction	Yes
Metal toxicity	Yes
Immune dysregulation/inflammation	Yes
Cerebral hypoperfusion	Yes

normal regulation of blood supply to the brain [16, 96, 128]. Mitochondrial dysfunction can lead to gastrointestinal (GI) disturbances by depleting glutathione levels because the GI tract is highly dependent on glutathione for its proper functioning [114]. Chronic gastrointestinal problems such as constipation are commonly found in autistic individuals [124].

The increased male to female ratio observed in autism may be due to oxidative stress because the lower levels of reduced glutathione (GSH) and mitochondria in males make them more susceptible to oxidative stress as compared to females. In animal studies, it has been found that oxidative damage to mitochondrial DNA is 4-fold higher in males as compared to females because of lower superoxide dismutase and glutathione peroxidase activities in males [14, 114]. A recent case-control study suggested that the autistic children have reduced plasma S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH) ratio, decreased GSH levels and major intracellular antioxidants as compared to normal children [67]. The intracellular GSH : GSSG redox system provides the essential intracellular environment which is required for normal immune function, detoxification capacity and membrane redox signaling [40, 104]. The autistic children have also shown the reduced levels of various metabolic precursors used for GSH synthesis resulting in inadequate GSH synthesis and increased oxidative stress [66].

Diagnosis

The diagnostic criterion of autism is based on clinical findings and specific behavioral symptoms of the autistic patients which meet the DSM-IV-TR criteria. According to these criteria [5], a child meets the diagnostic criteria for autism: (a) by documentation of at least six of the 12 behaviors described in the three category as shown below (Tab. 2), with at least two from the impairment in social interactions category and one each from the impairment in communication and the repetitive and stereotyped behavior patterns categories; and (b) the onset is before 3 years of age [70]. Studies have shown that the diagnosis of autism can be done accurately between two and three years of age [22, 120].

In structural MRI brain studies, many autistic children have shown the increased volume of the total brain and abnormalities in the cerebellum, limbic system (hippocampus and amygdala) and frontal lobe [32]. Pharmacological findings revealed that serotonergic dysregulation is also implicated in the pathophysiology of autism. It has been documented that high levels of serotonin in the blood enter the brain at the early stages of fetus development and cause loss of serotonin terminals, which results in persistent neurocircuitry damage and development of autistic disorder [82, 127]. In recent studies, it has been shown that neonatal serotonin depletion did not cause any impairment in spatial learning and memory and also there is no disruption of prepulse inhibition of acoustic startle reflex in adult rats [75, 107].

A child meeting the criteria for autism should also undergo a thorough medical examination which involves a detailed medical and developmental history, scrupulous physical examination to identify any neurocutaneous biomarker for tuberous sclerosis (including Wood's light examination), Asperger syndrome and dysmorphic features for FXS. Complete blood examination should be done to identify iron deficiency ane-

Tab. 2. Diagnostic criteria for autism [5]

A. Impairments in social interactions (four criteria)
1. Lacks eye-to-eye gaze, facial expression, gestures while interacting
2. Fails to develop peer relationships
3. Does not share interests with others (e.g., no bringing or pointing out objects)
4. Lacks social or emotional reciprocity
B. Impairment in communication (four criteria)
1. Has delayed development of speech
2. Does not initiate or sustain conversation
3. Has stereotyped and repetitive language or idiosyncratic language
4. Lacks make-believe play or social imitative play
C. Repetitive behaviors and stereotyped behavior patterns (four criteria)
1. Has stereotyped, restricted patterns of interest, abnormal in intensity or focus
2. Has inflexible adherence to specific, non-functional routines or rituals
3. Has stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping)
4. Has persistent preoccupation with parts of objects

mia and limited dietary habits. Audiometric and ophthalmic examinations should also be done to check whether there is any hearing and visual deficits or any communication disorder [47].

Therapeutic basis

Despite these advances in early diagnosis and intervention, no therapy has been yet proven to completely reverse the core symptoms of autism. In current practice, there is no specific treatment for autism but the recommended treatment for autism involves educational therapies: applied behavior analysis, speech therapy, sensory integration therapy, auditory therapy, etc. Based on various reports and parent surveys, it has been shown that food supplementation and alternative treatments aimed at intestinal healing and detoxification also helps in ameliorating the symptoms of autism. This has prompted autism research into a different treatment approach that autism should be treated as a whole body condition [118]. The recent approaches to autism treatment included various non-pharmacological and pharmacological therapy such as food supplementation, detoxification, dietary intervention, treatment of GI disturbances, treatment of chronic inflammation (Fig. 1) in the brain and intestines and immunologic treatments, etc. [60]. Nutritional intervention and complementary and alternative medicine (CAM) approaches are highly prevalent (about 74%) among children affected with ASD [56]. The broad heterogeneity of clinical and behavioral symptoms in autistic children indicates that no single treatment will benefit every autistic child. Thus, definition and characterization of subgroups of children who respond positively or negatively to intervention are necessary to be identified more clearly [66].

Non-pharmacological therapy

There is currently no known 'cure' for autism. The only treatment in ameliorating the core behavioral deficits in autistic children is early intensive behavioral and educational interventional therapy [70]. A team of trained and specialized healthcare professionals such as a developmental pediatrician, a child psychiatrist, an occupational (behavioral) therapist, a nutritionist, a speech therapist, a psychologist, a specialist teacher and a social worker [70] are necessary for the management of autism. There is an improvement in the cognitive, communication, adaptive and social functioning and reduction in inappropriate behaviors such as aggression, hyperactivity and temper tantrums after early (initiated before 4 years of

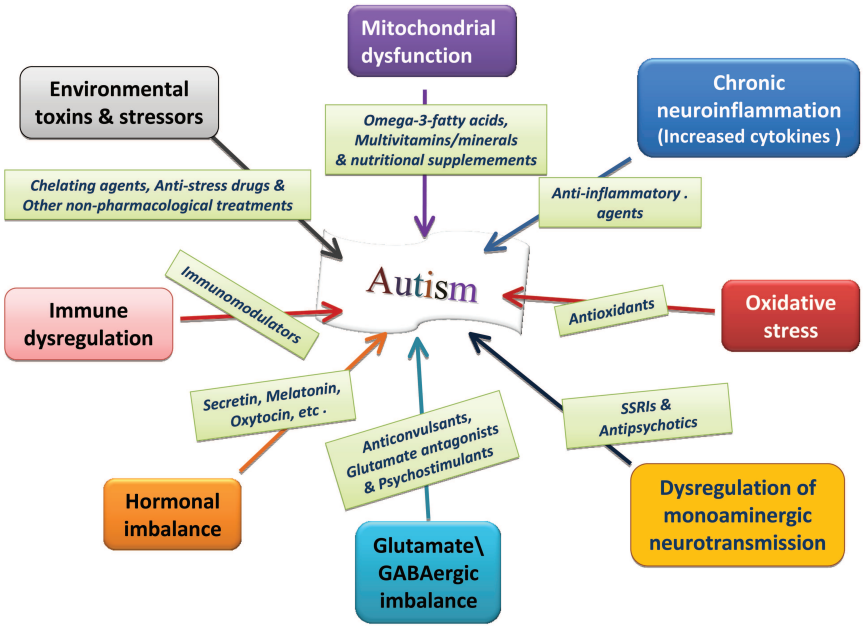

Fig. 1. Drug therapy and different targets in autism

age) intensive behavioral and educational therapy in autistic children [31, 86]. The interventions are highly individualized to target his/her specific deficits in imitation, attention, motivation, compliance and initiation of interaction. Individualized one-to-one therapy is provided in a distraction-free structured environment by behavioral therapists under supervision of a developmental pediatrician [34, 70, 86]. So, it is important to identify and refer children with ASD as early as possible to the Early Intervention Program to improve their life. There should be special schools for providing proper education to the autistic children so that they will not experience any difficulties in their schooling [71].

Complementary and alternative medicines

Complementary and alternative medical (CAM) treatments are commonly used for children with autism spectrum disorders. The use of CAM is increasing for both adults and children. The various approaches to complementary and alternative medicines (CAMs) used for the treatment of autistic disorders (ADs) include:

Vitamin C. It plays an important role in different body functions and in several metabolic pathways. In a crossover study, it has been shown that the children administering ascorbic acid (Vit. C) result in reduction of their stereotypic behaviors [39].

Pyridoxine and magnesium. They are nutritional supplements rich in pyridoxine and magnesium give beneficial effects to autistic individuals [93].

Melatonin. It is another popular CAM which shown to be helpful in the management of sleep disturbances in patients with developmental disorders [7].

Probiotics. In some autistic children, comparatively greater levels of pathogenic organisms have been found in their fecial flora. Studies have been reported that probiotics use provides beneficial effects in these children [51, 64].

Vitamin B_{12}. For the maintenance of normal methylation and antioxidant activity, the sufficient turnover of methionine cycle (vitamin B_{12} dependent) is needed. Many studies have suggested that vitamin B_{12} is helpful in combating oxidative stress in children with autistic disorder [7, 65].

Hyperbaric oxygen therapy (HBOT). HBOT is investigated as an alternative treatment for autism spectrum disorders. It has been proposed that HBOT improve the cerebral hypoperfusion, decrease neuroinflammation and oxidative stress in autism [113, 115, 132]. This cerebral hypoperfusion has been linked with repetitive behaviors, desire for sameness, and decreased language development seen in autistic individuals [119, 129].

Omega-3-fatty acids. Omega-3 and omega-6 fatty acids are recognized as vital building blocks for developing neurological systems. Omega-3 fatty acids are a commonly used complementary and alternative medical (CAM) treatment for autism (Fig. 1). A recent survey has shown that about 27.8% of families are using omega-3 fatty acids for treating their affected child [54]. Various studies have reported that the children with ASD possess decreased levels of omega-3 fatty acids as compared to control [8, 87]. Although the potential mechanism of action of omega-3 fatty acids for improving symptoms of ASD is unknown, neural tissue contains high concentrations of DHA (docosahexaenoic acid) and studies suggest that this fatty acid is essential for the growth and development of human brain [50]. Despite the high prevalence of use of omega-3 fatty acids among children with ASD's, there is very limited scientific evidence evaluating the safety and efficacy of these supplements in this population [9]. An antioxidant-rich dietary intervention might be a possible strategy to lower oxidative stress in autistic patients. Other CAM therapies include the use of mind-body medicines (yoga, music therapy), dietary supplements (amino acids, gluten free/casein free diets), GI medications (secretin), immune therapies, etc. [77].

Pharmacological therapy

Autism spectrum disorders cannot be cured completely with medications, but many pharmacologic agents may be effective in treating various behavioral symptoms that are interfering with daily life and that may be causing impairment or distress [126]. Moreover, there are only two Food and Drug Administration (FDA) approved medications, including risperidone and aripiprazole for managing its symptoms [79]. Psychotropic medications may be effective in

treating various behavioral symptoms of autism such as hyperactivity, lack of attention, agitation, insomnia, aggression, self-injury, irritability, repetitive and compulsive behaviors and anxiety [48]. Although, benefits have been reported with: (i) atypical antipsychotics (risperidone, olanzapine, clozapine) for temper tantrums, aggression, or self-injurious behavior; (ii) selective serotonin reuptake inhibitors (sertraline, citalopram, fluoxetine) for anxiety and repetitive behaviors; and (iii) psychostimulant (methylphenidate), opioid antagonist (naltrexone) for hyperactivity [3, 89] but the risk of drug toxicity must always be balanced against the benefits of reducing interfering behaviors [62, 70]. There are varieties of different pharmacological agents which are found to be effective in improving behavioral symptoms of ASD.

Atypical antipsychotics

Although clozapine has been reported to be effective in improving hyperactivity and aggression in autistic children, adolescents and adults, but has a limited usage because of the hematological safety monitoring that is necessary for patients taking the medication and a potential lowering of the seizure threshold in patients [26, 52, 133]. Ziprasidone possessed some beneficial effects for patients with autism spectrum without any significant weight gain or other adverse effect [84].

McDougle et al. found [83] that risperidone is better than placebo in treating irritability, repetitive behavior, aggression, anxiety, depression and nervousness. In addition to this, risperidone has also been shown to possess neuroprotective effect, modulate important astroglial functions and increase the antioxidant and neuroprotective activity in brain disorders such as ASDs [112]. Risperidone is well tolerated, showing no evidence of extrapyramidal side effects (EPS) or seizures except mild sedation [83]. Other side effects with use of risperidone include increased appetite, fatigue, dizziness and drowsiness [80].

Neurotransmitter reuptake inhibitors

Fluoxetine (selective serotonin reuptake inhibitor, SSRI) has shown several possible benefits, including reductions in rituals, stereotyped and repetitive behaviors in children and adolescents with autistic spectrum disorders (Fig. 1). However, fluoxetine has also produced some sort of adverse effects like disinhibition, hypomania, agitation, and hyperactivity [36, 45, 61]. Fluvoxamine has also shown the similar potential effects against autistic disorder as those by fluoxetine [78, 132]. In a double-blind, placebo-controlled trial, fluvoxamine has been found well tolerated in autistic adults and improved compulsive and repetitive behaviors and aggression [85]. Other SSRIs, including sertraline [81, 109], paroxetine [108] and escitalopram [100], also possessed the same potential benefits and adverse effects as fluoxetine and fluvoxamine. It has also been reported that the use of venlafaxine in autistic individuals showed the improvements in their restricted behaviors, interests, social deficits, hyperactivity and communication problems [19].

Tricyclic antidepressants

Nortriptyline has been found to be effective in children with ASD as it improved the hyperactivity, aggressiveness, and ritualized behavior, while imipramine is not well tolerated in autistic children [17, 76]. In a study, 58% of autistic subjects have found clomipramine to be superior to placebo and the antidepressant desipramine in improving autistic symptoms, anger, and compulsive and ritualized behaviors [53]. In another study, clomipramine has produced adverse effects such as sedation and a worsening of behaviors like aggression, irritability, and hyperactivity [117].

Anticonvulsants

In epileptic children, lamotrigine treatment has shown a decrease in autistic symptoms in 62% of the autistic subjects [123]. However, no significant difference between placebo-treated and lamotrigine-treated patients has been found in a double-blind, placebo-controlled study of 35 patients with autistic disorder. Divalproex sodium (sodium valproate + valproic acid, 1:1) has shown beneficial effects in patients with autism spectrum disorders (ASDs) and PDDs [60]. Several other reports from clinical studies have also shown that divalproex sodium produced clinical improvements in the various symptoms of autistic patients such as receptive language, affective instability, aggression, and social skills [6, 60, 63]. Rugino and Samsock found that levetiracetam may be useful in reducing hyperactivity, impulsivity, aggression, and affective lability [116].

Glutamate antagonists

Excessive glutamate levels have been found in post-mortem brain samples of some autistic individuals [111]. Several studies have been shown the usefulness of glutamate antagonists (amantadine, memantine) in autism. In a randomized double blind placebo controlled trial, amantadine has been found to be effective in improving the hyperactive behavior and inappropriate speech in children with autism [72]. The use of memantine in treatment of autistic individuals has been associated with the improvements in memory, hyperactivity, irritability, language, social behavior and self-stimulatory behavior but few patients have also experienced adverse effects including worsening of autistic behavior [28, 99].

Acetylcholinesterase inhibitors

Deficits in brain cholinergic function have been described in some individuals with autism [105]. Several studies have examined the use of acetylcholinesterase inhibitors, including rivastigmine, donepezil, and galantamine in children with ASD. The use of rivastigmine in children with autism led to significant improvements in overall autistic behavior and adverse effects including nausea, diarrhoea, hyperactivity and irritability [27]. Donepezil has also been reported to improve irritability and hyperactivity of autistic children [57]. Galantamine produced significant improvements in irritability, hyperactivity, social withdrawal, inappropriate speech, inattention, reduction in anger and autistic behavior in children with autism [94, 95].

Methylphenidate

Methylphenidate is a stimulant that is commonly indicated for autistic children and adolescents. In some controlled studies, methylphenidate was found to be effective in improving the behavior symptoms like hyperactivity, impulsivity and attention but it also produces some initial side effects such as anorexia, aggression, and insomnia [38, 55].

Clonidine

Oral or transdermal administration of selective α-2 agonist, clonidine, have shown improvement in hyperactivity, mood instability, aggressiveness and agitation in autistic individuals. The side effects were largely tolerable. A placebo-controlled double-blind clinical trial of clonidine in autism provides evidences for the clinical efficacy and safety of clonidine in autism and related disorders [44]. Clonidine (at bedtime) also produced improvements in sleep, night time awakenings, aggression and mood [88]. A retrospective study has shown that the use of guanfacine was associated with improvements in attention, hyperactivity, insomnia, and tics [110]. The most common adverse effects observed with guanfacine were insomnia, fatigue, blurred vision, headache, and mood alteration [13].

Naltrexone

Naltrexone is an opiate antagonist that has been evaluated in autism spectrum disorders (ASDs) on the basis of the reputed role of endogenous opioids such as β endorphin and encephalins in the regulation of social behavior [102]. It has been shown that naltrexone might be able to treat opioid system induced behavioral abnormalities seen in autistic patients [18]. Several studies have been reported significant improvements in various behavioral symptoms with the use of naltrexone in children with ASD [15, 74, 130]. Naltrexone treatment has also been reported to have significant improvements in self-injurious behavior, hyperactivity, social withdrawal, agitation and irritability in autism spectrum disorders [42].

Drugs under development

Loss of neuronal functions of certain brain areas in autism further leads to the development of behavioral and sensory complications such as attention deficits, hyperactivity, mood instability, aggressiveness, agitation, etc. The present scientific research directs us to a few things. One is being the plasticity of brain tissue, the second being nerve tangling in the brain and the third being uneven production of serotonin, all which may have a significant effect on evolution and degree of severity of autism in any particular individual. Apart from this, there are many other pathological changes occurred in autism such as gastric disturbances, oxidative stress, chronic inflammation and immunological problems.

Tab. 3. Drugs under different phases of development [#]

Drugs	Action	Developmental stage
KM 391	Acts on serotonin uptake	Preclinical stage
Docosahexaenoic acid	Omega-3-fatty acids	Clinical trials
Fluconazole	Antifungal action	Clinical trials
Methylphenidate	Psychostimulant	Clinical trials
Oxcarbazepine	Anticonvulsant and mood stabilizing drug	Clinical trials
Arbaclofen (STX209)	Specific GABA receptor agonist	Phase II
Buspirone	Psychoactive agent	Phase II
Citalopram	Selective serotonin reuptake inhibitor	Phase II
CX516	Cognition/memory enhancement	Phase II
Dimercaptosuccinic acid	Chelating agent	Phase II
Divalproex sodium	Anticonvulsant	Phase II
Donepezil HCl	Acetylcholinesterase inhibitor	Phase II
Lenalidomide	Anti-inflammatory	Phase II
Mecamylamine	Nicotinic antagonists	Phase II
Memantine	NMDA blocker	Phase II
Methylcobalamin	Vitamin	Phase II
N-Acetylcysteine	Antioxidant	Phase II
Olanzapine	Decrease disruptive behaviors in autism	Phase II
Oralgam	Human immunoglobulin	Phase II
Oxytocin	Hormone	Phase II
Pioglitazone	Antihyperglycemic	Phase II
R-baclofen	Specific GABA receptor agonist	Phase II
Riluzole	Sodium channel blocker	Phase II
Ziprasidone	Atypical antipsychotic	Phase II
Fluoxetine	Selective serotonin reuptake inhibitor	Phase III
Fluvoxamine	σ-1 and selective serotonin reuptake inhibitor	Phase III
Galantamine	Cholinesterase inhibitor	Phase III
Naltrexone	Opioid receptor antagonist	Phase III
Paliperidone ER	Atypical antipsychotic	Phase III
RG1068	Synthetic human secretin	Phase III
Bumetanide	Diuretic action	Phase III
D-cycloserine	NMDA modulator	Phase III
Saproterin dihydrochloride	An enzymatic cofactor	Phase III
Sertraline	Selective serotonin reuptake inhibitor	Phase III
Valproate	Anticonvulsant	Phase III
Divalproex sodium ER	Anticonvulsant	Phase IV
Levetiracetam	Anticonvulsant	Phase IV
Minocycline	Antibiotic	Phase IV
Risperidone	Atypical antipsychotic drug	Phase IV
Aripiprazole	Antipsychotic drug	Phase IV
Atomoxetine (Strattera)	Selective norepinephrine transporter inhibitor	Phase IV

[#] Source: http://clinicaltrials.gov/

Currently, there is no specific drug in the market that is approved to treat symptoms of autism. Preclinical and clinical research in the field of autism indicates the various pathobiological targets to develop new drugs for the treatment of autistic children. Table 3 summarized the various drugs under developmental stages. These drugs act on different targets to cure the behavioral as well as neurological symptoms of autism.

Conclusions

The recommended therapies for treating various behavioral symptoms of autism involve educational therapies: sensory integration therapy, applied behavior analysis, speech therapy, auditory therapy, etc. Various reports and parent surveys have shown that the food supplementation, dietary interventions and alternative treatments aimed at intestinal healing and detoxification help in curing the symptoms of autism. Psychotropic medications (antidepressants, antipsychotics, anticonvulsants and stimulants) are also found to be effective in treating various behavioral impairments in autistic individuals such as hyperactivity, lack of attention, agitation, insomnia, aggression, self-injury, irritability, repetitive and compulsive behaviors and anxiety.

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