International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 287-298 www.ijprajournal.com ISSN: 2456-4494

The Psychopharmacological treatment of Autism Spectrum Disorder

Abhilashi College of Pharmacy Nerchowk, Mandi(HP)
Supervised by : Mrs. Ravina Naik Assistant Professor Department of Pharmaceutical Chemistry.
Students: Palak Thakur , Palvi Kumari, Payal .

Date of Submission: 10-03-2025 Date of Acceptance: 20-03-2025

ABSTRACT
While behaviour intervention remain the mainstay of the treatment of autism spectrum disorder , several potential targeted treatments addressing the underlying neurophysiology of ASD emerged in the last few years. In this article we provide a review on psychopharmacological treatment of autism spectrum disorder including those used to address common comorbidities of the condition and upcoming new targets approaches in autism management. Fragile X Syndrome, the most common genetic disorder leading to ASD , and provide a treatment to other form of ASD.
Keywords: Autism spectrum disorder, Autism, Medications, Pharmacology, Treatment.

I. INTRODUCTION

Autism spectrum disorder (ASD) refers to " a range of conditions characterized by some degree of impaired social behaviour, communication and language, a narrow out repetitively." ASD is complex neurodevelopment condition that continues to exist through childhood and adulthood. Most of the disorders are discovered during the first five years of life . Patients with ASD often suffers from other medical conditions such as epilepsy, depression, anxiety or attention deficit hyperactivity disorder. Individuals with ASDs have wide range of intellectual functioning , ranging from high intelligence to substaintial intellectual impairment.. ASD as impairments in two main domains : (1) social communication and interaction, which comprises challenges in social - emotional reciprocity, challenges in using nonverbal strategies during social emotional reciprocity, and challenges developing , maintaining and understanding relationships, and (2) restricted, repetitive , and stereotyped patterns of behaviours, restricted interests, insistence on sameness and inflexible adherence to routines, as well as sensory stimuli.[1]. Classic medical management of medical conditions has largely revolved around pharmacological treatment. However, despite decades of research in ASD, current evidence has only established behavioural treatments as the mainstay of management to address the core symptoms of ASD.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 287-298 www.ijprajournal.com ISSN: 2456-4494

Figure 1. Autism Spectrum Disorder

Part of the reason for lack of efficacy in many treatment studies stems from the heterogeneous etiology underlying the overall term of ASD. Some studies have subdivided enrolled patients either by their genetic etiology or phenotypic features to address this.

Non-pharmacological (behavioral) Interventions

Lovaas released a paper in 1987 outlining a novel treatment that described in an article published in 1987, Lovaas described a novel treatment that improved IQ scores and academic competence in nearly half of children with ASD. Discrete trail training (DTT), also known as The Lovaas Method of Applied Behavior Analysis, is a long-term, intensive, highly structured, one-on-one behavior intervention for young children[2]. It has strong empirical support and has served as the basis for many evidence-based behavioral interventions currently in use. The Lovaas approach has now undergone several adjustments and adaptations as a result of decades of intensive research. These can be applied in various contexts, situations, and processes and have been shown to be effective in addressing the core impairments of ASD in social communication, speech, behaviors, plays, and learning[3].

Comprehensive treatment models (CTMs) and targeted interventions are the two categories into which Odom et al.[4] and Wong et al.[5]. have divided behavioral evidence-based interventions.

- It has been discovered that comprehensive treatment models that target the main symptoms of ASD improve young children's language, cognitive, and functional abilities through the use of long-term, intense interdisciplinary techniques in a naturalistic setting. Both parents and teachers can give instruction, either individually or in a group, in a classroom or at home. Well-known CTMs include the Early Start Denver model (ESDM) . and Early Behavior Intervention (EIBI)[6], Developmental, Pivotal Response Training (PRT). Individual Difference, Relationship-Based Model (DIR/Floortime, or Greenspan model) .and Training and Education for

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 287-298 www.ijprajournal.com ISSN: 2456-4494

Children with Autism and Related Communication Handicaps (TEACCH)[7].

- Focused interventions address a single skill or a specific area of developmental domain and are provided for a short time, until the skill is mastered. They can also be effective to address life- threatening or socially inappropriate behaviors that require rapid addressing. Example include social skill training, toilet training, modeling, connitive behavioral intervention, and behavioral strategies like prompting, ignoring time delay, reinforcement, discrete trail teaching and extinction. These can be implemented as a structured session or in a naturalistic setting at home, school , clinic, or community mental, or educational purposes. Peer-mediated instruction and Intervention(PMII), also known as "Peer Modeling." "Peer initiation Training," "peer support"[8] and Picture Exchange Communication System (PECS), are Picture Exchange Communication System (PECS) ,are also other examples of focused interventions.

Established Psychopharmacological Treatments

Over the past few decades, there has been a significant increase in the use of psychotropic medications; roughly two-thirds of adolescents with autism have received treatment with these drugs, particularly those who exhibit challenging behaviors and have co-occurring conditions such as intellectual disability (ID), medical, and mental health diagnoses. About 70% of people with autism have been found to have co-occurring mental health symptoms, which include mood, anxiety, irritability, aggression, and attention deficit and hyperactivity disorder (ADHD)[9]. According to Mandell et al., 20% of patients received three or more psychotropic medications, and 56% received at least one[10]. Multiple drugs, including off-label use (such as antipsychotic medications in younger children), are commonly used to treat individuals with ASD. Depending on the type of study, significant rates of polypharmacy have been recorded, ranging from 12 to 35%.

Uncertainty surrounds the rising prescription rates for people with ASD. For example, some authors have hypothesized that this could be due to advancements in clinical and diagnostic knowledge of co-occurring mental health conditions[20]. Additionally, demographic characteristics have been observed by other researchers to influence pharmacological treatment. In one major study, for example, people who were uninsured or only privately insured were less likely than Medicaid-covered people to use more than three medications [25]. Over the past few decades, there has been a significant increase in the use of psychotropic medications; roughly two-thirds of adolescents with autism have received treatment with these drugs, particularly those who exhibit challenging behaviors and have co-occurring conditions such as intellectual disability (ID), medical, and mental health diagnoses.

In addition to standard treatments for prevalent comorbidities of ASD, specific treatments for faulty pathways are used. One such medication is metformin, which effectively inhibits the mTOR pathway and this medication is effective when combined with selective serotonin reuptake inhibitors (SSRIs) for anxiety and stimulants for ADHD.

In addition to treating the symptoms of related psychopathology, prescribers should think about drugs as targeted therapies that can reverse neurobiological abnormalities and should be used in conjunction with behavioral and educational interventions as part of a customized treatment plan.

In addition to standard treatments for prevalent comorbidities of ASD, specialized treatments for faulty pathways are used. For instance, metformin can down regulate the mTOR pathway. This medication is effective when combined with selective serotonin reuptake inhibitors (SSRIs) for anxiety and stimulants for ADHD.

Prescribers must take into account drugs as targeted treatments in addition to treating symptoms of related psychopathology.

Prescribers should think about drugs as targeted treatments that can reverse the neurobiological abnormalities and as part of a customized therapeutic program that includes behavioral and educational interventions, in addition to treating symptoms of related psychopathology.

Basic Guidelines for Pharmacological Treatment of ASD

It can be difficult to diagnose and treat mental health conditions, particularly in people with a limited vocabulary, poor cognitive function, and ambiguous symptoms. Diagnostic overshadowing, or the inability to recognize alternative illnesses while a certain diagnosis is present, is frequent. Children and adolescents who struggle with communication must be evaluated with a high degree of clinical suspicion for co-occurring mental health disorders. When feasible,

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 287-298 www.ijprajournal.com ISSN: 2456-4494

managing doctors should get information from the child's family as well as from other healthcare professionals like teachers and therapists. Unwanted behaviors may be caused by changes in the environment or a lack of abilities, which should be taken into account in the care plan. When necessary, pharmacological therapies can help them participate in therapy and improve their day-to-day functioning.

Children with ASD are managed using the same psychopharmacological concepts as children with usual development. Prescribers should be aware, though, that children with ASD are more likely than children without ASD to experience negative side effects and to be more sensitive to the effects of medications. Therefore, compared to children who are neurotypical, pharmacological treatment should be initiated at lower doses and modified more gradually. To objectively assess the effectiveness of treatment in various contexts, it is essential to collect objective symptom measures from various sources both before and after the intervention.

Serotoninergic Medications

Serotonin, a crucial messenger specifically engaged in the central nervous system (CNS), cardiovascular system, and gastrointestinal tract, is regulated by serotoninergic drugs. There have been reports of elevated serotonin levels in the autistic population, and it has been hypothesized that serotonin dysregulation is linked to symptoms commonly observed in autistic people, such as anxiety and repetitive behaviors. Serotonin levels in the CSF are lower in young children (less than five years old) with ASD, according to PET studies[11].

Enzymes that convert tryptophan to serotonin are deficient in lymphoblastoid cell lines from ASD patients as compared to controls. According to these research, SSRI medication would help people with ASD by promoting neurogenesis and neuroprotection[12]. Tricyclic antidepressants, SSRIs, and SNRIs (serotonin-norepinephrine reuptake inhibitors) are the three categories of drugs that affect serotonin levels. One of the most often given drugs for autistic people to address anxiety, mood disorders, and irritability is an SSRI.

However, the advantages of SSRIs for reducing aggressiveness and the primary symptoms of ASD have been inconsistent among current clinical trials. In comparison to children who did not receive sertraline, a retrospective study of children with FXS (ages 12 to 50 months) showed improvement in the trajectory of both receptive and expressive language measures on the Mullen Scales of Early Learning (MSEL) in those treated with low-dose sertraline. Due to these findings, children with FXS aged 2 to 6 (60 percent of whom also had ASD) who were clinically treated with low doses of sertraline (2.5 to 5.0 mg/day) participated in a 6-month controlled experiment[13]. In comparison to those receiving a placebo, those receiving sertraline showed more progress in the MSEL's Cognitive T score as well as in the motor and visual subtests.

Comparing the children with FXS and ASD to the placebo group, there was a notable improvement on the Expressive Language subscale. Sertraline-treated participants significantly outperformed placebo-treated participants on a passive visual eye tracking measure of receptive vocabulary in the same controlled trial. According to these research, low-dose sertraline medication is beneficial for young children with FXS, both those with and without ASD. A similar trial, however, found no benefit of sertraline when compared to a placebo in young children with idiopathic ASD (without FXS) aged 2 to 6 who received low-dose sertraline[14].

Therefore, the genetic subtype of ASD affects how well a child responds to treatment, and all children with an ASD diagnosis need to undergo genetic testing, such as Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS) if the preliminary studies are negatives.

Atypical Antipsychotics.

Clinical trials have shown that risperidone, which is approved for children older than five, and aripiprazole, which is approved for children aged six to seventeen[36], are effective in reducing irritability and, to a lesser extent, repetitive behaviors. These two medications are approved by the FDA to treat irritability associated with ASD. Both of these atypical antipsychotic drugs have an affinity for the brain's dopamine, 5-HT, alpha-adrenergic, and histaminergic receptors. Additionally, they have comparable safety profiles; the most frequent adverse effects are sedation, weight gain, hyperprolactinemia, GI symptoms, exhaustion, and increased hunger; less frequently, activation symptoms include akathisia and restlessness. Additionally, they have been connected to more severe adverse effects such metabolic syndrome, dyslipidemia, hyperglycemia, extrapyramidal symptoms, and drug-induced movement problems. As a result, careful laboratory and clinical monitoring is advised. It is crucial to periodically reassess whether treatment should

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 287-298 www.ijprajournal.com ISSN: 2456-4494

continue because the safety and effectiveness of these drugs for the long-term management of irritability in autistic people have not been proven.

Because conventional antipsychotics have a narrower safety profile and a higher incidence of adverse reactions, including extrapyramidal symptoms like tardive dyskinesia, they have been used only in more severe cases that are not responsive to the newer generation medications since the development of atypical antipsychotics.

Stimulant Medications

Since stimulants have a quick clinical effect and there is sufficient evidence to support their usage and safety, they are typically the first line of treatment for co-occurring attention deficit and hyperactivity disorder (ADHD). Although the frequency varies greatly depending on the sample, about half of autistic children also fit the criteria for ADHD[16]. The goal of treating co-occurring ADHD symptoms in autistic people should be to improve their everyday functioning in a variety of contexts, including learning, and ideally achieve long-term functional outcomes by addressing related symptoms that impair academic performance, peer relationships, and emotional regulation—all of which are important indicators and mediators of functional challenges in adulthood

A thorough prior medical history, family history, and physical examination with an emphasis on the cardiovascular system should all be obtained by the pre-scribing clinician before beginning a patient on a regimen in order to evaluate the possible risks for pharmacotherapy.

To objectively assess the impact of frequent side effects associated with medication for ADHD, such as changes in appetite, hypertension, weight loss, sleep difficulties, headaches, and abdominal pain, it is crucial to collect pretreatment baseline data and closely monitor the patient. Stimulant therapy may help with baseline sleep issues, which do not seem to predict stimulant-related sleep issues. Before beginning therapy, adolescents should have their substance use and abuse evaluated. The amphetamines are generally somewhat more effective than the methylphenidate derivatives, which are typically better tolerated. There are two major families of stimulants[17].

Amphaetamines were marginally more effective than methylphenidate in lowering clinician-rated core symptoms of ADHD at around 12 weeks, according to a systematic review and network meta-analysis that included 81 published and unpublished randomized trials in over 10,000 neurotypical children. However, amphetamines were less tolerable than a placebo, and methylphenidate was better tolerated than amphetamines. There was no evidence of an impact on core ASD symptoms or an improvement in social interaction, but a specific systematic review of four crossover trials involving 113 participants aged 5 to 13 years revealed low-quality evidence that short-term methylphenidate treatment may improve hyperactivity and inattention in children with ASD. The only significant adverse side effect, according to parents, was decreased appetite.

In the largest crossover trial, approximately 50% of children with ASD responded to methylphenidate based on the hyperactivity subscale of the Aberrant Behavior Checklist (ABC); the effect size ranged from 0.20 to 0.54, depending upon dose and rater, with greater improvement at higher doses; then, this modest effect supports that Methylphenidate exerts a lower effect on primary ADHD symptoms in individuals with ASD compared to those in the neurotypical population. Six of 66 children in the double-blind phase (9.1%;) discontinued treatment due to adverse effects, including irritability, repetitive behaviors, tics, insomnia, and reduced appetite.

The onset of unacceptable side effects or an inability to achieve satisfactory improvement in the primary symptoms of ADHD at the highest dosage are indicators of treatment failure. A minimum of 50% of the kids who showed signs of a poor reaction or adverse reactions to one medicine would react well to another. The prescriber should assess additional factors, such as (1) the presence of a comorbid psychiatric diagnosis, (2) unrealistic expectations regarding the expected clinical response, (3) misuse or medication diversion, and (4) noncompliance with the regimen, for children who do not respond to two different medications. Every six months, children on a stable maintenance dose should be monitored for side effects and clinical response.

Alpha_2_adrenergic Agonists

Alpha-2-adrenergic agonists, such as guanfacine and clonidine, are commonly used in children under the age of five who have ADHD or hyperarousal, have poor response to a stimulant trial, or selective norepinephrine reuptake inhibitors, have unacceptable side effects, or have significant co-occurring conditions (such as sleep issues). However, there is also evidence that alpha-2 agonists can improve core ADHD symptoms. Alpha-2-agonist research on ASD is, however,

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 287-298 www.ijprajournal.com ISSN: 2456-4494

scarce and has small sample numbers. According to reports, guanfacine is a safe and efficient treatment for impulsiveness and hyperactivity in kids with ASD[18]. Guanfacine's most frequent adverse effects include agitation, aggressiveness, constipation, and sedation. According to a small crossover trial, clonidine may also help people with ASD by reducing hyperactivity, improper speaking, stereotyping, irritability, and hyperarousal behaviors .While atomoxetine and alpha-2-adrenergic agonists are more effective than placebo in lowering the basic symptoms of ADHD, they are less effective as a class than stimulants, according to data from randomized trials, systematic reviews, and meta-analyses.

To objectively assess the response to treatment in various contexts, it is therefore crucial to collect objective targeted symptom measures both at baseline and during treatment. Methylphenidate and atomoxetine were found to have better effects than placebo in treating ADHD symptoms in a recent review of nine controlled trials involving 430 children with ASD. However, the response for hyperactivity symptoms was lower than that seen in neurotypical populations using both medications[19].Individuals with weaker cognitive functioning were linked to worse treatment outcomes.

Melatonin

Children with ASD often report sleep problems, which may have an impact on their behavior, day-to-day functioning, and family life. Low melatonin levels may have an impact on autistic children's circadian rhythm, according to some research[20].

Clinicians may suggest the use of melatonin, which is typically well accepted and has a low incidence of side effects, in situations when behavioral and environmental sleep therapies have been tried with little success. The use of prolonged-release melatonin in autistic people who don't react well to normal release formulations is becoming more and more supported by research.

The FDA does not regulate the over-the-counter medication mela-tonin. Parents and caregivers should look for a formulation that has melatonin as the sole active ingredient when they buy melatonin.

N_acetylcysteine

Another over-the-counter (OTC) antioxidant that can help with the excitation:inhibition (E:I) imbalance that is present in some types of ASD is N-acetylcysteine (NAC). NAC reduces the E:I imbalance in two ways: it decreases glutamatergic neurotransmission, and cysteine increases the synthesis of glutathione, a crucial antioxidant. Additionally, cysteine is produced when cysteine is oxidized, which aids in lowering glutamatergic neurotransmission[21]. In contrast to a placebo, Hardan and colleagues conducted a controlled experiment in which they increased the dosage of NAC from 900 mg once day for four weeks to bi-daily dosing for four weeks and finally tri-daily dosing for the final four weeks. They randomized 33 ASD subjects, ages 3.2 to 10.7 years, and found that patients treated with NAC significantly improved on their key end measure, the irritability subscale on the ABC, after 12 weeks of treatment ($p < 0.001$) as compared to those treated with a placebo. Additional improvements in stereotypical behaviors were observed in individuals treated with NAC compared to placebo, with significant improvements on the RBS-S Stereotypies subscale ($p < 0.014$) and the SRS Autism Mannerisms subscale ($p < 0.045$)[21] .

Despite the infrequent patient experiencing mild gastrointestinal side effects or not liking the taste, NAC was well tolerated.

Dietary Supplements

Sulforaphane

One naturally occurring isothiocyanate is sulforaphane, which can be found in cruciferous plants like broccoli. Humans with neurodegenerative and neurodevelopmental problems as well as a number of animal models have been used to study sulforaphane, an antioxidant, anti-inflammatory, and mitochondrial protective agent[22]. A sulfur-rich dietary phytochemical called sulforaphane has the ability to cross the blood-brain barrier and trigger the nuclear factor erythroid 2 related factor 2 (Nrf2) signaling cascade, which in turn promotes the expression of over 200 antioxidant genes involved in the central nervous systems detoxification and neuroprotection. Superoxide and other reactive oxygen species (ROS) are reduced, the proteozome system is upregulated to break down unfolded or misfolded proteins, autophagy is improved, pro-inflammatory cytokines are inhibited, heme toxicity is prevented, and neuronal cells are protected from Aβ42-mediated cytotoxicity.A randomized trial of young males with moderate to severe ASD, aged 13 to 27, who received sulforaphane (n = 29) vs a placebo (n = 15) for 18 weeks is one of the few investigations conducted on ASD patients[. The Aberrant Behavior Checklist

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 287-298 www.ijprajournal.com ISSN: 2456-4494

(ABC), the Clinical Global Improvement Scale (CGI-I), and the Social Responsiveness Scale 2 (SRS) all showed notable gains.

This successful trial prompted a more thorough investigation of children with ASD, which had 57 children aged 3 to 12 participating in a 15-week randomized controlled trial with sulforaphane followed by a 15-week open label trial.

Sulforaphane did not significantly improve the Ohio Autism Clinical Impressions Scale, the key end measure; however, sulforaphane considerably improved the ABC, a secondary measure, when compared to a placebo, but the SRS did not. Furthermore, there were notable changes in the biomarkers on sulforaphane compared to placebo, including the glutathione redox status, mitochondrial respiration, inflammatory markers, and heat shock proteins. These improvements were also associated with improvements on the ABC. They used Avmacol, a commercial sulforaphane product manufactured by Nutrimax, which comes in a dosage of 2 to 8 tablets daily, depending on the child's weight (equivalent to 2.2μmol/kg/day).

Although the primary outcome measure, the Ohio Autism Clinical Impressions Scale, did not The supplement was well tolerated and no serious side effects were reported.Other antioxidants, such as omega-3 fatty acids[23], have been investigated in ASD with varying degrees of success. These antioxidants encourage glutathione recycling by making it easier for oxidized glutathione to be converted to reduced glutathione. In a more recent trial, 111 kids with ASD between the ages of 2.5 and 8 were randomly assigned to receive either a placebo, 2000 IU of vitamin D per day, 722 mg of omega-3 per day, or both treatments for a year. During the course of a year of therapy, 73 patients had a significant decrease in their major outcome measure, irritation on the ABC subscale, for those receiving both therapies ($p < 0.001$), as well as for those receiving vitamin D alone.

Although biomarkers of oxidative stress would be useful to investigate in future research to better identify those who may benefit from this medication, these results suggest that antioxidants may be a helpful supplementary treatment in some ASD patients.

Emerging Targeted Treatments with a Possible Role in ASD

A. Oxytocin

The neuropeptide oxytocin (OXT), which is produced in the hypothalamus, is essential for social interaction. Existing research has demonstrated that OXT improves social processing in normally developing people right away after delivery (better facial expression recognition, improved eye contact). OXT has typically been beneficial for persons with ASD; trials have shown improvements in emotion identification, social reciprocity, and repetitive behaviors. All of these trials, however, only looked at the immediate (within a few weeks) advantages of taking OXT. Following an initial 4-week course of oxytocin treatment, a new double-blind, randomized, placebo-controlled research in people with ASD revealed improvements in self-reported repetitive behaviors and good mood at one year after treatment[24]. However, no significant therapeutic benefits were seen in this same trial for social responsive-ness with OXT Oxytocin (OXT) is a neuropeptide synthesized in the hypo-thalamus that plays a critical role in social functioning. Extant literature has shown that OXT enhances social pro-cessing in typically developing adults (enhanced eye con-tact, better emotion recognition in faces) immediately after its administration . There have been generally positive results of OXT in adults with ASD, with trials showing improvements in repetitive behaviors, social reciprocity, and emotion recognition . However, all these trials stud-ied only short-term benefits[74-77], (within a few weeks) of demon-strate any OXT specific improvements in social respon-siveness or repetitive behavior in children with ASD .

However, a recent randomized controlled experiment (RCT) found no discernible differences in aberrant behavior, social communication, or cognition between the OXT and placebo groups. It has been demonstrated that intranasal OXT increases effective connectivity between nodes of the brain's reward and socioemotional processing systems and increases activation in the brain regions known to be involved in perceiving and thinking about social-emotional information at the neural network level[25]. Although animal studies have suggested that long-term OXT administration may result in elevated basal OXT levels, the clinical implications of this are unknown. To yet, no adverse effects have been observed in these investigations on children with ASD. Relevantly, there is yet insufficient proof to support OXT's long-term positive effects. levels with prolonged OXT use; the resulting clinical consequences are unknown. Relevantly, there is yet insufficient proof to support OXT's long-term benefits in treating the primary symptoms of autism. Even in placebo-controlled trials, the inherent constraints of

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 287-298 www.ijprajournal.com ISSN: 2456-4494

reporting bias are likely to be present because the great majority of studies in children use parent-reported outcome measures of social and behavioral problems.

It's also uncertain whether the benefits of OXT administration in the lab transcend to the real world, which is another crucial factor to take into account. OXT is not a single therapeutic option for ASD because its function up to this point has been restricted to its rapid effects following administration. However, as demonstrated by a recent meta-analysis, which included both adults and children, OXT does appear to have generally positive effects on social symptoms of ASD.

Clinical trials in this field are still underway, and there is some encouraging research examining the impact of OXT in conjunction with other therapeutic methods like behavior therapy and probiotics. Additionally, age, gender, and potentially hereditary factors may influence how OXT affects ASD. Therefore, even though OXT has a lot of potential, it is not yet a common treatment for people with ASD[26].

B. Bumetanide

A well-known loop diuretic, bumetanide functions by blocking the sodium—potassium—chloride co-transporters NKCC1 and NKCC2. Because of its natural chloride-related antagonist properties, which are connected to GABA-ergic inhibition, bumetanide has been proposed as a possible treatment for autism. Two placebo-controlled randomized controlled trials have demonstrated that bumetanide reduces widespread ASD symptomatology in children after a 3-month course of treatment[27]. The SRS and the Childhood Autism Rating Scale (CARS), two tests employed in these trials, are screening instruments for ASD. After three months of bumetanide, parents stated that all six children in an open-label trial with severe ASD and intellectual handicap had improved in their conversational skills. However, there were no treatment benefits on the core symptoms of ASD as assessed by the SRS-2 in a recent double-blind, placebo-controlled, phase 2 superiority trial among children with ASD who did not have substantial intellectual handicap. With no significant negative effects, it did provide treatment benefits on the repeated behavior scale. Despite not being a randomized controlled trial, another study has indicated that bumetanide and ABA therapy may work together to improve ASD symptoms on the CARS[28].

Two phase 3 clinical trials are now underway, which could provide more details about bumetanide's possible advantages in ASD. According to certain functional MRI-based data, bumetanide helps people with ASD perceive faces more emotionally, spend more time staring at biological stimuli, and lessen their abnormal amygdala activation when making eye contact. In any case, there is conflicting data on bumetanide's ability to address the primary symptoms of ASD based on recent research.

C. Metformin

In the past ten years, targeted therapies that reverse recognized neurobiological problems in ASD subgroups where there is also evidence of improvement have been available. The most prevalent single gene etiology of ASD, FXS, is the subgroup of ASD that is setting the standard for targeted therapy. Furthermore, postmortem investigations have demonstrated that patients with idiopathic ASD who do not have a fragile X mutation also have deficiencies in the brain of FMRP, the protein that is absent or deficient in FXS. Consequently, FXS serves as a model for focused therapies in other ASD subtypes, and therapies that are effective in treating FXS may also be helpful for treating other ASD subtypes. Therefore, we will discuss some of the focused treatment studies using currently available medications that are not FDA authorized for ASD or FXS.Studies on animals with FXS have shown an overactive insulin receptor, increased expression of the signaling pathways for mitogen-activated protein kinase/extracellular signal-related kinases (MAPK/ERK) and mammalian target of rapamycin complex 1 (mTORC1), and increased levels of MMP-9 in the absence of FMRP, the protein that the FMR1 gene produces[30]. In addition to being the main treatment for type 2 diabetes, the bi-guanide metformin can also make obese people feel less hungry. Thus, metformin investigations were initially conducted in obese FXS patients, frequently exhibiting the Prader-Willi phenotype of FXS.

A small number of FXS patients between the ages of 4 and 60 who received clinical metformin treatment showed improvements in their overeating as well as on the ABC subscales measuring social avoidance, hostility, and irritability. Additionally, parents reported that their children's expressive language skills in conversation had improved. The Azrieli Foundation-funded MIND Institute is conducting a controlled study with metformin at three locations: two in Canada (Edmonton and Montreal) and one in the USA to examine the possible linguistic

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 287-298 www.ijprajournal.com ISSN: 2456-4494

improvements (NCT03479476, NCT03862950). In a four-month randomized controlled experiment, patients between the ages of 6 and 45 are recruited. The main outcome measure is the Expressive Language Sampling, but there are also event-related potentials, ocular NIH Toolbox, eye tracking, and other behavioral metrics are evaluated. In 2022, the results will be accessible. Metformin has been used in several open-label studies, such as one with children with FXS aged 2 to 7, where behavioral and developmental gains were shown on the MSEL[31].

According to individual case studies, two adults with FXS had an improvement in their IQ after using metformin for more than a year, and a child who began taking the medication just prior to puberty did not develop macroorchidism[32].

D. Lovastatin

The FDA has approved lovastatin, a popular statin, to reduce hypercholesterolemia or hyperlipidemia in both adults and children. It accomplishes this by blocking 3-hydroxy-3methylglutaryl coenzyme A (3HMG-CoA) reductase. This activity reduces the MEK-ERK pathway's excessive protein synthesis, which is enhanced in FXS. Excess protein synthesis and epilepsy were both recovered in FXS knockout (KO) mice after lovastatin therapy[33]. Trials on FXS patients were prompted by these animal research. 32 children with FXS, ages 10 to 17, were treated in a randomized controlled trial (RCT) for 20 weeks at a dose of 10 to 40 mg daily, as tolerated[34].

Additionally, a speech-language pathologist conducted four sessions every week for 12 weeks to administer Parent Implemented Language Intervention (PILI) to all of the patients via distance video teleconferencing[35]. During collaborative story-telling sessions with their children, parents applied a set of language facilitation practices they had learned. The primary outcome measures included the CGI-I, behavioral measures (ABC), and other language scales, as well as the quantity of utterances and new words used. Thus, the effects of lovastatin plus PILI were compared to those of PILI alone with a placebo in this study.

Surprisingly, both groups showed notable gains over baseline, but the results were identical; that is, PILI by itself showed as much improvement as lovastatin plus PILI, indicating the effectiveness of intensive linguistic intervention.

Gene Therapy

Despite the fact that doctors cannot use this therapy on their patients, there are some fascinating research papers available, especially since the development of CRISPR/Cas9 technology. It's fascinating to consider the idea of treating ASD or other neurodevelopmental diseases where the mutation is known by injecting a normal gene or protein into the central nervous system. The use of antisense oligonucleotides (ASOs) to quiet harmful RNA or gene products is another instance of gene therapy. ASOs have been used to activate the paternal copy of UBE3A in the central nervous system (CNS) in order to make up for the missing mother copy in Angelman syndrome, where the maternal copy of UBE3A is either mutated or absent.

Recently, five people with Angelman syndrome, aged five to fifteen, participated in a controlled trial of the ASO GTX-102. As part of the protocol, GTX-102 was injected intrathecally once a month for four months at increasing doses. However, an adverse consequence of leg weakness was noted at the higher doses resulting to an inability to walk in two patients. Anti-inflammatory medications were used to treat these individuals once it was discovered that this side effect was connected to inflammation at the site where the LP was performed. Additional gene therapy therapies for ASD and other neurodevelopmental diseases have a promising future.

II. CONCLUSION

In order to treat the primary symptoms of ASD in children, behavioral interventions are the mainstay of the current evidence-based management of the disorder. As people age, the primary function of pharmaceutical therapy is to treat co-morbid disorders linked to ASD. These drugs, which include stimulants and anti-psychotics, are crucial for the clinical treatment of individuals with ASD. However, a number of recent patient successes are detailed here as a result of the development of targeted treatments for subgroups of ASD where the genes causing the disorder are known and the neurobiology and potential targeted treatments have been studied to reverse the neurobiological abnormalities at least in the animal models.

Notably, there are similarities amongst the diseases that cause ASD, indicating that treating one disorder specifically will help treat others. For

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 287-298 www.ijprajournal.com ISSN: 2456-4494

example, many kinds of ASD are characterized by GABA deficiencies, and many of the subtypes of ASDas mentioned above are likely to benefit from drugs like CBD that act as agonists for the GABA system. Since many types of ASD are linked to mitochondrial dysfunction, drugs that address this issue are probably beneficial for a wide range of ASD subtypes[36]. Thanks to CRISPR/Cas 9 technology, gene therapy is starting to fulfill its promise for a number of ailments, including Duchene Muscular Dystrophy, Spinal Muscular Atrophy, and even Angelman Syndrome

Many more types of ASD will be addressed with gene therapy in the coming years due to CRISPR/Cas 9 technology. In the interim, you can try some of the treatments listed below, and more will soon be accessible.

REFERENCES

[1]. Johnson J, Spitzer R, Williams J. Diagnostic and Statistical Manual of Mental Disorders-IV TR. Washington, DC: American Psychiatric Association; 2000.

[2]. Slocum TA, Detrich R, Wilczynski SM, Spencer TD, Lewis T, Wolfe K. The evidence-based practice of applied behavior analysis. The Behavior Analyst. 2014;37(1):41—56.

[3]. Leaf JB, Leaf R, McEachin J, Taubman M, Alai-Rosales S, Ross RK, et al. Applied behavior analysis is a science and, therefore, progressive. Journal of autism and developmental disorders. 2016;46(2):720—31.

[4]. Odom SL, Boyd BA, Hall LJ, Hume K. Evaluation of comprehensive treatment models for individuals with autism spectrum disorders. J Autism Dev Disord. 2010;40(4):425—36. 14.

[5]. Wong C, Odom SL, Hume KA, Cox AW, Fettig A, Kucharczyk S, et al. Evidence-based practices for children, youth, and young adults with autism spectrum disorder: a comprehensive review. J Autism Dev Disord. 2015;45(7):1951—66.

[6]. Reichow B, Barton EE, Boyd BA, Hume K. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). The Cochrane database of systematic reviews. 2012;10:Cd009260.

[7]. Mesibov GB, Shea V. The TEACCH program in the era of evidencebased practice. J Autism Dev Disord. 2010;40(5):570—9.

[8]. Hume K, Steinbrenner JR, Odom SL, Morin KL, Nowell SW, Tomaszewski B, et al. Evidence-based practices for children, youth, and young adults with autism: third generation review. Journal of Autism and Developmental Disorders. 2021:1—20.

[9]. 9.Simonoff E, Pickles A, Charman T,Chandler S, Loucas T, Baird G. Psychiatric Disorder in children with autism spectrum disorders :Prevalence,comorbidity,and association factors in a population-drived sample.J Am Acad Child Adolesc Psychaitry.2008;47(8) 921-9.

[10]. Mandell DS, Morales KH, Marcus SC, Stahmer AC, Doshi J, Polsky DE. Psychotropic medication use among Medicaidenrolled children with autism spectrum disorders. Pediatrics. 2008;121(3):e441—8.

[11]. Chandana SR, Behen ME, Juhász C, Muzik O, Rothermel RD, Mangner TJ, et al. Significance of abnormalities in developmental trajectory and asymmetry of cortical serotonin synthesis in autism. Int J Dev Neurosci. 2005;23(2—3):171—82

[12]. Jansson L,L louhivuori L, Wigren H-k, Nordstrom T,Louhivuori V, Castren M,et al. Brain derived neurotrophic factor increase the motility of a perticular N-methyl-D-aspartate/ GAVA — responsive subset of neural progenitor cells. Neuroscience.2012; 224:223-34

[13]. Hess LG,Fitzpatrick SE , Nguyen DV , Chen Y, Gaul KN, Schneider A,et al.A Randomized,Double blind, PleceboTrial of low dose sertraline in young children with fragil. x syndtrom. General of developemental and bheavioral pediatric: JDBP.2016;37(8):619.

[14]. Potter LA, Scholze DA, Biag HMB, Schneider A, Chen Y, Nguyen DV, et al. A randomized controlled trial of sertraline in young children with autism spectrum disorder . Front Psych.2019;10:810.

[15]. Owen R, Sikich L, Markus RN, Corey-Lisle P, Manos G, McQuade RD, et al. Aripiprazole in the treatment of irritability

in children and adolescents with autstic disorder. pediatric 2009;124(6):1533-40.

[16]. Mansour R, Ward AR, Lane DM Loveland KA, Aman MG, Jerger S, et al. ADHD severity as a predictor of cognitive task performance in children with autism (ASD). Research in developmental disabilities. 2021;111:103882.

[17]. Cortese S, Admo N, Del Giovane C, Mohr-Jensen C, Havies AG, Carucci S, et al. comparative efficacy and tolerability of medication for attention — deficit hyperactivity disorder in children, adolescent, and adults: a systematic review and network meta — analysis. The Lancet Psychiatry. 2018;(9)727-38.

[18]. Seahill L, Aman MG, McDougle CJ, McCracken JT, Tierney E, Dziura J et al. Positive effect of methylphenidate on inattention and hyperactivity inpervasive development disorder: an analysis of secondary measure. Biol Psychiat . 2007;61(4):538-44.

[19]. Rodrigues R, Lai MC, Beswick A, Gorman DA, Anagnostou E, Szatmari P, et al. Practitioner Review: Pharmacological treatment of attention-defcit/hyperactivity disorder symptoms in children and youth with autism spectrum disorder: a sys_tematic review and meta-analysis. J Child Psychol Psychiatry. 2021;62(6):680—700.

[20]. Carmassi C, Palagini L, Caruso D, Masci I, Nobili L, Vita A, et al. Systematic review of sleep disturbances and circadian sleep desyn_chronization in autism spectrum disorder: toward an integrative model of a self-reinforcing loop. Front Psych. 2019;10:366.

[21]. Hardan AY, Fung LK, Libove RA, Obukhanych TV, Nair S, Herzenberg LA, et al. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. Biol Psychiat. 2012;71(11):956—61.

[22]. Jardim FR, Almeida FJS, Luckachaki MD, Oliveira MR. Efects of sulforaphane on brain mitochondria: mechanistic view and future directions. J Zhejiang Univ Sci B. 2020;21(4):263—79.

[23]. Bent S, Bertoglio K, Ashwood P, Bostrom A, Hendren RL. A pilot randomized controlled trial of omega-3 fatty acids for autism spectrum disorder. J Autism Dev Disord. 2011;41(5):545—54.

[24]. Bernaerts S, Boets B, Bosmans G, Steyaert J, Alaerts K. Behav ioral efects of multiple-dose oxytocin treatment in autism: a randomized, placebo-controlled trial with long-term follow-up. Molecular autism. 2020;11(1):1—14.

[25]. Gordon I, Jack A, Pretzsch CM, Vander Wyk B, Leckman JF, Feldman R, et al. Intranasal oxytocin enhances connectivity in the neural circuitry supporting social motivation and social per_ception in children with autism. Sci Rep. 2016;6:35054.

[26]. Huang Y, Huang X, Ebstein RP, Yu R. Intranasal oxytocin in the treatment of autism spectrum disorders: a multilevel meta_analysis. Neuroscience & Biobehavioral Reviews. 2021.

[27]. Kong X-J, Liu J, Liu K, Koh M, Sherman H, Liu S, et al. Probiotic and oxytocin combination therapy in patients with autism spectrum disorder: a randomized, double-blinded, placebo-controlled pilot trial. Nutrients. 2021;13(5):1552.

[28]. Du L, Shan L, Wang B, Li H, Xu Z, Staal WG, et al. A pilot study on the combination of applied behavior analysis and bumetanide treatment for children with autism m. J Child Adolesc Psychophar_macol. 2015;25(7):585—8.

[29]. Ben-Ari Y, Lemonnier E. Using bumetanide to treat autism appears promising but further clinical trials are needed to confirm this approach. Wiley Online Library; 2021.

[30]. Fatemi SH, Folsom TD. The role of fragile X mental retarda_tion protein in major mental disorders. Neuropharmacology. 2011;60(7—8):1221—6.

[31]. Dy ABC, Tassone F, Eldeeb M, Salcedo-Arellano MJ, Tartaglia N, Hagerman R. Metformin as targeted treatment in fragile X syndrome. Clin Genet. 2018;93(2):216—22.

[32]. Biag HMB, Potter LA, Wilkins V, Afzal S, Rosvall A, Salcedo- Arellano MJ, et al. Metformin treatment in young children with fragile X syndrome. Molecular genetics & genomic medicine. 2019;7(11):e956.

[33]. Protic D, Kaluzhny P, Tassone F, Hagerman RJ. Prepubertal metformin treatment in fragile X syndrome alleviated macroor_chidism: a case study.. Advances

in Clinical and Translational Research. 2019;3(1):1—5.

[34]. Osterweil EK, Chuang S-C, Chubykin AA, Sidorov M, Bianchi R, Wong RK, et al. Lovastatin corrects excess protein synthesis and prevents epileptogenesis in a mouse model of fragile X syn_drome. Neuron. 2013;77(2):243—50.

[35]. Thurman AJ, Potter LA, Kim K, Tassone F, Banasik A, Potter SN, et al. Controlled trial of lovastatin combined with an open-label treatment of a parent-implemented language intervention in youth with fragile X syndrome. J Neurodev Disord. 2020;12(1):1—17.

[36]. Frye RE, editor Mitochondrial dysfunction in autism spectrum disorder: Unique abnormalities and targeted treatments. Seminars in pediatric neurology; 2020: Elsevier