Journal of High School Science

The future of autism medicine: analyzing drugs in development

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Submitted: April 21, 2025, Revised: version 1, June 16, 2025, version 2, June 19, 2025
Accepted: June 19, 2025

Abstract

Autism spectrum disorder (ASD) is a complex disease characterized by difficulties in social interaction and the presence of restricted and repetitive behaviors. It was identified over 80 years ago with ~ 2.8% of children in the United States being affected. Many factors, including genetic and environmental, contribute to the development of the disease. Hundreds of genes have been identified as being associated with ASD. However, there is no FDA-approved pharmacological treatment specifically addressing its core symptoms, although the FDA has approved two drugs to treat irritability and aggression in ASD patients. Non-pharmacological treatments, particularly behavioral therapies, remain the primary approach for symptom management. Nevertheless, many drugs targeting ASD-associated genes are in development. In this work, the pharmacological treatments that have entered clinical trials were identified and grouped based on clinical stage, drug modality, and drug target. The results showed that most drugs in clinical development are small molecules, with a focus on improving synapse function. Certain drugs, including bumetanide, L1-79, and cannabidiol, have demonstrated significant improvements in treating ASD core symptoms based on available clinical data. Additionally, expression profiles of the drug-targeted genes were evaluated. Several of these genes were found to be differentially expressed in ASD patients, providing a stronger rationale for therapeutic targeting. Clinical activity congregated around drugs targeting moderately differentially expressed genes, presumably because targeting lower gene expression was bereft of efficacy, while targeting high differential gene expression could reasonably be inferred to cause toxicity and off-target effects.

Keywords

Autism Spectrum Disorder, Drug target, Clinical trials, Pharmacological treatments, Drug modality, Differentially Expressed Genes, Therapeutic targeting, Neurotoxicity, Synaptic, Autism

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https://doi.org/10.64336/001c.141192

Introduction

Autism spectrum disorder (ASD) was first described in the 1940s (1). It is a complex neurodevelopmental condition that has been affecting a growing number of people (1). While it is a spectrum with a wide range of symptoms, the core symptoms of ASD include challenges in social interactions, repetitive behavior, and lack of adaptability (2). ASD patients also often experience various non-core symptoms, such as sleep disturbances, anxiety, attention deficit hyperactivity disorder, and gastrointestinal dysfunction (2).

The underlying pathogenic mechanisms of ASD remain unclear. However, many factors related to genetics, immunology, inflammation, and the environment likely contribute to its occurrence and development (3). In the past twenty years, significant progress has been made in understanding the genetic basis of ASD. Multiple genes have been identified as risk factors, such as SHANK3, CASPR2, CDH8, PTEN, among many others (3). These genes primarily function in major molecular or cellular pathways, including those related to transcription and translation, synaptic signaling, epigenetics, and inflammatory signaling. Alterations in these genes impact various signaling pathways, which could affect the structure and function of neuronal networks in the brain and ultimately lead to the development of ASD (1).

These advances in understanding the mechanisms of ASD provide the molecular basis for ASD drug development. Although there is still no cure specifically for the core symptoms of ASD, some medications have demonstrated encouraging therapeutic effects (4). Among these medications, risperidone and aripiprazole are the only two drugs that have been approved by the United States Food and Drug Administration (FDA) for the treatment of irritability associated with autistic disorder (2). Many others are under clinical investigation, with the effects of cannabinoids and probiotics especially promising (2). Alongside pharmacology treatment, non-pharmacological approaches help patients develop social and self-care skills. These methods include behavioral and dietary interventions, music therapy, yoga, and others (4). This paper identified pharmacological drugs that were actively in clinical development as of January 20, 2025, and analyzed their drug targets, modalities, mechanisms of action, target expression profiles, and clinical results. This work summarized the ongoing efforts in ASD treatments and highlighted trends in pharmacological innovation.

Methods

Database search and analysis

The drugs were searched on ClinicalTrials.gov using “autism spectrum disorder” or “autistic disorder” as the condition or disease, as of January 20, 2025 (5). Additional drug details, including drug modalities and drug targets, were obtained from journal articles accessed via PubMed and publicly available online resources, including company websites and press releases. The drugs were then categorized based on clinical stage, drug modality, and drug target. The Differential Expression (DE) p-values for drug targets were similarly obtained through a literature search.

Data analysis

The autism cases per 1,000 children were plotted over the years using a line chart in Excel. The number of drugs was plotted against drug modality and drug target using separate column charts in Excel. Within each drug modality or drug target category, the number of drugs at each clinical stage was represented with different colors. Clinical trial activity was plotted against DE (log) p-values using an XY chart in Excel. The clinical trial activity was defined as the sum of the number of drugs associated with their corresponding DE p-values, each multiplied by a weighting factor based on the clinical trial stage. The weighting factors were arbitrarily assigned as 1, 1.5, 2, 2.5, 3, and 4 representing Phases I, I/II, II, II/III, III, and approved stages, respectively.

Results

The number of patients with ASD has increased over the years

Autism was discovered over 80 years ago, and its name was changed to autism spectrum disorders in 2013, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (4). ASD includes autism, Asperger's syndrome, and pervasive developmental disorders not otherwise specified (PDD-NOS) (4). Despite its highly variable features and severity, ASD has two major symptoms; difficulty in social interaction and restricted, repetitive behaviors.

The number of patients diagnosed with ASD has been increasing, partly due to intense research and advancement in diagnostic procedures. The frequency of children diagnosed with ASD was 1 in 150 in 2000, 1 in 68 in 2010, and 1 in 36 since 2020, as of January 20, 2025 (Figure 1) (6). More boys than girls have been diagnosed with ASD, with a ratio of 4.3:1 (3). The frequency of adults diagnosed with ASD is close to that of children.

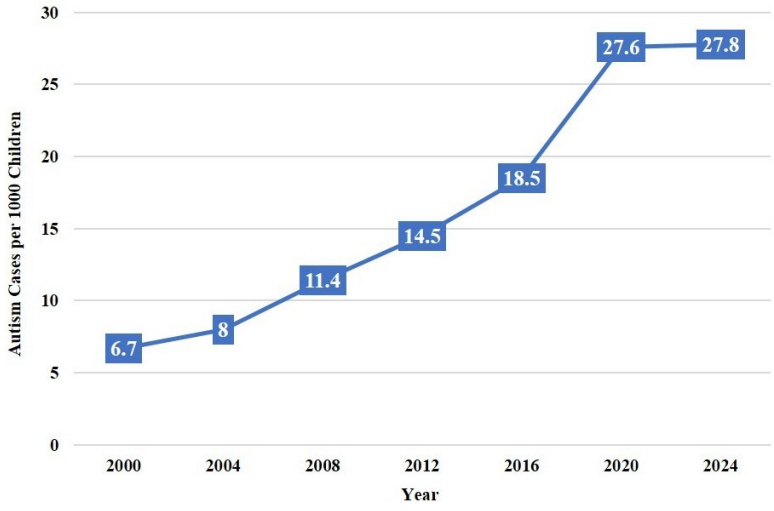

Figure 1. Autism cases per 1000 children over the years.

The majority of the drugs in clinical trials are small molecules

The treatment of ASD falls into two categories: pharmacological and non-pharmacological. Non-pharmacological treatment has been the main approach for managing the core symptoms of ASD (4). With most programs designed for young children, behavioral intervention works most effectively when initiated early. Over the past decade, the use of pharmacological treatment has significantly increased. Many emerging targeted drug therapies have demonstrated promising clinical results. Of the 68 drugs actively in clinical development as of January 20, 2025, the majority (46) are small molecules (Figure 2). Among these, two drugs, risperidone and aripiprazole, have been approved by the FDA to treat irritability and aggression in autistic children. Additionally, nine drugs are in Phase III clinical trials, three in Phase II/III, nineteen in Phase II, and thirteen in Phase I. Out of these, sixteen drugs are biological therapies, including seven cell therapies, five microbiome-based therapies, two antibody therapies, and one gene therapy. The most advanced stage for biological treatments is Phase III.

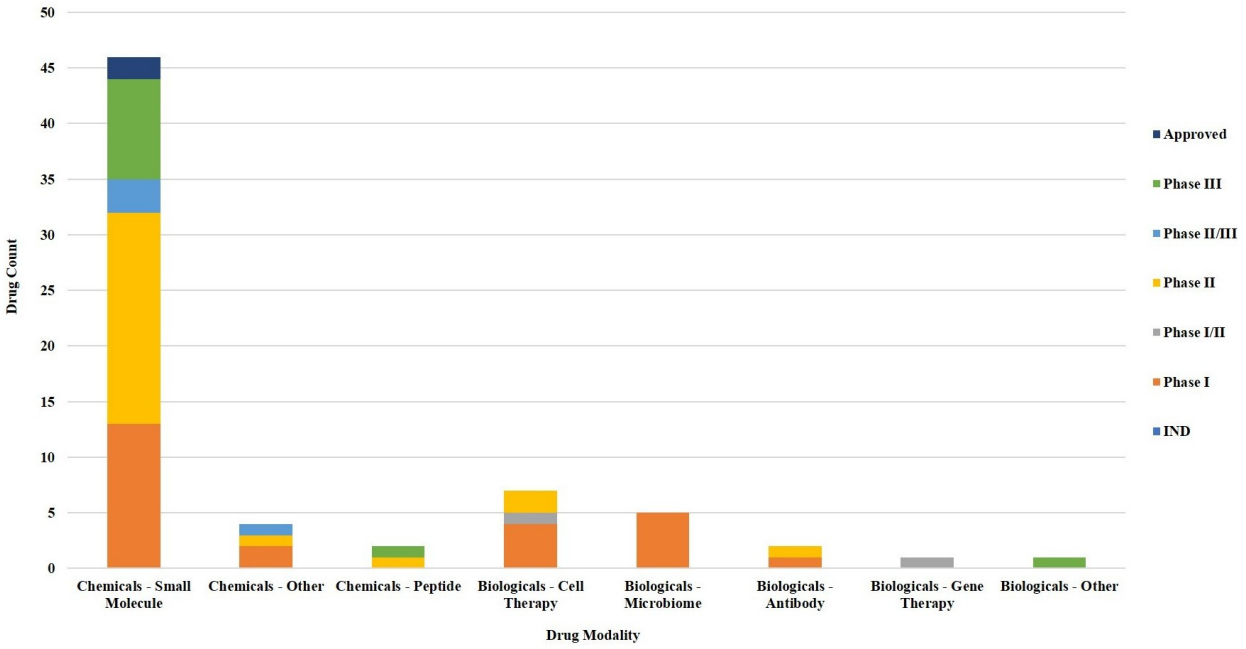

Figure 2. The majority of the drugs in clinical trials are small molecules. Drug progression in clinical trials for various categories.

Most drugs in clinical trials target synaptic signaling pathways

Drugs in active clinical development were then grouped based on molecular targets (Figure 3). Most drugs act on the synaptic signaling pathways, targeting receptors that function in the synapse, such as cannabinoid (CB) receptors, serotonin and dopamine receptors, and gamma-aminobutyric acid (GABA) receptors. Drugs with disclosed targets are listed in Table 1.

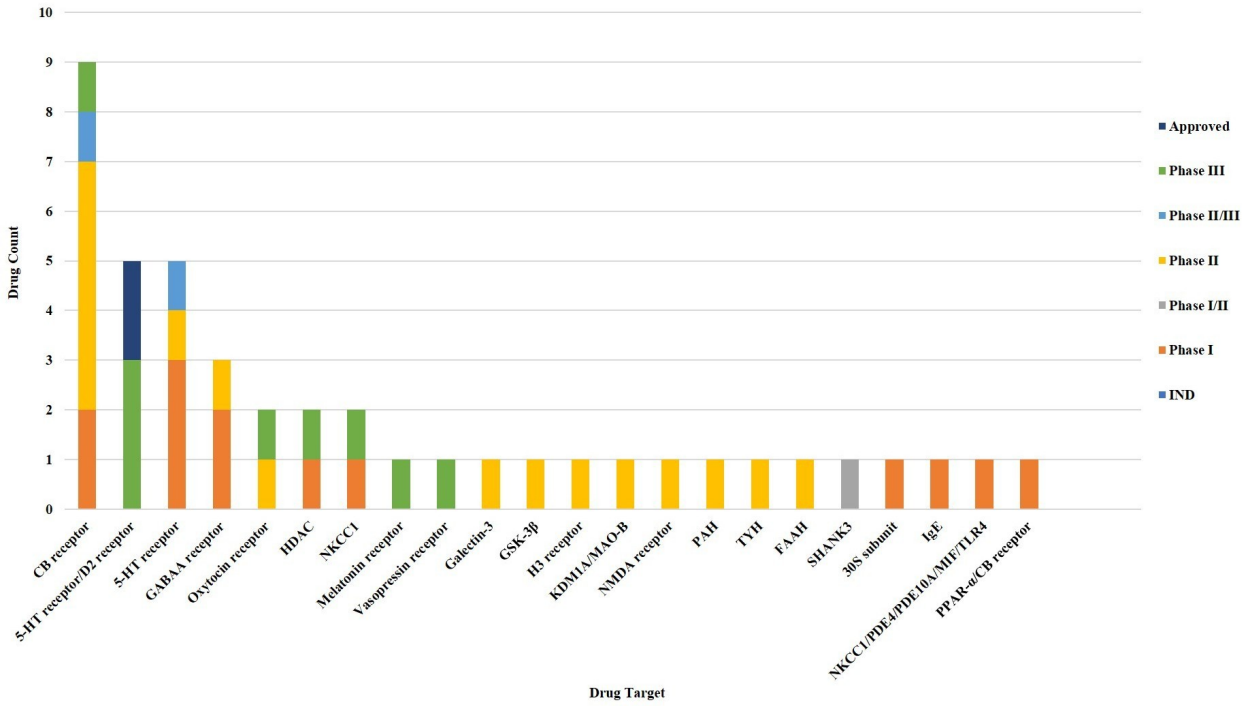

Figure 3. Most drugs target synaptic signaling pathways. Drug progression in clinical trials for the various gene targets and/or signaling pathways.

Table 1. Drugs in clinical trials with known targets for ASD

Drug Name	**Highest Phase**	**Target**	**Drug Modality**	**Original Organization**
Risperidone	Approved	5-HT receptor/D2 receptor	Small Molecule	Johnson & Johnson
Aripiprazole	Approved	5-HT receptor/D2 receptor	Small Molecule	Otsuka
Brexpiprazole	Phase III	5-HT receptor/D2 receptor	Small Molecule	Otsuka
Cariprazine	Phase III	5-HT receptor/D2 receptor	Small Molecule	Gedeon Richter
Lumateperone	Phase III	5-HT receptor/D2 receptor	Small Molecule	Bristol-Myers Squibb
Balovaptan	Phase III	AVPR1A	Small Molecule	Roche
CBD50	Phase III	CB receptor	Small Molecule	MediPharm Labs
Sulforaphane	Phase III	HDAC	Small Molecule	Evgen Pharma
Tasimelteon	Phase III	MT1/MT2	Small Molecule	Vanda Pharmaceuticals
Bumetanide	Phase III	NKCC1	Small Molecule	Neurochlore; Roche; Servier
Oxytocin	Phase III	Oxytocin	Peptide	Travere Therapeutics
Pimavanserin	Phase II/III	5-HT receptor	Small Molecule	Ipsen
Epidiolex	Phase II/III	CB receptor	Small Molecule	Jazz Pharmaceuticals

ML-004	Phase II	5-HT receptor	Chemicals - Other	MapLight Therapeutics
ZYN002	Phase II	CB receptor	Small Molecule	Harmony Biosciences
Cannabidiol	Phase II	CB receptor	Small Molecule	Virpax Pharma; Jazz Pharmaceuticals; Nanomerics
Orally Dissolving Cannabis	Phase II	CB receptor	Small Molecule	GCANRx
Cannabidivarin	Phase II	CB receptor	Small Molecule	Jazz Pharmaceuticals
JZP541	Phase II	CB receptor	Small Molecule	Jazz Pharmaceuticals
JNJ-42165279	Phase II	FAAH	Small Molecule	Johnson & Johnson
Alogabat	Phase II	GABAA receptor	Small Molecule	Roche
TB006	Phase II	Galectin-3	Antibody	Truebinding
Tideglusib	Phase II	GSK-3β	Small Molecule	Noscira
Pitolisant	Phase II	H3 receptor	Small Molecule	Bioprojet
Vafidemstat	Phase II	KDM1A/MAO-B	Small Molecule	Oryzon Genomics
Memantine	Phase II	NMDA receptor	Small Molecule	Merz Pharma
TI-001	Phase II	Oxytocin	Peptide	Trigemina
Sapropterin	Phase II	PAH	Small Molecule	BioMarin Pharmaceutical
L1-79	Phase II	TYH	Small Molecule	Yamo Pharmaceuticals
JAG201	Phase I/II	SHANK3	Gene Therapy	Broad Institute
Minocycline	Phase I	30S subunit	Small Molecule	Pfizer
Zolmitriptan	Phase I	5-HT receptor	Small Molecule	AstraZeneca
Midomafetamine	Phase I	5-HT receptor	Small Molecule	Lykos Therapeutics
Psilocybin	Phase I	5-HT receptor	Small Molecule	Sandoz
AJA001	Phase I	CB receptor	Chemicals - Other	AJNA
Palmitoylethanolamide + Cannabidiol	Phase I	CB receptor	Small Molecule	Pure Green
RO6953958	Phase I	GABAA receptor	Small Molecule	Roche
[^{11}C] Ro15-4513	Phase I	GABAA receptor	Chemicals - Other	Roche
Sodium Butyrate	Phase I	HDAC	Small Molecule	--
Omalizumab	Phase I	IgE	Antibody	Roche
IAMA-6	Phase I	NKCC1	Small Molecule	IAMA Therapeutics
STP1	Phase I	NKCC1/PDE4/ PDE10A/MIF/TLR4	Small Molecule	Stalicla
Palmitoylethanolamide	Phase I	PPAR-α/CB receptor	Small Molecule	SciSparc

CB receptors

Nine drugs target CB receptors, which are the most frequently targeted receptors in current clinical trials. CB receptors are part of the endocannabinoid system (ECS) and are located presynaptically, where they regulate neurotransmitter release. By modulating neurohormone levels and synaptic signaling, they play a critical role in synaptogenesis, plasticity, and neural connectivity (7). Thus,

drugs that target CB receptors may have potential in treating ASD.

Serotonin and dopamine receptors

Five drugs target the 5-hydroxytryptamine (5-HT) receptor and dopamine D2 receptor, including two approved drugs, risperidone and aripiprazole, and three in Phase III clinical trials; brexpiprazole, cariprazine, and lumateperone. They bind to serotonin and dopamine receptors and act as serotonin and dopamine antagonists. Excess dopaminergic D2 and serotonergic 5-HT2A activity is thought to contribute to various mood disorders (8). These drugs may help reduce this activity and alleviate ASD symptoms. In addition, five drugs, including pimavanserin, ML-004, zolmitriptan, midomafetamine, and psilocybin, target the 5-HT receptor (serotonin receptor), functioning as 5-HT agonists. These drugs do not interact significantly with dopamine receptors. Their mechanisms of action are not well studied, but through binding to serotonin receptors, they may help regulate serotonin signaling and affect ASD symptoms.

Excitatory and inhibitory synaptic targets

Several drugs in clinical trials for ASD target genes involved in excitatory and inhibitory signaling and aim to reestablish the balance between the two. Three of these drugs, Alogabat, RO6953958, and [^{11}C] Ro15-4513, target the GABA type A receptors, which mediate inhibitory neurotransmission and help maintain excitatory-inhibitory balance in the brain (3). Bumetanide and IAMA-6 are two drugs that target the sodium-potassium-chloride cotransporter 1 (NKCC1), a membrane transporter that regulates chloride ion transport. NKCC1 is essential for maintaining chloride levels inside cells, which in turn influences GABAergic signaling and the overall effects of GABA. Bumetanide and IAMA-6 inhibit NKCC1, shifting GABAergic signaling toward a more inhibitory state. This effect could potentially address the excitatory-inhibitory imbalance observed in ASD patients (9). Memantine is a drug currently in Phase II clinical trials for the treatment of ASD. It binds to N-methyl-D-aspartate (NMDA) receptors and acts as an NMDA receptor antagonist. These receptors are a subtype of the glutamate receptor in the brain involved in excitatory signaling and are crucial to learning, memory, and synaptic plasticity (10). Memantine blocks NMDA receptors and helps reduce excessive glutamate activity, which can otherwise result in neurotoxicity. Therefore, Memantine may protect neurons from damage and improve cognitive function in autistic patients (10). JAG201 is a gene therapy currently in the Phase I/II clinical stage for ASD. It uses an adeno-associated virus vector to deliver a functional copy of the SHANK3 gene to neurons. SHANK3 encodes a synaptic protein that is essential for the development and function of excitatory synapses. Mutations or deletions in SHANK3 have been observed in patients with ASD (11). By re-expressing functional SHANK3, this treatment could potentially restore the normal excitatory synaptic function in patients with ASD (11).

Other targets

Two synthetic oxytocin drugs, one in Phase III and the other in Phase II clinical trials, are being studied for ASD treatment. Both drugs target the oxytocin receptor (OTR), which has been associated with increased ASD risk (12). OTR is a G protein-coupled receptor that

activates downstream signaling when oxytocin binds to it. Oxytocin itself is a neuropeptide produced in the brain, known to affect social behavior (12). Treatment with synthetic oxytocin modulates OTR signaling and may reduce some ASD symptoms. Additionally, two histone deacetylase (HDAC) inhibitors, sulforaphane (Phase III) and sodium butyrate (Phase I), are being evaluated in clinical trials as potential treatments for ASD. These drugs regulate the expression of genes involved in synaptic function, brain inflammation, and oxidative stress. By inhibiting HDACs, they may improve the symptoms in patients with ASD (13). Tasimelteon is a melatonin receptor agonist currently in a Phase III clinical trial for ASD. It binds strongly to human melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2). These receptors regulate circadian rhythms, sleep-wake cycles, and brain development. Melatonin has been explored as a possible treatment for ASD for over twenty years. Studies have suggested that it can increase sleep duration, improve communication, and reduce social withdrawal and anxiety (14). Tasimelteon selectively activates MT1 and MT2 receptors and mimics the effects of natural melatonin. By promoting sleep regulation, it could ease some symptoms of ASD (14). Balovaptan, which targets arginine vasopressin receptor 1A (AVPR1A), is in Phase III clinical trials for ASD treatment. AVPR1A has been linked to social communication difficulties and autism (15). Balovaptan blocks AVPR1A activity, which may help rebalance the signaling involved in social behavior and improve communication. Other drugs currently in clinical trials for ASD target molecules such as the peroxisome proliferator-activated receptor alpha (PPAR-α), the histamine H3 receptor, and additional targets involved in neurodevelopment and neuronal function.

Certain drugs have shown promising efficacy in treating the core symptoms of ASD

Among the drugs in clinical trials, several aim to treat the core symptoms of ASD, such as balovaptan, cannabidiol, JNJ-42165279, memantine, sapropterin, sulforaphane, and L1-79. The results have varied, with some showing negative outcomes while others demonstrating promising efficacy in treating the core symptoms (Table 2).

Table 2. Clinical trials results for drugs targeting core symptoms of ASD

Drug Name	**Target**	**Phase**	**Trial #**	**Sponsor**	**Results**
Balovaptan	AVPR1A	Phase III	NCT03504917	Roche	Negative
JNJ-42165279	FAAH	Phase II	NCT03664232	Janssen	Negative
Alogabat	GABAA	Phase II	NCT04299464	Roche	Negative
Memantine	NMDA receptor	Phase II	NCT01592747	Forest Laboratories	Negative
Sapropterin	PAH	Phase II	NCT00850070	The Children's Health Council	Significant improvement in secondary measures
Sulforaphane	HDAC	Phase I/II	NCT02561481	University of	Significant

				Massachusetts, Worcester	improvement in secondary measures
Bumetanide	NKCC1	Phase III	NCT04766177	Sherief Abd-Elsalam	Positive ($p<0.001$)
L1-79	TYH	Phase II	NCT05067582	Yamo Pharmaceuticals	Positive ($p=0.0115$)
Cannabidiol	CB receptor	Phase II	NCT03900923	NYU Langone Health	Positive

Balovaptan, targeting AVPR1A, did not improve social communication in autistic patients in Phase III trials (16). JNJ-42165279, an inhibitor of fatty acid amide hydrolase (FAAH), did not demonstrate clinically meaningful improvements in the core symptoms of ASD in Phase II studies (17). Alogabat, targeting GABAA receptor, did not show any benefit after 12 weeks of treatment compared to placebo in a Phase II trial (18). Memantine, targeting NMDA receptors, failed to achieve the primary efficacy endpoints in a double-blind, placebo-controlled Phase II trial, although it showed considerable improvement in the social response of patients in the open-label study (19).

Sapropterin, targeting phenylalanine hydroxylase (PAH), did not exhibit significant improvement in the primary measures in the Phase II study, such as in the (Clinical Global Impressions–Improvement or severity tests) CGI-I and CGI-S (20). However, there were significant improvements in the secondary measures of social awareness, autistic mannerisms, hyperactivity, and inappropriate speech (20). These results suggested that sapropterin may offer benefits in reducing certain symptoms of ASD. Sulforaphane, targeting HDACs, demonstrated a positive effect on the primary outcome measure in the Phase I/II study, although the effect was not statistically significant (21). However, there were significant improvements in the secondary outcome measures, including in the Aberrant Behavior Checklist (21).

Bumetanide, which targets NKCC1, showed significant improvement in treating core symptoms of ASD in a Phase III clinical trial (NCT04766177), including in the Childhood Autism Rating Scale (CARS) and most other outcome measures ($p < 0.001$) (22). L1-79, targeting tyrosine hydroxylase (TYH), also showed a statistically significant improvement in the socialization standard score ($p = 0.0115$) during the first 12 weeks of the Phase II trial (NCT05067582) (23). Cannabidiol, targeting the CB receptor, significantly improved the core symptoms of ASD in a Phase II study (NCT03900923). The clinical response to cannabidiol was dose-dependent, with mean CGI-I scores ranging from 3.17 at 3 mg/kg/day ($n = 6$) to 2.56 at 6 mg/kg/day ($n = 9$), and 2.25 at 9 mg/kg/day ($n = 8$) (24).

Correlation of drug responses with target gene expression profiles

The expression profiles of these drug-targeted genes in healthy subjects and individuals with ASD were then analyzed to assess whether there existed a correlation between gene expression and drug efficacy. Some of these molecular targets were differentially expressed

in ASD patients compared to healthy controls, as demonstrated by RNA-seq data summarized from the literature (Table 3) (25–29). Gene Ontology (GO) enrichment analysis revealed that upregulated genes were enriched in GO categories related to immune, inflammatory response, cell adhesion, and regulation of cell proliferation, while downregulated genes were enriched in GO categories implicated in synaptic function (25, 30).

Additionally, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis showed significant enrichment of synaptic signaling, neurodevelopmental, and glutamatergic pathways in ASD samples compared to controls (31).

Table 3. Differential expression of ASD drug targets in patients compared to controls.

Gene Symbol	Description	DE P-Value	Reference
GABRA1	GABAA Receptor Subunit Alpha-1	$1.55x10^{-5}$	(25)
HDAC1	Histone Deacetylase 1	$3.15x10^{-5}$	(25)
OXTR	Oxytocin Receptor	$1.16x10^{-4}$	(25)
GRIN2A	NMDA Receptor Subunit 2A	$4.97x10^{-4}$	(25)
GRIN3A	NMDA Receptor Subunit 3A	$5.35x10^{-4}$	(26)
LGALS3	Galectin-3	$2.90x10^{-3}$	(25)
CB2R (CNR2)	Cannabinoid Receptor 2	$3.0x10^{-3}$	(27)
SHANK3	Sh3 And Multiple Ankyrin Repeat Domains 3	$6.58x10^{-3}$	(28)
HTR3B	5-HT Receptor 3B	$8.42x10^{-3}$	(25)
HTR2C	5-HT Receptor 2C	0.01	(25)
MAO-B	Monoamine Oxidase B	0.02	(26)
GRIN2C	NMDA Receptor Subunit 2C	0.02	(26)
CB1R (CNR1)	Cannabinoid Receptor 1	0.06	(27)
DRD1	Dopamine Receptor D1	0.06	(26)
HTR1F	5-HT Receptor 1F	0.10	(26)
KDM1A	Lysine Demethylase 1A	0.13	(26)
HTR2A	5-HT Receptor 2A	0.17	(26)
HRH3	Histamine H3 Receptor	0.17	(26)
FAAH	Fatty Acid Amide Hydrolase	0.36	(26)
SLC12A2 (NKCC1)	Solute Carrier Family 12 Member 2	0.51	(26)
GSK-3β	Glycogen Synthase Kinase 3 Beta	0.99	(26)
AVPR1A	Arginine Vasopressin Receptor 1A	> 0.05	(29)
PAH	Phenylalanine Hydroxylase	NR	
TYH	Tyrosine Hydroxylase	NR	
MTNR1A (MT1)	Melatonin Receptor 1A	NR	
MTNR1B (MT2)	Melatonin Receptor 1B	NR	

DE: differential expression, NR: not reported.

Based on the DE p-values, GABRA1 (GABAA receptor subunit alpha-1), HDAC1 (histone deacetylase 1), OXTR (oxytocin receptor), GRIN2A (NMDA receptor subunit 2A), GRIN3A (NMDA receptor subunit 3A), LGALS3 (Galectin-3), CB2R (cannabinoid receptor 2), SHANK3 (SH3 and multiple ankyrin repeat domains 3), and HTR3B (5-HT receptor 3B) showed strong differential expression, with p-values < 0.01 (26-30). These genes were significantly dysregulated in ASD, implying a stronger rationale for therapeutic targeting and greater potential for drug efficacy. For example, drugs targeting 5-HT receptor/D2 receptor, such as risperidone and aripiprazole, have been approved for use in children with autism, though not for core symptoms. Cannabidiol, which targets cannabinoid receptors, and sulforaphane, an HDAC inhibitor, demonstrated significant improvements in the core-symptoms of ASD in Phase II clinical trials (21, 24). Memantine, an NMDA receptor antagonist, showed significant improvements in the social response of patients in the open-label study (19). However, Alogabat, which targets the GABAA receptor, did not show any clinical benefit (18). Clinical efficacy data are still pending for TI-001 (targeting OXTR, Phase II), TB006 (targeting Galectin-3, Phase II), and JAG201 (SHANK3 gene therapy, Phase I/II).

In contrast, some drugs demonstrated significant improvement in the core symptoms of ASD, even though their targets were not differentially expressed in ASD patients. Bumetanide targets NKCC1, whose expression is not significantly altered in ASD patients. Nevertheless, bumetanide showed significant improvement in treating the core symptoms of ASD (22), potentially by modulating NKCC1 function, rather than by its expression. Similarly, the two enzymes PAH and TYH are not differentially expressed in ASD, but sapropterin (targeting PAH) and L1-79 (targeting TYH) exhibited improvements in treating ASD by modulating enzymatic activity and regulating dopamine synthesis (20, 23).

Additionally, the number of drugs targeting each gene at each clinical stage was quantified, as shown in Table 4. Clinical trial activity was calculated as the sum of the number of drugs associated with the corresponding DE p-values, each multiplied by an arbitrary weighting factor based on the clinical trial stage, and was subsequently plotted against the DE p-values. The weighting factors were 1, 1.5, 2, 2.5, 3, and 4 for Phases I, I/II, II, II/III, III, and approved stages, respectively (Table 4). It is apparent that clinical trial activity is not solely affected by the differential gene expression in ASD; other factors, such as off-target effects, formulation, and toxicity profiles, also play a role. However, the activity did seem to congregate at p values between 3E-03 and 8E-03 (Figure 4), which may serve as a first-approximation indicator: very low expression may correlate with disproportionately low activity, while very high expression may be associated with increased off-target effects and toxicity. Since clinical trial success is time-dependent, it should be noted that clinical trial activity may not directly correlate with clinical success. However, a first-mover advantage may reflect positive clinical and market sentiment centered around the aforementioned p-values.

Table 4. The number of drugs at each clinical stage for each drug target with differential expression p-values is shown below. For drugs that target a family of genes, the counts were assigned to the gene with the lowest p-value. For instance, within the NMDA receptor family, the drugs were counted under GRIN2A only, while the counts for other genes such as GRIN3A or GRIN2C were marked as not determined (ND).

Gene Symbol	Description	DE P-Value	Approved	Phase III	Phase II/III	Phase II	Phase I/II	Phase I
GABRA1	GABAA Receptor Subunit Alpha-1	$1.55x10^{-5}$	0	0	0	1	0	2
HDAC1	Histone Deacetylase 1	$3.15x10^{-5}$	0	1	0	0	0	1
OXTR	Oxytocin Receptor	$1.16x10^{-4}$	0	1	0	1	0	0
GRIN2A	NMDA Receptor Subunit 2A	$4.97x10^{-4}$	0	0	0	1	0	0
GRIN3A	NMDA Receptor Subunit 3A	$5.35x10^{-4}$	ND	ND	ND	ND	ND	ND
GRIN2C	NMDA Receptor Subunit 2C	0.02	ND	ND	ND	ND	ND	ND
LGALS3	Galectin-3	$2.90x10^{-3}$	0	0	0	1	0	0
CB2R	Cannabinoid Receptor 2	$3.0x10^{-3}$	0	1	1	5	0	2
CB1R	Cannabinoid Receptor 1	0.06	ND	ND	ND	ND	ND	ND
SHANK3	Sh3 And Multiple Ankyrin Repeat Domains 3	$6.58x10^{-3}$	0	0	0	0	1	0
HTR3B	5-HT Receptor 3B	$8.42x10^{-3}$	2	3	1	1	0	3
HTR2C	5-HT Receptor 2C	0.01	ND	ND	ND	ND	ND	ND
DRD1	Dopamine Receptor D1	0.06	ND	ND	ND	ND	ND	ND
HTR1F	5-HT Receptor 1F	0.10	ND	ND	ND	ND	ND	ND
HTR2A	5-HT Receptor 2A	0.17	ND	ND	ND	ND	ND	ND
MAO-B	Monoamine Oxidase B	0.02	0	0	0	1	0	0
KDM1A	Lysine Demethylase 1A	0.13	ND	ND	ND	ND	ND	ND
HRH3	Histamine H3 Receptor	0.17	0	0	0	1	0	0
FAAH	Fatty Acid Amide Hydrolase	0.36	0	0	0	1	0	0
SLC12A2 (NKCC1)	Solute Carrier Family 12 Member 2	0.51	0	1	0	0	0	1
GSK-3β	Glycogen Synthase Kinase 3 Beta	0.99	0	0	0	1	0	0
AVPR1A	Arginine Vasopressin Receptor 1A	> 0.05	0	1	0	0	0	0
PAH	Phenylalanine Hydroxylase	NR	0	0	0	1	0	0
TYH	Tyrosine Hydroxylase	NR	0	0	0	1	0	0
MTNR1A	Melatonin Receptor 1A	NR	0	1	0	0	0	0
MTNR1B	Melatonin Receptor 1B	NR	ND	ND	ND	ND	ND	ND

DE: differential expression; NR: not reported; ND: not determined

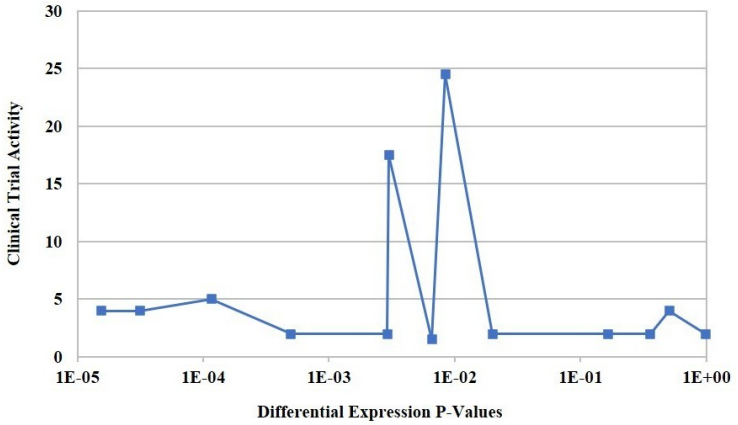

Figure 4. Clinical trial activity peaks at moderate differential expression p-values. The X-axis is logarithmic. Clinical trial activity is found by summing the columns of Table 4, for relevant rows of p-values.

It is clear that genes showing significant dysregulation in ASD often provide a stronger rationale for therapeutic targeting. These genes are more likely to be involved in the underlying pathogenic mechanisms of ASD. Therefore, drugs targeting them may have a higher likelihood of being efficacious. However, clinical activity seems to be greatest for drugs that target genes that show modest (but not large) differential expression. It may be speculated that greater differential expression may be associated with genes that significantly influence multiple signaling pathways; thereby causing off-target or toxic effects for drugs that use these as targets. Conversely, drugs targeting moderately expressed genes may exert therapeutic effects by modulating protein function (rather than expression), altering signaling pathways sufficiently downstream, or targeting systems whose transcriptomic dysregulation is – for the most part – confined to narrow physiological domains.

Discussion

Autism spectrum disorder affects ~ 2.8% of children in the United States (1/36), and no specific pharmacologic treatments address the core symptoms. The two FDA-approved drugs, risperidone and aripiprazole, treat irritability and aggression in children with autism, but do not target the core symptoms (2). Thus, there is an urgent need to develop pharmacologic treatments specifically for the core symptoms. Significant progress has been made over the last decade, with many drugs currently in development. Some of these drugs, including cannabidiol, memantine, bumetanide, and sapropterin, are being investigated in clinical trials to treat the core symptoms of ASD, despite already being approved for other conditions, like migraine, sleep disturbances, and anxiety (4). Most drugs in clinical trials are small molecules, with a limited number of drugs being biologics. The genes involved in the synaptic functions are the main targets for pharmacologic drug development, especially the endocannabinoid system, serotonin/dopamine signaling, and GABAergic signaling. While some drugs have not demonstrated efficacy in clinical trials, others,

such as bumetanide, L1-79, and cannabidiol, have shown promising efficacy in treating the core symptoms of ASD. However, further studies are needed to validate their safety and effectiveness before being approved for use. Additionally, numerous drugs are in the preclinical stage. Differential gene expression analysis, alongside GO and KEGG pathways enrichment analysis, is emerging as a valuable strategy for identifying promising drug targets for ASD. Furthermore, as more ASD risk-associated genes are identified, gene therapy is gaining more interest as a potential approach to edit the genes at risk and restore their normal function.

Despite the structured approach used in this paper, some limitations need to be acknowledged. The analysis was based on publicly available clinical trials, which may be incomplete or not up to date. In some cases, the drug targets and drug modalities were obtained from the literature rather than being explicitly stated in trial records. Moreover, the limited number of large-scale Phase III studies makes it difficult to assess how broadly the current efficacy findings for treating core ASD symptoms can be applied. Regular follow-up and cross-referencing multiple data sources will be needed to provide a timely and comprehensive view of the evolving ASD treatment landscape.

Conclusion

In summary, this work analyzed the current clinical therapeutic landscape of ASD. While no FDA-approved treatments target the core symptoms of ASD, significant progress has been made in drug development. As of January 20, 2025, 68 drugs were in active clinical development, the majority of which are small molecule drugs. Synaptic signaling is a major focus of drug development, likely due to the involvement of many risk-associated genes in synaptic function. Some of these drugs have shown encouraging safety and efficacy results in clinical studies. Additionally, moderate differential gene expression was found to be most correlated with clinical trial activity; probably because of efficacy deficit at the lower end and toxicity and off-target effects at the higher. It is hence tantalizing to speculate that targeting those genes that are moderately (but not excessively) expressed in ASD – or, indeed, in any disease – may yield the most clinically productive molecules for therapeutic intervention. This work provides insights into future trends in ASD drug development and may help guide future research efforts.

Acknowledgments

I would like to thank Dr. Yuelin Yang for providing guidance on literature searches, reference citations, and drug research.

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