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Drug Discovery, Development and Precision Medicine for Autism Spectrum Disorder: A Personal Opinion on the Current State

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Scoping review

Abstract

Introduction: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder/condition. Medical interventions for this condition are mainly pharmacological, and generally not tailored to precisely address the specific underlying issues in each ASD individual. Despite the extensive efforts to develop new or repurpose existing drugs over the decades, the range of medications that address this condition remains very limited.

Findings: Progress in drug development has been hindered by research design limitations and the complex, heterogeneous nature of the ASD itself. Therefore, this article first discusses preclinical and clinical studies aimed at finding effective treatments, highlighting their shortcomings and potential solutions. It then delves into the complexity of ASD and the implications for drug development, such as its phenotypic and genetic heterogeneity and multifactorial etiology, and unclear diagnostic boundaries with other developmental disorders.

Exploiting the advantages of new technologies, current autism treatment research is steering towards prioritizing genetic and molecular data over phenotypic data, emphasizing the need for biologically meaningful and quantifiable biomarkers to identify biologically defined and clinically actionable subgroups within ASD, amenable to specific treatments.

The critical role of precision medicine is underscored as a comprehensive, fundamental approach to biology-based drug development and personalized treatments. Achieving this goal requires an integrated analysis of multilayered data, utilizing multi-omics, systems biology, and machine learning approaches.

Conclusion: Lastly, the article provides a brief overview of current initiatives and private sector efforts focusing on precision medicine treatments for neurodevelopmental disorders, highlighting their progress in developing drugs through this innovative approach.

Keywords: Autism, drug development, biomarkers, multi-omics, precision medicine

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1. Introduction

Autism Spectrum Disorder (autism) is a neurodevelopmental disorder characterized by impaired social communication and interaction and repetitive behaviours and interests. The worldwide prevalence of ASD is characterized by steady increase, with variations across countries and regions. It is estimated that around 1% of the world population is affected by ASD (Talantseva et al., 2023).

ASD is usually treated with non-medical (behavioural, speech and language, occupational, educational etc.) interventions and/or medical treatments. The former are considered as primary, as they aim to address the core symptoms of ASD (Aishworiya et al., 2022), while the latter, mostly pharmacological, manage the associated symptoms and co-occurring conditions like irritability, ADHD, sleep disorders etc. (Persico et al., 2021).

Based on the advances in the basic neuroscience understanding of ASD, the last couple of decades were marked by intense autism intervention research. Although some progress in pharmacological interventions for ASD was produced, still, only two medications, the atypical antipsychotics risperidone and aripiprazole are approved by the regulatory agencies for ASD, solely for alleviating irritability. The currently available pharmacological options (either approved or off-label) are incapable of improving the fundamental, core deficits of ASD (McCracken et al., 2021).

Admittedly, a number of challenges have emerged over the years, hindering the progress of developing medications for ASD, including the heterogeneity of the condition (in the clinical presentation, etiology with intricated genetic and environmental causes), symptom overlap and blurry boundaries with other neurodevelopmental (NDD) and psychiatric disorders, as well as uncertainty and lack of consensus regarding the design, conduction of preclinical and clinical trials and validity of study outcome measures and endpoints (Baribeau & Anagnostou, 2021). Nevertheless, continuous efforts and innovative approaches are arising to surmount these challenges, facilitating faster and more efficient drug development for autism and neurodevelopmental disorders. Cutting-edge technologies utilize powerful, high throughput methods that integrate large amounts of data to profile autism subtypes, leveraging genetics, systems biology and clinical presentation. Multi-omics, machine learning and artificial intelligence aided approaches pave the way to targeted, precision medicine treatments.

This article examines the acknowledged challenges and limitations that burden the research and development of pharmacological interventions for ASD. It also explores the potential new pathways and efforts toward innovative, patient-centered treatments.

To provide a concise and accessible overview of the topic, the following databases were searched for relevant articles: PubMed, Google Scholar, and the Cochrane Database of Systematic Reviews. Additionally, the clinical trials databases ClinicalTrials.gov and the European Union Clinical Trials Register were explored for reports on interventional clinical studies for autism. Nevertheless, this article is not an exhaustive overview of all relevant literature and data on autism drug development; rather it reflects the author's perspective on this evolving process.

2. Identified limitations and challenges for drug development for autism

Interest in researching new therapeutic options for autism is expanding. To illustrate, searches of two online clinical study databases were conducted. On ClinicalTrials.gov, using the keyword "autism" and selecting interventional studies, 1,410 studies were found as of May 2024, with about 427 ongoing (ClinicalTrials.gov, 2024). The European Union Clinical Trials Register (2024) revealed 85 autism interventional studies, 41 of which are ongoing. However, it's important to note that these examples only include clinical interventional studies, which are the final steps in a series of trials for proving a drug's suitability for a specific disorder. Developing new drugs, from candidate molecules to safe, effective products, is a complex, long-term process involving academia, biopharmaceutical industry, and regulatory bodies (Díaz-Caneja et al., 2021).

2.1 Implementation of preclinical and interventional clinical trials

2.1.1 Translation of basic and preclinical to clinical trials

Despite progress in developing numerous preclinical, in vivo, animal models for ASD, these studies often fail to translate their results to human clinical studies (Kostić & Buxbaum, 2021). Fundamental differences in brain development and function, particularly the neocortex, between humans and animals limit animal models' ability to replicate human brain development and reliably identify the mechanisms leading to neurodevelopmental disorders. The failure of clinical trials based on successful animal studies confirms this limitation (Zhao & Bhattacharyya, 2018). Szatmari, Charman & Constantino (2012) use the term "valley of death", describing the gap between basic and preclinical ASD research and clinical trials. They emphasize the importance of bridging both the gap from preclinical to clinical studies and from clinical studies to real-world practice.

In vitro models utilizing human induced pluripotent stem cells (iPSC) hold promise for overcoming this barrier. These models generate neuronal cultures or 3D organoids with the genetic-molecular signature of individuals with ASD, enabling the study of pathogenetic mechanisms. Brain organoids derived from pluripotent stem cells retain the human genomic signature, aiding the investigation of monogenic and polygenic alterations in autism (Baldassari et al., 2020). Moreover, being a tool for understanding underlying

pathophysiology of the investigated cells, this technique can also be used for high-throughput screening of drugs or drug-like compounds and point to potential candidate medications, targeting specific molecular entities for ASD. It also shows promise in identifying responders to specific therapies, as it enables testing the effects of drugs on patient-derived cultured neurons (Darville et al., 2016; Kostić & Buxbaum, 2021; Rao et al., 2022; Villa et al., 2021).

The value of iPSC in drug development, has its limitations (e.g., an inherent inability to assess clinical efficacy, side effects, and issues related to pharmacodynamics, metabolism of the candidate medication by other cell types, etc.), but efforts are being made to overcome these challenges (Ortuño-Costela et al., 2019).

2.1.2 Clinical study design

Neuropsychiatric research, including clinical interventional studies and biomarker testing in ASD, commonly employs a case-control design, treating the condition as a uniform group. In the clinical interventional studies, the ASD group receiving the investigated treatment is compared (in terms of efficacy and safety) to the group of controls, usually matched persons with autism who either receive no treatment or a "standard" treatment. While these studies assess the statistical significance of mean value differences between groups, they often overlook the within-group variability. This methodological approach is inadequate for the notably heterogeneous ASD population from which the research sample is drawn (Loth et al., 2021b). In many of these studies, a subset of participants appears to respond to the treatment very well, but a significant benefit is not found in the overall treated group, due to the etiological heterogeneity of ASD (Beversdorf et al., 2023).

Another concern arises from studies with small sample sizes. Such studies may suffer from low statistical power, as well as the possibility of effect size inflation. Over time, attempts at replication often fail to reproduce the originally reported effects due to the likely overestimation of effect sizes in the small-sample studies (Lombardo et al., 2019).

An approach could be particularly useful in evaluating treatments in conditions where it is difficult to obtain a large number of participants or in highly clinically heterogeneous conditions, in evaluating treatments. In this design, individuals who are about to receive an investigational agent serve as their own controls, as it monitors the changes (often biomarker changes alongside clinical parameters) observed in each individual over a specified period of time (Clayton, 2019).

2.1.3 Outcome measures and endpoints in clinical studies

Effective therapy assessment relies on quality outcome measures and selected study endpoints. Despite prior efforts, consensus on outcome measures in ASD intervention studies remains elusive. While core and associated symptoms improvements are typical study endpoints, evaluating changes in problem behaviour, cognitive skills, quality of life, and global functioning is also crucial (Provenzani et al., 2021).

Most ASD drug trials use parent- or professional-filled questionnaires/scales as outcome measures. Since these instruments primarily serve for ASD diagnosis/screening, they are ill-suited for assessing therapy-induced change over time. These instruments are relatively insensitive to changes, and unsuitable for repeated administration at short intervals to track treatment trajectory. Moreover, whether completed by parents or professionals, they are inherently subjective and susceptible to placebo and other non-specific effects (Wang, 2019).

2.1.4 Placebo effect/response in clinical studies

The significant placebo effect/response, observed in numerous clinical studies assessing potential ASD treatments, is concerning. This effect can obscure or minimize the differences between the drug (intervention) group and the control group, potentially leading to the failure of clinical trials and the unjustified dismissal of effective drugs as therapeutic options. Various factors are assumed to be the reason for the large placebo response in the population of children with autism, such as: increased expectation/hope of parents for their children participating in clinical trials, the course and changes over time in the symptomatology of autism which often includes periods of improvements and exacerbation, the attention and care that the participants/parents in the clinical trial receive (King et al., 2013).

To minimize the risk for large placebo response in interventional clinical studies in ASD, possible predictors of placebo should be taken into account. These include participant related factors (e.g., baseline ASD severity, presence of an associated condition) and design- and intervention-related factors (e.g., participant selection, caregiver ratings of improvement) (Siafis et al., 2020). Most importantly, clinical studies must incorporate more objective and measurable endpoints to mitigate the significant placebo effect (Pérez-Cano et al., 2023).

2.1.5 Optimal time for intervention

Autism is a developmental disorder, with its roots beginning during intrauterine life. Some autistic individuals likely develop their neurodevelopmental phenotype as a consequence of a perinatal or neonatal complications. Research by Satterstrom et al. (2020) indicates that many risk genes for ASD are expressed during middle to late gestation. However, these genes can have varying roles throughout life. Similarly, epigenetic and environmental risk factors can impact different developmental periods, starting from fetal life. Thus, identifying the optimal age for intervention in clinical studies is crucial. While clinical trials for ASD medications typically begin with adults for safety reasons, the target population for these therapies is often in early childhood, when the biological processes they target are developing. Therefore, the failure of a drug to demonstrate benefit in adults with

ASD may be due to its administration at an age where the relevant developmental processes have already completed (Baribeau & Anagnostou, 2021; McCracken et al., 2021; Veenstra-VanderWeele & Warren, 2015).

2.2 Problems related to the ASD itself

2.2.1 Phenotypic heterogeneity of ASD

Despite commonly shared characteristics, autism exhibits significant inter-individual variations, including diverse symptom presentations even within monogenic forms (McCracken et al., 2021). These differences span etiology, pathogenesis, developmental trajectory, cognitive and behavioural traits, adaptive functioning, therapy response, prognosis, and outcome (Lombardo et al., 2019). Moreover, ASD individuals have higher rates of co-occurring developmental, neuro-psychiatric, immunological, and other medical conditions compared to the general population (Koceski & Trajkovski, 2021; Trajkovski et al., 2008), including cancers (Trajkovski, 2024; Vuković et al., 2023; Wells, 2022), indicating a multifaceted, multisystemic condition often referred to as "autisms". Beyond a mere nosological concern, this heterogeneity poses a clinical challenge and significantly impedes the development of effective pharmacological treatments.

2.2.2 Unclear diagnostic boundaries with other developmental and neuropsychiatric disorders

Core and associated characteristics of ASD often coincide with those of other developmental and psychiatric disorders, and this coincidence has also a genetic ground – ASD has a strong genetic correlation with other neurodevelopmental disorders (Satterstrom et al., 2020). For instance, deficits in the social domain are common in children with ADHD, and hyperactivity/impulsivity symptoms are frequently seen in children with ASD. Approximately three-quarters of genetic variability in ASD is shared with ADHD (Lichtenstein et al., 2010). The unclear diagnostic boundaries carry the potential for inadvertently including participants with unclarified, uncertain or even mistaken ASD diagnoses in clinical trials, which can further result in compromised study outcomes and failure to replicate findings. Research trends support a dimensional view of psychopathology, contrasting the categorical orientation prevalent among clinicians. However, for drug approval studies, a categorical orientation is exclusively accepted, necessitating subjects' inclusion based on established diagnostic categories (Baribeau & Anagnostou, 2021).

2.2.3 Genetic heterogeneity and multifactorial etiology of ASD

Autism is a condition with solid genetic background, but also environmental influences contribute to the risk for developing autism. In support of this, the concordance for ASD in monozygotic twins is not 100%, but lower. Heritability amounts to 70-80% (h2 = 0.7-0.8) (Ramaswami & Geschwind, 2018).

The genetic architecture of ASD is extremely complex. Several modes of genetic variability have been identified that can contribute to the risk for ASD (Iakoucheva, Muotri & Sebat, 2019; Ramaswami & Geschwind, 2018):

- highly penetrant, rare, de novo mutations in one gene, which lead to the loss of functions of the gene. These are often mutations in only one nucleotide in a gene [single nucleotide variants (SNVs)].
- copy number variants (CNVs) – duplications or deletions of more than 1000-2000 base pairs in one chromosome, occurring de novo or inherited.
- single nucleotide polymorphisms (SNPs) – frequent, common gene variants. These are not considered as mutations, have a small effect and contribute additively to the total polygenic risk for ASD.

Recent whole-genome sequencing studies of families with multiple ASD-affected children detected a significant risk contribution from rare inherited variants, which was not found in simplex families. Autistic children from multiplex families show an increased burden of rare inherited variants in known ASD risk genes, and the ASD polygenic risk score is overtransmitted from nonautistic parents to these children. This suggests an additive genetic risk architecture involving combinations of both rare and common variations (Ruzzo et al. 2019, Cirnigliaro et al., 2023).

ASD is also observed in individuals with some monogenic syndromes (such as the fragile X-chromosome syndrome, Rett syndrome, Timothy syndrome, etc.) and syndromes caused by large chromosomal rearrangements (e.g. Down syndrome). Then, there are possible influence on the risk for ASD from mutation in the non-coding part of the genome, the effects of which are difficult to ascertain. Further adding to the complexity, the majority of ASD-associated genes exhibit pleiotropy, variable expression, incomplete penetrance and are behaviourally non-specific (Baribeau & Anagnostou, 2021).

When all this is complemented with the epigenetic and environmental contribution for the individual risk for ASD, identifying a clear biological target for future treatments becomes challenging. Additionally, recruiting homogeneous sample sizes for studies is difficult. Researchers hope that stratifying genetic variants into common pathways and characterizing ASD genetic subtypes will lead to internally homogeneous and biologically distinct clusters, facilitating targeted therapies and precision medicine (Baribeau & Anagnostou, 2021).

3. Possible directions for overcoming limitations in drug development

Utilizing the advantages of new technologies, autism research is adopting a "genetics first" or "molecular data first" instead of the traditional "phenotype first" approach, prioritizing genetic and molecular data

over phenotypic data for studying and stratifying ASD (Arnett, Trinh & Bernier, 2019).

So far, no single biological characteristic, molecular pathway, or biomarker common to the majority of persons with ASD has been identified. Instead, shared clinical traits may result from diverse underlying pathophysiological mechanisms. Consequently, drug therapies for ASD can only be effective in certain individuals, depending on both the drug's pharmacodynamics and the individual's autism pathophysiology. Thus, the focus in ASD drug therapy is on precision or stratified medicine, using biomarkers to identify homogeneous subgroups within the ASD or NDD affected population. These subgroups, which will have distinct biological characteristics, could then be selectively included in clinical trials to expedite drug development (Loth, 2021a).

Beversdorf et al. (2023) suggest adding “Phase 2m”, a marker exploration phase to the process of clinical drug development, It should include a set of biomarkers in a moderately large participant pool in order to determine which subjects respond best, thus guiding the design and statistical power of subsequent phase 2 and 3 trials.

One of the approaches that holds promise for identifying biomarkers and appropriate stratification for ASD is the "multi-OMICS". This approach integrates research across various domains, including genetics, epigenetics, transcriptomics, proteomics, metabolomics, microbiome testing, neuroimaging, eye-tracking and other (Beversdorf, 2016; Mesleh, 2021). In fact, the power of the precision medicine comes exactly from the integrative analysis of multidimensional datasets (Kostić & Buxbaum, 2021), i.e., from combining "multi-OMICS" knowledge. Analyzing the multilayered volumes of biomedical data enables the identification of patient subgroups with shared pathophysiology and potential for precise, targeted therapy.

As summarized by Pérez-Cano et al. (2023, p.9), in order to overcome the current obstacles and problems encountered in previous ASD clinical studies, it is crucial to use robust modeling strategies that account for ASD heterogeneity by ensuring cross-cohort replication. Additionally, in order to mechanistically identify changes in core deficits upon therapy, quantifiable biomarkers are required as primary endpoints. Measurable endpoints will make it possible to evaluate treatment effects more precisely and avoid the large placebo effect that has been seen in previous clinical trials.

4. Current efforts and initiatives

Several academic-led projects, biotech companies, and collaborative initiatives are exploring the integration of large datasets and developing computational models to characterize and stratify individuals with ASD. These efforts aim to enhance precise diagnostics and support the creation of precision medicine-based therapies. Utilizing clinical data, systems biology, multi-omics, and machine learning technologies, these initiatives guide the development of treatments for autism and other heterogeneous conditions. Examples of such projects are presented below.

AIMS-2-TRIALS (Autism Innovative Medicine Studies-2-Trials) was a European multicenter consortium aimed at developing precision treatments for autism. The consortium conducted a variety of studies to examine the biology of autism, its developmental trajectories, and variability. Observational studies were performed at multiple levels to identify and validate diagnostic and prognostic biomarkers for specific subgroups. Additionally, the research investigated biomarkers that could predict therapeutic responses and explored new drugs (AIMS-2-TRIALS, 2024; Loth, 2021a).

POND (Province of Ontario Neurodevelopmental Disorders Network) is a Canadian integrated research network focusing on understanding the neurobiology of autism and other NDDs, and translating these findings into effective treatments. POND employs various research platforms, including genetics, epigenetics, immunology, behaviour, cognition, and neuroimaging. By May 2024, over 3,000 individuals with neurodevelopmental disorders and controls were assessed across these platforms. Comprehensive clinical, behavioural, and biological data from each participant are collected and analyzed to enhance understanding of underlying biology and accelerate the development of targeted interventions (POND, 2024).

The Swiss biopharmaceutical company Stalicla has developed a sophisticated platform integrating systems biology, multi-omics, and machine learning to identify biologically-based subgroups of individuals with neurodevelopmental disorders (NDDs) and guide the development of tailored treatments. Using this platform, a clinically and biologically defined subgroup of patients with ASD (ASD Phenotype 1) was identified.

This subgroup exhibits a convergent molecular pathophysiology characterized by metabolic and transcriptomic alterations linked to hyperactivation of NF-κB and NRF2 transcription factors. Clinically, it is defined by two non-behavioural signs: an enlarged head circumference and worsening of core ASD symptoms during infections or fevers. The subgroup was clinically confirmed, and the biological convergence related to NF-κB and NRF2 dysregulation was validated in an observational and bio-sampling study of individuals with idiopathic ASD. Screening for drugs to address these transcriptional alterations led to the identification of STP1, a combination of a PDE4/3 inhibitor (ibudilast) and an NKCC1 inhibitor (bumetanide), which effectively down-regulated NRF2 and NF-κB in vitro, in patient-derived cell lines.

The safety and tolerability of STP1 were confirmed in a randomized, double-blind, placebo-controlled, parallel-group phase 1b study involving ASD Phenotype 1 adults. Pharmacokinetic endpoints, electrophysiological parameters, and pharmacodynamic/efficacy

were secondary endpoints in this phase. Future phase 2 and 3 studies with larger number of participants and longer exposure are anticipated to test the efficacy in this subpopulation of ASD (Pérez-Cano et al., 2024; Gomez-Mancilla et al., 2024).

These developments support the employment of integrative systems biology to characterize mechanistically defined and clinically actionable subgroups in ASD, thereby advancing appropriately tailored treatments (Pérez-Cano et al., 2024).

5. Conclusions

Autism and the other neurodevelopmental disorders are behaviourally defined conditions without confirmed biological bases. Diagnostic constructs and classifications of NDD have proven unpredictive of underlying pathophysiology, as diverse physiological distortions are found in individuals with the same NDD diagnosis. Consequently, "one-size-fits-all" treatments based solely on the (behaviourally based) diagnoses are unlikely to yield significant improvements, as they cannot compensate or correct the particular physiological deficit present in each affected individual.

Over the decades, basic autism research and preclinical trials of promising new treatments have failed to translate into successful early-stage clinical trials. Similarly, numerous clinical trials attempting to repurpose existing medications for autism have yielded unconvincing effectiveness results and failed to be replicated.

As discussed, current methods of conducting interventional clinical studies are not entirely suitable for testing drugs for highly heterogeneous conditions. Participants are recruited based solely on their diagnosis, without using biomarkers predictive of treatment response.

Outcome measures and endpoints are often subjective and unquantifiable, and results are evaluated based on endpoint mean values, which are unlikely to show significant differences from the placebo, in heterogeneous groups. Cases within the test group that exhibit extraordinary response to the treatment are often overlooked because they contribute little to the mean values. This leads to failed clinical trials and disappointing conclusions. All this points to the need for biology-centered drug development for autism, focusing on creating medications that address various disrupted molecular pathways, which may converge into specific autism subgroups with shared underlying pathophysiology. Advanced technology can now integrate and analyze extensive data (from genetic to environmental) to discern subgroups and guide appropriate drug selection and development. We are already seeing bold attempts in this direction. Although not a fast-track or straightforward alternative, this comprehensive bottom-up approach is worth exploring and committing to, as it aims to address the fundamental causes of autism and their consequences.

Conflict of interests

The author has no relevant conflict of interests to declare.

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