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Drug development for Autism Spectrum Disorder (ASD): Progress, challenges, and future directions

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Abstract

In 2017, facing lack of progress and failures encountered in targeted drug development for Autism Spectrum Disorder (ASD) and related neurodevelopmental disorders, the ISCTM with the ECNP created the ASD Working Group charged to identify barriers to progress and recommending research strategies for the field to gain traction. Working Group international academic, regulatory and industry representatives held multiple in-person meetings, teleconferences, and subgroup communications to gather a wide range of perspectives on lessons learned from extant studies, current challenges, and paths for fundamental advances in ASD therapeutics. This overview delineates the barriers identified, and outlines major goals for next generation biomedical intervention development in ASD. Current challenges for ASD research are many: heterogeneity, lack of validated biomarkers, need for improved endpoints, prioritizing molecular targets,

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comorbidities, and more. The Working Group emphasized cautious but unwavering optimism for therapeutic progress for ASD core features given advances in the basic neuroscience of ASD and related disorders. Leveraging genetic data, intermediate phenotypes, digital phenotyping, big database discovery, refined endpoints, and earlier intervention, the prospects for breakthrough treatments are substantial. Recommendations include new priorities for expanded research funding to overcome challenges in translational clinical ASD therapeutic research.

Keywords

Autism; Treatment; Clinical trials; Endpoints; Biomarkers; Children; Drug development

1. Introduction

Autism Spectrum Disorder (ASD) is recognized as a common (1 – 2.5% prevalence in children) (Baio et al., 2018; Christensen et al., 2019; Delobel-Ayoub et al., 2020; Guthrie et al., 2019; Maher et al., 2019; Zablotsky et al., 2019) syndrome of childhood-onset delays and deviations in social communication and interaction, narrowed and unusual interests, repetitive behaviors, and sensory hypersensitivities, that, for most individuals, predicts lifelong impairments in real world functioning. Two decades of increases in intervention research funding with advances in the basic neuroscience understanding of ASD has not produced progress in pharmacological interventions for ASD core deficits. Despite modest gains in evidence for treating associated symptoms (Handen et al., 2015; Scahill et al., 2015), currently available approaches (drug and non-drug) are too often insufficient to enable adult independent functioning. Efforts to develop medicines to address core features of ASD have failed to produce any approved agents that mitigate fundamental deficits or advance skills, leaving an unclear roadmap for future drug development efforts and investments in this area. Identified challenges are listed in Table 1.

Concerned that ASD clinical therapeutics could stall, in 2017 the International Society of CNS Clinical Trials and Methodology (ISCTM), together with the European College of Neuropsychopharmacology (ECNP), created an ASD Working Group. The Working Group is composed of experts from academia, clinical care, industry, and regulatory agencies. The Group’s charge was to review and identify the landscape of challenges encountered in ASD drug development, find consensus on key issues including research tools and methodologies, and to generate recommendations for the field, funding agencies, potential sponsors, and oversight groups. Through a series of face-to-face meetings, teleconferences, extensive literature review, and solicitation of comments from experts, a catalog of challenges and opportunities for progress has been assembled. This report shares the findings of the Working Group (and accompany-ing commentaries) to stimulate further discussion, prioritize actions, and hopefully contribute to future progress to meet the major unmet therapeutic needs of individuals and families with ASD and related disorders through successful drug development.

2. Challenges: current state of drug treatments for ASD

For two decades, the US has made significant research investments of over $110 million USD in ASD research networks and centers (not including single projects), including clinical and translational treatment studies. Funding included randomized clinical trials (RCT) of risperidone (three), methylphenidate, guanfacine, secretin (two), aripiprazole plus language intervention, citalopram, fluoxetine, oxytocin (two), escitalopram, buspirone, and a wide range of behavioral interventions. Additional clinical trials are ongoing. These large-scale programmatic NIH ASD research efforts continue under the Autism Centers of Excellence (ACE) Centers and Networks programs. In the European Union, the largest world-wide, multi-center, multidisciplinary, multinational research consortium focused on ASD and related disorders, the European Autism Interventions-A Multicentre Study for Developing New Medications (EU-AIMS; www.eu-aims.eu) is well underway, funded by the Innovative Medicines Initiative 2 (IMI2), that includes emphases on biomarker identification and personalized treatment approaches. Other cross-collaborative opportunities, such as the POND network in Canada have aligned with and contributed significantly to the effort to gather complementary data, along with efforts from privately funded foundations and industry.

At the same time, pharma-supported Phase II and III ASD and Fragile X Syndrome (FXS) trials of aripiprazole, mGluR5 antagonists, arbaclofen, fluoxetine, memantine, balovaptan, and lurasidone have been completed, as well as smaller controlled studies of oxytocin, vasopressin, D-cycloserine, N-acetylcysteine, CX516, and donepezil. While many RCTs have focused on associated symptoms such as irritability, hyperactivity, and anxiety as primary endpoints, an increasing number have been directed toward core deficits, such as social withdrawal for arbaclofen in ASD and FXS. To date, only three EMA and two US FDA indications have been approved, all for associated symptoms of “irritability” or insomnia associated with ASD. Systematic reviews applying accepted standards of evidence find only “possible” indications at best for the use of other agents for other behavioral endpoints in individuals with ASD (Ameis et al., 2018).

Although drug development for neurodevelopmental disorders (NDDs) has proved daunting and determined by some companies to represent unacceptable risk, better understanding of the genetics and neurobiology of ASD is changing this view. Compounds currently in clinical development (see Table 2) reflect a large number of molecules with diverse mechanisms of action in various stages of clinical development. A broader view, including compounds in preclinical development, are available in Supplementary Table 1. Taken together, the ASD and NDD space appears to be maintaining activity and gaining momentum. The Working Group’s intention is to support broader interest in this area by offering recommendations for early phase planning and go/no-go decision-making, identifying areas for methodologic advancements, and highlighting key findings in the service of “de-risking” additional drug development efforts.

2.1. Translational failures of preclinical targeted treatments

An exciting new era of testing targeted treatments for ASD and related disorders was spurred 15 years ago by foundational basic science and persuasive theories of the role

of CNS excitatory-inhibitory (E/I) signaling imbalances in ASD and FXS derived from animal models (Rubenstein and Merzenich, 2003; Bear et al., 2004). Multiple successful pharmacologic preclinical “rescues” of ASD-like behavioral analogues in animal models appeared consistent with disrupted excitatory glutamatergic and inhibitory GABAergic signaling (Dölen et al., 2007; Gandal et al., 2012) and other associated signaling abnormalities, such as serotonin (Veenstra-VanderWeele and Blakely, 2012; Muller et al., 2016). Yet, translational clinical trial results in FXS and idiopathic ASD examining benefits on core ASD features of the GABA-B agonist arbaclofen, mGluR5 antagonists mavoglurant and basimglurant, the glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist memantine, and others have been disappointing (Aman et al., 2017; Erickson et al., 2017; Youssef et al., 2017; Anagnostou, 2018). No conclusive evidence exists to support efficacy of any drug for the treatment of ASD core deficits despite multiple attempts. Related failures include lack of benefit for agents in trials for children with Down Syndrome, Angelman Syndrome, prevention of ASD symptoms and cognitive decline in tuberous sclerosis complex (TSC) and neurofibromatous type 1 (NF1), where preclinical “rescues” of animal models could not be confirmed in clinical studies (van der Vaart et al., 2015; Sonozogni et al., 2018; Overwater et al., 2019). One bright note is the positive efficacy reported, albeit small in magnitude, for trofinetide in Rett Syndrome (Glaze et al., 2019), with a follow up Phase III study in progress.

These programs also exposed a number of fundamental weaknesses in methodology, knowledge gaps, and conceptual models in clinical translational research involving these disorders (Veenstra-VanderWeele, 2017). In retrospect, human clinical trials proved the E/I imbalance theory of FXS and ASD to be overly simplistic, lacking the needed specificity of identifying and quantitating key circuit or network E/I disruptions with linkages to core features of these syndromes. Without identified “targets” and assays to determine adequacy of drug normalization of E/I function, it is perhaps not surprising that so many drug development efforts derived from the theory have failed.

These failures to find new treatments for ASD parallel the challenges encountered in drug development for other neuropsychiatric disorders (Paul et al., 2010), but progress in ASD lags behind other areas. The degree of difficulty and high failure rate in translating basic science findings into clinical applications has been described in the past as entering the “Valley of Death” (Szatmari, P. 2012), leading to a growing gulf between basic and clinical research in NDDs. At the same time, accelerating basic science and lessons learned from clinical research experience have prompted serious efforts to advance the science of clinical drug development and point to opportunities for methodologic enhancements to improve odds for eventual success in this space. In the next sections, we will identify specific challenge areas encountered, representing opportunites for trial improvements, and offer possible strategies for progress.

3. Opportunities for ASD clinical trial improvements

3.1. Dealing with ASD phenotypic heterogeneity

The phenotypic heterogeneity of ASD is broad and multi-dimensional. Such heterogeneity has long been acknowledged as a challenge for treatment development and was captured

in the earliest case descriptions of the disorder (Kanner, 1943) and differences in outcomes (Kanner, 1971). The range of overall severity of ASD is extensive (Wing and Gould, 1979). Level of symptoms, atypical and challenging behaviors, and delays (and corresponding impairment) can also differ within each of the two core ASD domains of social communication/interaction and repetitive behaviors and restricted interests (includes sensory sensitivity). Overlaid on these ASD symptom domains is marked variability in language ability and intelligence (IQ), ranging from nonverbal/profound intellectual disability (ID) to "hyperverbal"/superior IQ. ASD impairments show a high degree of lifetime persistence, although outcomes differ (Magiati et al., 2014). Disappointing outcomes in social functioning (Orsmond et al., 2013), ability to live independently, and employment (Roux et al., 2013), even in the cognitively able (Howlin and Magiati, 2017), compels the search for improved treatments. Possible latent classes that model outcomes and may signify relevant subgroups within ASD have been reported (Bal et al., 2015); given that noverbal IQ and language remain strong outcome predictors adulthood (Eaves and Ho, 2008; Howlin et al., 2014; Bal et al., 2015; Stringer et al., 2020), they deserve consideration as treatment targets.

One major weakness of much prior ASD therapeutic research is an implicit assumption that the cause of dysfunction across the domains of social relatedness, communication, and repetitive behaviors/restricted interests within an individual reflects a unitary process or neurobiology. While consolidation into the current, single spectrum diagnosis of ASD (DSM-5; APA Press, 2013) of Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder, Not Otherwise Specified was prompted by efforts to increase diagnostic reliability and limited justification for their separate categories, it did not presume a singular ASD etiology across or within the syndrome. Indeed, ASD likely represents a group of different disorders that share some core ASD symptoms but differ in risk factors, neurobiology, and phenotypic expression (Muhle et al., 2018). The current behavioral criteria for ASD show validity as a diagnostic category (Frazier et al., 2009; T.W. 2012), but multiple lines of research are probing putative separable, independent elements of ASD and their underlying correlates (Happe et al., 2006; Mazefsky et al., 2008; Frith, 2012). Refining the phe.notypic characterization of ASD should facilitate identifying distinct versus shared pathophysiologies, conceivably representing discrete treatment targets requiring different treatments (Waterhouse and Gillberg, 2014; Arango, 2019; Parellada, 2019). Sub-typing by sensory features may be another fruitful dimension for clinical trials (Tillman et al., 2020). However, identification of "biotypes" in other areas such as psychosis has revealed that multiple underlying influences can converge in shared phenotypic manifestations (Clementz et al., 2018). Examing various stratifications of phenotype and querying those for drug response may be a further necessary step in ultimate treatment personalization.

3.2. Considering severity subtyping in trials

Extant data supports ASD as composed of multiple phenotypic traits or dimensions, each normally distributed in the population and only modestly related to one other (Ronald et al., 2006). ASD clinical trial selection and endpoints have generally not reflected these separable characteristics, with greater sample heterogeneity and likely loss of sensitivity to change. Earlier studies, typically relying on a single instrument for ASD symptoms,

suggested ASD was modeled best as a one-dimensional underlying factor (Constantino and Todd, 2003; Constantino et al., 2004) or as two dimensions. Subtyping ASD by severity has garnered support with two and three clusters noted, interpreted to reflect overall degree of developmental "compromise" (Waterhouse et al., 1996; Prior et al., 1998). At the symptom level, three severity subtypes were identified with differing ages at diagnosis, adaptive functioning, language, and cognitive ability, defined by severity of social communication deficits versus restricted interests and repetitive behaviors (Georgiades et al., 2013). Incorporating a broader set of phenotypic data identified two distinct subgroups defined by levels of overall severity across multiple symptom (ADOS and ADI-R scores), anthropomorphic, and adaptive behavior measures (Vineland Adaptive Behavior Scales), demonstrating convergent validity by greater subtype familiality and genotypic correlations (Veatch et al., 2014). Another subtyping approach involves the identification of individuals who demonstrate a large (> 1 standard deviation of expected) deficit in daily living skills versus their IQ, despite having IQ scores in the normal range (>85). One report noted 56% of the 417 children and adolescents comprising the Simons Simplex Collection to manifest a "daily living skills deficit" (Duncan and Bishop, 2015). Total Social Responsiveness Scale-2 scores (SRS-2, Constantino et al., 2004), appreciated now as an overall severity measure of the whole of ASD core symptoms, language delay, *and* associated behaviors (Hus et al., 2013; Sturm et al., 2017), were found in genome-wide significant linkage with loci at CHR8p21.3 and 8q24.22 (Lowe et al., 2015), supporting the validity of overall severity as a possible biologically based dimension within ASD.

Lower sample severity may impact sensitivity to detect change in clinical trials for ASD and related disorders (King et al., 2013) by association with higher placebo response, though not confirmed in a meta-analysis of ASD RCT's (Masi et al., 2015). Baseline total scores on the Aberrant Behavior Checklist – Community Version (ABC - CV - Total) for subjects in the negative mGluR5 trials of basimglurant (Yousef et al., E. 2018) and mavoglurant (Berry-Kravis et al., 2016) in FXS were > 50% lower than the samples in positive ASD pivotal trials for risperidone (McCracken et al., 2002) and aripiprazole (Marcus et al., 2009; Owen et al., 2009), and Clinical Global Impression – Severity (CGI – S) severity scores also showed lower overall severity, largely driven by study inclusion/exclusion criteria. Similar, though less marked, lower sample severity (by 20 – 30%) is also noted for negative trials of arbaclofen for FXS and ASD.

3.3. Subtyping social functioning and social behavior endpoints in ASD

The difficulties in overall social functioning of individuals with ASD reflects the cumulative impact of multiple related, but not necessarily linked, weaknesses and atypicalities in social behavior, including problems of "social communication" or skill (SC) and "social interaction" or adaptation (SI) at the phenotype level, forming the three "social" domain criteria required for the DSM-5 diagnosis of ASD. These deficits are not necessarily well represented as a unitary dimension in children or adults with ASD, despite evidence for shared genetic associations influencing social communication and adaptive functioning scores in high functioning children with ASD and the general population (Robinson et al., 2016). The discrepancy between granular social phenotyping studies and genetics likely relates to the limited variability explained by genetics and differences at the extreme

ends of behaviors and abilities. About 30% of children with ASD never develop phrase speech, representing an important subgroup with severe disability and impairment of adaptive functioning, but likely with differing familial/genetic structures (Taylor et al., 2014). Few drug trials have targeted this specific subgroup and the majority of experimental medicine trials in ASD and neurogenetic disorders have excluded them (Tager-Flusberg and Kasari, 2013). The SC domain alone is increasingly understood as subdi- vided into subdimensions, each potentially contributing to social disability, with differences in definition and interrelationships. Social communication can be impacted by differences in social cognition, social motivation, social anxiety or withdrawal, and social skills (conversational ability, integrating verbal and nonverbal communication; A.A. Pallathra et al., 2018). Measures of *basic language skill acquisition and functional usage* (age of phrase speech, Vineland Communication scores, ADI-R items, ADOS subscale scores, natural language samples, SRS items) emerge as separable from *social interaction quality* (relatedness, social interest and approach) in multiple studies, showing distinctive factor structures and heritabilities (Frazier et al., 2014; Bishop et al., 2016; Ronald et al., 2006; Kim et al., 2019a). For example, further fractionation of SC into a familial “joint attention” dimension demonstrated suggestive linkage at 11q23 (Liu et al., 2011), and use of “age at first word” as a QTL showed initial suggestive linkage at 7q35 (Alarcon et al., 2002) which was attenuated in an expanded sample, but suggested linkage at 3q and 17q (Alarcon et al., 2005).

Attention to variability in social drive has emerged from studying social adjustment of children with ASD, who often report loneliness and desire for friendships (Locke et al., 2010; Kasari et al., 2011). Adolescents with ASD indicated reduced social pleasure versus typically developing controls (Chevallier et al., 2012), and most adults with ASD scored above clinical cutoffs as anhedonic (Carré et al., 2015), with significant relationships between hedonic impairment and severity of ASD. Comparing children and adolescents with ASD versus a non-ASD psychiatric sample, two thirds of the ASD versus one fourth of the psychiatric group met criteria for social anhedonia (Gadow and Garman, 2020). Neural activation of reward circuit components during social, nonsocial, and vicarious reward processing is also atypical (Scott-Van Zeeland et al., 2010; Dichter et al., 2012; C. Clements et al., 2018; Greene et al., 2020), however there may be prominent sex differences (Lawrence et al., 2020). Intranasal oxytocin increased activation to non-social, but not social rewards in children with ASD (Greene et al., 2018). Reduced reward responses in early childhood are believed to lead to cascading negative effects on social development, but social responsivity is rarely assessed in ASD clinical trials, specified for inclusion/exclusion, or nominated as a treatment target *per se*. Distinct individual differences in desire for social engagement among study participants may not be well-assessed; decreased salience of social interaction as a source of pleasure may be a challenge to increasing prosocial behavior and demonstrating improvement in clinical trials.

Examining relationships between four elements of social behavior (social cognition, social motivation, social anxiety or withdrawal, and social skills) and ASD phenotypic measures revealed that social motivation measures were significantly (though only moderately) and broadly correlated with most but not all measures of anxiety, social skills, and ASD severity, but were not significantly correlated with social cognition measures (Pallanthra

et al., A.A. 2018); measures included represented a broad sampling of well validated tools. Others identify potentially five elements (M. Uljarevíc et al., 2020c). Social cognition (understanding facial expressions, other's perspectives) measures were notable for their absence of relationships to other categories of social behavior. Overall, social functioning is determined by multiple elements that are relatively independent and hence may require separate interventions and measurement approaches. These data also support considering social motivation as a defined treatment target and afford some initial assessment of the measurement characteristics of available clinical tools.

3.4. Repetitive, restricted behavior subtyping as endpoints

The other DSM-5 ASD diagnostic domain of repetitive behaviors and restricted (or circumscribed) interests (RRBs) is an important source of additional disability, interference, and stigmatization. The broad domain of RRBs is composed of multiple subtypes, based upon factor analyses, neurocognitive correlates, independent familial correlations, heritability estimates, and genetic associations (Silverman et al., 2002). Clinically, RRB severity may be influenced by co-occurring emotional disorders; early childhood RRBs may predict later anxiety (Baribeau et al., 2019). Multiple studies support the separation of restricted interests (RI), so-called "higher-order" behaviors, from repetitive sensory-motor (stereotypic; RSM), or "lower order" behaviors (Turner, 1999; Frazier et al., 2014b), but other studies and reviews identify up to four subtypes (Honey et al., 2012; Uljarevíc et al., 2020a). The further subdivision of "insistence on sameness" (IS) is supported by differing associations with other clinical characteristics (Lam et al., 2008). Results differ by type of measures used. Applying measures that capture a broader array of RRBs than the ADI-R, such as the Repetitive Behavior Scale – Revised (RBS-R; Bodfish et al., 2000), factor analyses and family data find support for at least three factors, as well as self-injurious behavior, another possible separable dimension of repetitive behavior. Sib-pair correlations of IS and RI appear more familial that RSM behaviors (Lam et al., 2008); genome-wide linkage for IS was observed at 2q37.1-q37.3, and for RSM at 15q13.1-q14 (Cannon et al., 2010) and 19q13.3 (Liu et al., 2011). Another report found that 7 of the 12 total ADI-R RRB items were significantly familial, and genome-wide association was identified at 17q21.33 for the single symptom of "the degree of the repetitive use of objects or interest in parts of objects", suggesting further fractionation within RRBs may emerge (Cantor et al., 2018). Taken together, data support additional efforts to identify refined RRBs subtypes with stronger biological linkages as treatment endpoints.

3.5. ASD cognitive deficits as treatment targets

Largely ignored as ASD trial targets compared to schizophrenia drug development, research has attempted to identify ASD cognitive phenotypes (Happe and Firth, 1996; Ibrahim et al., 2016). Results add to ASD heterogeneity and potential treatment targets as quantifiable endpoints.

The overlap of ID in the majority of "classic autism" was hypothesized to reflect autism risk load (Folstein and Rutter, 1977; Szatmari and Jones, 1991). However, co-occuring ID *per se* in ASD probands was not found to increase sibling risk (Szatmari et al., 1996), and recently diagnosed cohorts of ASD from US community surveillance show that 70% or

more of 8-year old children with ASD are cognitively able, with IQ's falling within normal range (Baio et al., 2018); population-based registries of 7 – 9 year old children with ASD from three EU countries found 11 – 21% were diagnosed with ID (Delobel-Ayoub et al., 2020). Furthermore, population studies find little overlap between extremes of autistic traits and IQ (Hoekstra et al., 2010). "Syndromic" ASD does show substantially higher rates of co-occurring ID, but the syndromic ASD-associated causative loss of function single gene mutations or CNV gene disruptions only represent 15% of overall ASD (syndromic and idiopathic ASD together) genetic risk. Therefore, the risk factors for the majority of ASD-associated cognitive differences remain unexplained (Ramaswami and Geschwind, 2018). Substantial research has attempted to define the cognitive phenotype(s) of high-functioning individuals with ASD versus neurotypical controls, identify the relationships of cognitive differences to symptom domains, and their distal impact on adaptive functioning. Cognition appears to be an important intermediate phenotype of ASD, and deserves consideration as a tractable treatment target.

Research on cognition in ASD has been limited by presumptions of singular cognitive theories accounting for diverse features of ASD. The primary cognitive deficits proposed in social cognition (Baron-Cohen, 1988), executive function (Ozonoff et al., 1991), central coherence, or selective attention aimed to predict core ASD symptoms, but each proved to have limitations (Happe et al., 2006; Frith, 2012). Recent systematic reviews and meta-analyses (Demetriou et al., 2018; Velikonja et al., 2019) have provided a more comprehensive understanding of social and nonsocial cognition in ASD and highlight intervention targets (Keehn et al., 2013).

Deficits in both social and nonsocial cognitive domains are robustly associated with ASD, and are mostly consistent in studies from schoolage into adulthood. Performance on tasks assessing Theory of Mind (ToM) understanding and emotion processing (eg, face recognition, social memory) show large effect size differences ($g = -0.8$ to -1.1) in adults with ASD versus neurotypical adults (Velikonja et al., 2019) comparable to deficits seen in young adults with early psychosis (Pepper et al., 2018). Estimates of social cognition in children with ASD are more variable, in part due to the complex interactions of developmental level, IQ, and language competency but nevertheless differ from typically developing schoolage and older children (Charman et al., 2011; Demetriou et al., 2018). Though studies differ, meta-analyses also show large ($g = -0.60$) effect size reductions in performance across a broad range of nonsocial cognitive domains combining child and adult studies (Demetriou et al., 2018).

Individual profiles vary considerably between social and nonsocial cognitive ability, and across subdomains of nonsocial cognition, defying any effort to identify a singular ASD profile. Importantly, aspects of both social and nonsocial cognitive ability have shown complex but significant associations with symptom severity in various ASD core domains. (Joseph and Tager-Flusberg, 2004; Jones et al., 2018). For example, multiple studies have linked the perseverative features of RRBs to measures of inhibition and cognitive inflexibility in ASD (De Vries and Geurts, 2012; Lopez et al., 2005; Yerys et al., 2009; Faja and Darling, S. 2019; Bos et al., 2019). Other reports note executive functions predicting overall ASD severity (Leung et al., 2016) and adaptive functioning (Ozonoff et al., 2004).

Conversely, poorer ToM has beeen associated with externalizing and self-injurious behaviors in adolescents with ASD (Carter Leno et al., 2019), but not social behaviors (Travis et al., 2001).

Taken together, social and non-social cognitive deficits associated with ASD are important, given their links to core deficits, associated symptoms, and daily functioning (Wallace et al., 2016). They deserve greater consideration as treatment targets but are infrequently declared primary or even secondary endpoints of treatment. Standardization and adaptations of measurement approaches for cognition is needed, especially given the difficulty in creating cognitive batteries suitable for children and adolescents with broad ability and age ranges. Some studies have succeeded in this regard (Scahill et al., 2015b). Thus far treatments with established efficacy on behavioral outcomes such as irritability and hyperactivity have not shown drug-related cognitive impairments but lack cognitive benefits (Aman et al., 2008; Scahill et al., 2015b). The etiology of ASD-associated cognitive deficits are poorly understood. The identification of drugs with significant cognitive enhancement effects in ASD would certainly represent an important therapeutic advance.

3.6. ASD comorbidities: more treatment evidence needed

Added phenotypic complexity in ASD results from the high frequency of co-occurring non-ASD problem behaviors. Besides epilepsy (7 – 25%) (Jokiranta et al., 2014; Mouridsen et al., 2010; Lukmanji et al., 2019) in individuals with ASD, impairing externalizing and internalizing disorder symptoms are common. The majority of older school age children, adolescents, and adults with ASD can be expected to suffer from at least one additional Axis I psychiatric disorder (Leyfer et al., 2006; Simonoff et al., 2008; Houghton et al., 2017; Rosen et al., 2018; Lai et al., 2019; Mosner et al., 2019), and the little longitudinal data available finds these problems to be persistent over years (Simonoff et al., 2013). Estimates of rates of specific co-occurring conditions varies widely, influenced by multiple methodologic (direct assessment versus clinic records) and sample (age, country, registry versus speciality clinic) differences, leading to uncertainty regarding the true degree of overlap of other psychopathology with ASD (Rosen et al., 2018). Studies of clinic or treatment-seeking youth with ASD note substantially higher comorbidity rates (Kaat et al., 2013; Sikora et al., 2012; Lecavalier et al., 2019), while registry-, insurance record-, and population-based studies find lower rates of these common accompanying disorders (Simonoff et al., 2008; Houghton et al., 2017; Lai et al., 2019). Regardless of specific study considerations, elevated rates of all Axis I psychiatric disorders in studies of ASD represent consistent findings in the literature, even for lower prevalence diagnostic groups, such as depression, schizophrenia spectrum disorders, and bipolar disorders, notwithstanding the diagnostic challenges involved (Houghton et al., 2018; Rosen et al., 2018). ASD thusly functions as a general risk factor for psychopathology, increasingly evident over the first three decades of life (Houghton et al., 2017; ibid 2018). Beyond adaptive skill deficits, the source of heightened risk for psychopathology in individuals with ASD is not clear, though could reflect genetic correlations with other mental disorders (Rommelse et al., 2010). From the view of ASD unmet treatment needs, co-occurring psychiatric conditions in ASD represent important contributors to functional impairment, family burden, and outcome in ASD.

Anxiety symptoms and diagnoseable anxiety disorders of all types overlapping with ASD are very common (White et al., 2009; A.J. Kaat et al., 2013), estimated in a meta-analysis to affect 40% of youth with ASD (van Steensel, Bogels, Perrin, 2011). Besides specific phobias, social anxiety disorder emerges as the most common anxiety disorder among individuals with ASD, reported in about 1 of 4 (Simonoff et al., 2008; van Steensel, Bogels, Perrin, 2011; Bejerot et al., 2014). Generalized anxiety disorder has been reported in 10% of children and adolescents with ASD (Simonoff et al., 2008; van Steensel, Bogels, Perrin, 2011). Anxiety disorders have been associated with greater parental reports of youth depression, social dysfunction, and parental stress in ASD (Kerns et al., 2015); social anxiety is noted to be predictive of aggression (Pugliese et al., 2013). Atypical anxiety symptoms have also been noted (Kerns et al., 2020). Rates of Obsessive-Compulsive Disorder (OCD) in individuals with ASD are also increased several-fold relative to the general population (Houghton et al., 2018), with rates averaging between 10 – 20% (van Steensel, Bogels, Perrin, 2011). Rigorous clinical trials evaluating pharmacotherapy for anxiety disorders and OCD in ASD are lacking.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a very common co-occurring diagnosis in children and adolescents with ASD, present in the majority of clinic treatment-seeking youth (Joshi et al., 2010; A.J. Kaat et al., 2013). In community samples and large insurance databases, ADHD is found co-diagnosed in 28 – 35% of school age children and adolescents in individuals with ASD (ADHD + ASD)(Simonoff et al., 2008; Lai et al., 2019). Adaptive functioning and quality of life are further impaired by ADHD comorbidity (Sikora et al., 2012). Comparing groups of children 7 – 16 years with ASD, ADHD, and ASD +ADHD on adaptive functioning, the ASD + ADHD group had lowest scores across all adaptive behavior domains (though not significant) and effect size differences between ASD versus ASD + ADHD were all $d = 0.4 – 0.5$ (Ashwood et al., 2015). ADHD symptom severity predicted up to 12% of the variance in adaptive functioning in children with ASD (Yerys et al., 2019). In the EU-AIMS LEAP sample, comprised primarily of older adolescents and adults with ASD, ADHD inattention and hyperactivity/impulsivity symptom counts separately were highly correlated with parent-reported ASD severity measures (Charman et al., 2017), similar to other reports (Holtmann et al., 2007; Rao and Landa, 2014). Other disruptive behavior disorders are equally common among children and adolescents with ADHD. While an evidence base for the pharmacotherapy of ADHD and other disruptive behavior disorders is growing (RUPP Autism Network, M. 2005; Handen et al., 2015; Scahill et al., 2015), overall it remains thin (Sturman et al., 2017; Patra et al., 2019).

Rates of depression and suicidality have been noted more recently to be increased among children, adolescents, and adults with ASD (Chandrasekhar and Sikich, 2015; Greenlee et al., 2016; Pezzimenti et al., 2019), and estimated to be 4-fold more common than the general population, especially in higher-functioning indviduals with ASD, across the lifespan (Pezzimenti et al., 2019). Using a structured diagnostic interview modified for youth with ASD, Leyfer et al. (2006) found 10% of a child and adolescent sample to meet criteria for major depressive disorder, similar to reports of depression diagnoses in the Interactive Autism Network database (Rosenberg et al., 2011); rates in adolescents and adults increase markedly (Bakken et al., 2010). Using dimensional thresholds, 27% of adolescents and 22% of adults with ASD scored in clinical ranges for depression (Charman et al., 2017).

Subsyndromal depression has been noted to 10 −14% of children and adolescents with ASD (Leyfer et al., 2006; Simonoff et al., 2008). Suicidal plans and attempts were found to be common in over one third of respondents in a survey of adults from a specialty clinic (Cassidy et al., 2014), and some predictors have been identified (McDonnell et al., 2019). Suicide emerged as the second-most common cause of mortality amongst high-functioning adults with ASD from a general population registry (Hirvikoski et al., 2016). Multiple reviews highlight the lack of rigorous clinical trials testing any form of intervention for depression and suicidality in ASD (DeFilippis, 2018; Pezzimenti et al., 2019).

Severe mood problems, including irritability, a construct of symptoms of agitation, aggression, self-injurious behavior, and intense mood lability, represents another common and impairing symptom domain seen in 10 – 25% of individuals with ASD in the community, and is mostly independent of IQ and ASD severity (Emerson et al., 2001; Bakken et al., 2010; Simonoff et al., 2012). Severe mood problems are even more common in clinic samples (Joshi et al., 2018), increase in adolescence and young adults, and high problem levels predict persistence across 4 years of adolescence (Simonoff et al., 2012). Descriptions of catatonia in ASD overlap considerably with severe mood problems (Wachtel, 2019), but the diagnostic distinction remains challenging. Irritability often prompts consideration of drug therapy due to its burden on the individual and family, threat of more restrictive placements, or hospitalization. Evidence supports the efficacy of some atypical antipsychotics, but side effect burdens limit their use.

The high rates of comorbid psychopathology in ASD and their additive burden on adaptation in ASD should call for greater programmatic research efforts to identify efficacious drug therapies for ASD-specific comorbidities. A weakness of many targeted treatment trials is insufficient characterization of co-occuring psychiatric symptoms, whether categorical or dimensional, which could exert confounding effects. In addition, the notable co-occurrence of symptomatology of varying disorders and their impact on adaptive functioning also raises questions about the relationship between disruptive and anxious symptoms with the definition of the ASD phenotype(s). Most importantly, ASD therapeutics development for symptoms outside of conventional “core” ASD domains deserves continued attention by researchers, regulatory agencies, and sponsors.

3.7. Taking heterogeneity apart/putting it together

How do these varying characteristics of the ASD phenotype inform ASD drug development efforts? We argue there are multiple implications for studies of targeted treatments for ASD and related disorders. These findings suggest ASD severity, separable phenotypic dimensions, cognition, and comorbidities can be operationally defined and may serve as grouping definitions and/or refined treatment endpoints reflecting constrained etiologic heterogeneity, and be linked to differential treatment response. Alternatively, greater genotyping access to identify more individuals with shared genetic lesions, can lead to increased feasibility of clinical trials of syndromic forms of ASD and related disorders with shared etiopathogenesis. More research is needed, but extant findings also suggest shared pathways and mechanisms relevant to the behaviors of interest and could assist in nominating targeted treatments. However, the genetic diversity of ASD is enormous, and

besides the low-frequency highly penetrant mutations, genetics will not inform treatment in near future. The best supported subdomains of behavior call for additional research to develop more precise measurement approaches that reflect the expected spectrums of severity and that are more sensitive to change with intervention, in line with the NIMH Research Domain Criteria mission (RDoC; www.nimh.nih.gov/research-priorities/rdoc/index.shtml; Insel et al., 2010). Similarly, as we will describe below, identifying the neural circuitry linked to these behaviors and functional readouts of circuit function and dysfunction will lead to more sensitive measures of treatment effects and target engagement. In addition, greater convergent validation of underlying genetic associations and neural correlates should expand our understanding of relevant mechanisms of subdomain impairments, and perhaps classes of compounds that merit clinical development.

3.8. Circuitry and potential for ASD biomarkers

The search for drug treatments for ASD core symptoms and associated features has suffered from the lack of identified tractable and quantifiable biological endpoints (biomarkers) reflecting proximal signaling and neural circuit dysfunctions believed to underpin distal behavioral symptoms, based on emerging understanding of the clinical neuroscience of ASD (Port et al., 2017; Muhle et al., 2018). The need for biomarkers in ASD is great. Validated biomarkers have multiple applications to improve ASD drug development efforts (Loth et al., 2017), and nomenclature has been harmonized within The Biomarkers, Endpoints and other Tools (BEST) glossary (https://www.ncbi.nlm.nih.gov/books/NBK326791/). BEST categories include: susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamics/response, and safety biomarkers. As summarized by McPartland (2017), for a biomarker to be clinically relevant and possess utility, it should capture variation within a specified functional domain, reflect individual differences and changes across development, demonstrate reliablility, be widely accessible and hopefully economical. The majority of existing studies have focused on ASD susceptibility/risk or diagnostic biomarker identification, and suffered from small samples, narrow age and IQ ranges, and differences in paradigms. A listing of putative ASD biomarkers under research is presented in Table 3. Results have varied but show promise.

Validated biomarkers in ASD could have multiple, important applications as above, but caution is required. The complexity and heterogeneity of ASD places limits on how informative and reproducible biomarkers can perform when applied in broad clinical contexts. As research increas- ingly identifies transdiagnostic features of brain disorders (Gillan and Seow, 2020), interpretations of the meaning and clinical utility of ASD-linked biomarkers must be carefully and rigorously tested before broad recommendations for their use, even in clinical trials, can be offered.

Major efforts are underway in international multi-site networks to identify and validate ASD-related biomarkers from multi-method testing in large cohorts including typically developing participants, most notably the EU-AIMS Longitudinal European Autism Project (LEAP; Loth et al., 2017) and the Autism Biomarkers Consortium for Clinical Trials (ABC–CT; http://www.asdbiomarkers.org; Webb et al., 2020). Probes of social brain circuitry are central in these efforts, given extensive data on typical and atypical social cognition,

and identified deviations in social cognitive functioning in ASD (Cipolotti et al., 1999; Ozonoff et al., 1991), representing opportunities for possible biomarkers (Dawson et al., 2012a; Webb et al., 2017; Modi and Sahin, 2018). The social brain network is highly conserved across species, although the salience of varying stimuli differ across species; in humans vision is the dominant modality for the processing of social information (Modi and Sahin, 2017). The structural social brain network globally integrates function across multiple nodes, linking the amygdala with primary and associative cortical areas, hippocampus, ventral striatum reward areas, cerebellum, and medial prefrontal cortices (Dawson et al., 2012a; Li et al., 2018; DeMayo et al., 2019). Resting electroencephalogram (EEG) recordings, event-related potentials (ERPs), eye tracking during presentation of social versus non-social stimuli, pupillometry responses to emotional faces, fMRI activation to emotional stimuli, and accuracy of facial emotion detection are methods which have some support as susceptibility/risk and diagnostic biomarkers distinguishing groups of individuals at-risk or diagnosed with ASD compared to low risk or unaffected controls. Each method possesses some advantages and weaknesses as biomarkers for broader application. However, their limitations have also been noted.

Several eye tracking indices appear to discriminate between infants, toddlers, children, and adolescents with ASD versus typically developing controls, however some reviews highlight the inconsistency of findings (Guillon et al., 2014), leading to suggestions for refined techniques such as combining frequency-tagging EEG with eye tracking (Vettori et al., 2020). The trajectory of salience of biological motion assayed by eye tracking in very young children is complex but differentiates those with later diagnoses of ASD (Klin, Schultz, Jones, A. 2015) and has been suggested as a possible early risk screening measure. Less eye tracking data in adolescents and adults with ASD are available; reports suggest more limited diagnostic specificity (Bours et al., 2018; Dijkhuis et al., 2019; Black et al., 2020), inconsistent correlations with ADOS severity measures, and no correlation with adaptive functioning (Del Valle Rubido et al., 2018). Nevertheless, eye tracking has emerged as a putative early diagnostic biomarker of ASD, and may also possess sensitivity for monitoring treatment effects in young children. One open-label trial evaluating the safety of umbilical cord blood for treating core autism symptoms demonstrated that improvements in social attention assessed via eye-tracking correlated with improvements in a wide range of social communication endpoints (Dawson et al., 2017; Murias et al., 2018a). Although sample size in this study was small and design lacked a comparison, these and other results (Greene et al., 2021) support further studies examining eye-tracking as a potentially viable monitoring or early efficacy biomarker in ASD trials.

ERPs in response to face processing, auditory stimuli, and multisensory stimuli have been widely explored as an output of the integrity of multiple circuits, and, though results vary, abnormalities have been observed across all stimuli type in both idiopathic and syndromic ASD participants (Dawson et al., 2002; Siper et al., 2016; Modi and Sahin, 2017). Given relevance of face processing to social communication, substantial evidence has emerged showing atypical ERPs in younger individuals with ASD evoked by presentation of emotional faces or alternating series of upright or inverted faces interspersed with non-face stimuli. The magnitude of differences in specific elements of the visual ERP, especially P1 and N170 components, have been significantly correlated with degree of impairments in

memory for faces (McPartland et al., 2004) and social behavior (Brandwein et al., 2015; Neuhaus et al., 2016), albeit modestly. Twin studies document the heritability of some components of ERPs to such tasks, especially for the N170 latency to faces (Shannon et al., 2013; Neuhaus et al., 2016). A meta-analysis of 18 studies provides support that differences in the ERP N170 component, particularly prolonged latency, but not P1 differences, discriminate individuals with ASD and without ASD diagnoses, with an estimated effect size after statistical adjustment of $g = 0.5$ (Kang et al., 2017). The N170 is thought to reflect processing in primary or secondary visual cortex downstream of thalamic nuclei, and similar N170 deficits have been seen in individuals with Rett syndrome (LeBlanc et al., 2015). Weaknesses include lack of disorder specificity (versus indexing shared face recognition deficits)(Feuerriegel et al., 2015; Tavares et al., 2016); inconsistent sensitivity to treatment effects (Dawson et al., 2012b; Faja et al., 2012; Key and Corbett, 2020), modest associations with behavioral measures of social function (Key and Corbett, 2020), large interactions of age, IQ, and hemisphere, and cautions regarding differing ERP reference schemes (Sysoeva et al., 2018) exerting influences on ERP results. Encouragement for development and testing of other ERPs is found in the negative FXS controlled minocycline trial (Leigh et al., 2013), where a subset of participants showed improved habituation to auditory stimulation (Schneider et al., 2013).

Multiple components of resting state EEG (rsEEG) show strong test-retest reliability, especially alpha power (Winegust et al., 2014). The literature on resting state EEG profiles in ASD is confounded by a host of methodologic and sample differences (Wang et al., 2013). However, resting state quantitative EEG (qEEG) spectral power across the entire frequency spectrum from youth and adults with ASD versus unaffected controls has been summarized as an inverted-U shaped curve, with excessive power in low- and high-frequency bands and reduced power in the alpha band, hypothesized as consistent with dysfunctional gamma-aminobutyric acid (GABAergic) inhibitory tone and its effects on connectivity (Wang et al., 2013). Advances in analytic approaches have revived interest in EEG as a possible diagnostic/risk biomarker and a window into ASD's neurobiology (Strzelecka, 2014; Schwartz et al., 2016; Heunis et al., 2016, 2018; Shou et al., 2018). but with much variability across studies (Lefebvre et al., 2018). Reduced resting state alpha power (Cantor et al., 1986; Dawson et al., 1995; Wang et al., 2013), alpha power suppression (reduction in eyes open versus eyes closed; Mathewson et al., 2012), reduced alpha desynchronization during attention tasks (Keehn et al., 2017), and alpha coherence measures (Dickinson et al., 2018) have been associated with ASD and ASD traits.

Resting state EEG has showed significant differences by genotype for the deletion genotype of Angelman Syndrome, the non-deletion genotype, and typically developing children (Frolich et al., 2019a). EEG signatures in specific ASD-related genetic syndromes have also been identified that may reflect their fundamental biology. In children with duplications of 15q11.2-q13.1 (Dup 15q syndrome), excess 15q $GABA_A$ receptor subtype expression is arguably reflected in the excess beta spectral power observed in humans with the syndrome (Frolich et al., 2016), as mimicked by midazolam administration in controls (Frolich et al., 2019b). Taken together, EEG under resting and activation conditions deserves additional examination for informativeness as a diagnostic/risk biomarker, coupled with novel analytic methods (Heunis et al., 2016), and could contain predictive biomarker information. In an

open label trial of young children with ASD, higher baseline posterior EEG beta power was associated with a greater degree of improvement in social communication symptoms (Murias et al., 2018b). Besides feasibility across a wide age span, an advantage of EEG and ERP indices is translatability across species, with parallel findings in multiple mouse models of ASD. Such translational properties enable large scale preclinical screening of potential targeted compounds in search of viable candidates for human trials. The relatively low cost of EEG, its millisecond temporal sensitivity, reliability, tolerance for movement, and increasingly automated analytics are clear advantages as a biomarker method (McPartland, 2016; 2017).

With regards to RRBs, a synthesis of preclinical and clinical studies of RRBs points to disordered basal ganglia – prefrontal cortex and cerebellar function (Wilkes and Lewis, 2018). RRBs lack validated related clinical biomarkers, although intermediate neurocognitive phentoypes show the most promise as potential RRB target engagement endpoints, including cognitive flexibility (D'Cruz et al., A.M. 2016), inhibitory control (Lopez et al., 2005; Agam et al., 2010; Schmitt et al., 2018; Faja & Darling, S. 2019), maintenance of response sets on cognitive tasks (South et al., 2007; H.L. Miller et al., 2015), and motor performance (Ravizza et al., 2013). Human functional imaging correlates of RRBs are limited, but data suggest hypoactivation of the anterior cingulate cortex during target detection in ASD with an inverse relationship between ACC activation and repetitive behaviors (Shafritz et al., 2008), and reduced rsfMRI function connectivity between nucleus accumbens and premotor/midlle frontal cortex (Akkermans et al., 2019). Activation of the ACC and inferior frontal gyrus discriminated between minimal versus clinical improvement in repetitive behavior with citalopram in two cases (Dichter et al., 2010). Preclinical data suggest deficits in basal ganglia indirect pathway activation are related to RRBs (Lewis et al., 2019), but clinical studies have not examined possible relationships between RRBs and metabolite concentrations, despite accumulating evidence of reduced regional cortical GABA concentrations in ASD in most (Rojas et al., 2014; Drenthen et al., 2016; Port et al., 2017; Puts et al., 2017) but not all studies (Carvalho Pereira et al., 2018). Probes of basal ganglia-mediated inhibitory control deficits may emerge as intermediate targets for RRBs.

The search for potential diagnostic/risk biomarkers also includes biomedical measures with possible links to ASD subphenotypes (Gabriele et al., 2014a). Whole blood (WB) serotonin (5-hydroxytryptamine, 5-HT) concentrations are familial and highly heritable (Abney et al., 2001), and elevated WB5-HT represents the first biomarker discussed for ASD (Schain and Freedman, 1961), a finding that continues to replicate in subsets of 25 – 48% of individuals with ASD, even after controlling for confounding age and IQ effects (Leboyer et al., 1999; Gabriele et al., 2014b). Combining WB5-HT concentrations and its intermediate metabolite N-acetlyserotonin with melatonin yielded discrimination between patients and controls with sensitivity of 80% and specificity of 85% (Pagan et al., 2014). Much remains un-explained about the differences reported in the pathway in ASD versus controls and much broader replication is needed. Neuropeptides have been explored as diagnostic biomarkers. In one study, 5-HT cerebrospinal fluid (CSF) arginine vasopression (AVP) concentrations discriminated between ASD and controls and was correlated with ADOS severity (Oztan et al., 2018), but plasma AVP did not differ between groups despite its moderate correlation with CSF concentrations (Carson et al., 2015). The two largest studies of oxytocin in youth

with ASD found no evidence for differences versus typically developing controls (Miller et al., 2013; Parker et al., 2014).

High hopes exist for biomarker impact on ASD clinical trials. Ultimately, combinations of markers with cognitive or behavioral subphenotyping may prove fruitful (Veenstra-VanderWeele and Blakely, 2012; Loth and Evans, 2019). With regards to current ASD studies, diagnostic imprecision is much less a concern, whereas ASD-related monitoring, pharmacodynamics/response, prognostic, predictive, and safety biomarkers would have high impact.

3.9. ASD genetics and drug development

Our understanding of ASD genetic architecture has progressed substantially in the past decade (Ramaswami and Geschwind, 2018). The high heritability estimate for ASD ($h^2 > 0.7$) belies the complexities of its underlying genetics. Three major pathways of genetic variation contributing to individual risk have been identified, including highly penetrant rare *de novo* loss-of-function (LoF) single-gene mutations, common variants (Grove et al., 2019), and *de novo* or inherited copy number variations (CNVs) (Sebat et al., 2007; Weiner et al., 2017). ASD genetic complexity also involves varying phenotypes, or pleiotrophy, associated even with monogenic disorders, such as phenotypic variation seen with mutations in *NRXN3* and *FOXP2* genes. Efforts to consolidate the multitude of effects of mutations in diverse gene families by examining gene networks and expression profiling has identified convergence in several shared pathways and gene modules (Gandal et al., 2018), encouraging the ultimate goal of pinpointing more homogenous ASD etiologic subgroups “druggable” by specific, targeted compounds (Geschwind and State, 2015; Gandal et al., 2016). However, proof of concept therapeutic attempts in monogenetic ASD-related syndromes of TSC1, NF1, and FXS have been disappointing and reflect considerable heterogeneity even in single-gene disorders. Such discrepant findings may reflect that: multiple pathway disruptions can lead to ASD; genetic background is important even in monogenetic disorders; and that adaptation to drugs may occur, similar to the development of tumor resistance in oncology. Importantly, these translational failures highlight the lack of sensitive measures of target engagement to guide dosing to achieve “normalization” of the nominated pathway in order to impact cognitive and developmental trajectories.

Nevertheless, accumulating genetic data in ASD is getting closer to enabling genomics-driven therapeutics, as supported by early efforts in schizophrenia and other complex genetic disorders (Gandal et al., 2016; Plenge, 2019). The application of polygenic risk scores (PRS) has potential to facilitate drug development in ASD. PRS represents a continuous, quantitative, aggregate measure of genetic liability for complex human traits and diseases such as ASD (Fang et al., 2019). PRS could enable enrichment for clinical trial selection or identify subgroups that share relevant pathophysiology. PRS predicted response and novel/combinatorial treatment strategies for pharmacotherapy in some schizophrenia datasets (Ruderfer et al., 2016; So et al., 2017; Li et al., 2018). Applying PRS scores to schizophrenia GWAS databases and drug pharmacogenomic profiles confirmed enrichment for antipsychotics, supporting concept validity, and nominated novel drug classes of selective calcium channel blockers and antiepileptics as potential theraputics. With further

progress (larger samples) in ASD genetics, parallel studies employing similar methods could be groundbreaking, but are not yet feasible. Application in ASD could validate biomarkers or subphenotypes, nominate novel therapeutic targets, and parse drug response heterogeneity in clinical trials. Such research should have high priority.

3.10. Prioritization of molecular target compounds

The diversity of ASD-related molecular pathologies emerging from genetics, postmortem studies, and preclinical ASD models presents a daunting challenge for ranking and selecting drugs for human studies. The time, cost, and high failure rate of early phase clinical trials forms a major bottleneck for progress in ASD therapeutics; conversely, improving the approach to prioritizing molecular targets could have a major positive impact (Paul et al., 2010). The NIMH New Experimental Medicines Fast-Fail program represented one approach to rigorous selection of a lead compound. The general evaluation criteria are shown in Table 4. Overall, the criteria represented a response to perceived weaknesses in extant research including: lack of clear understanding of target mechanism and compound target engagement in preclinical studies; lack of direct evidence of target engagement, or no tractable measures of circuit level or pharmacodynamics readouts to guide dosing and validate effect; insufficient human data of clinical effects of target engagement, and weak linkage of target or compound to a relevant circuit represented within an RDoC domain. By requiring evidence be acquired to satify each of these criteria before experimental efficacy trials are pursued, early, less costly “fails” would presumably facilitate greater late-stage study “wins”. Applying these criteria to ASD research, there are numerous examples of gaps in knowledge that likely relate to failures of lead compounds, such as: insufficient data to appreciate disorder effects on the selected target, lack of established target engagement in the study population; poor translation of functional measure from preclinical to clinical assessment; over-reliance on subjective reports; insufficient efforts to identify specific behavioral domains with links to circuit dysfunction with objective endpoints, and possible confounding developmental effects on dosing, pharmacodynamics, and pharmacokinetics.

3.11. Role of technology in clinical trials

The search for objective, highly standardized, quantifiable, and reliable behavioral measures for clinical trial endpoints has embraced technology. The advent of an array of wearable sensors, video capture, and unobstrusive recording devices capturing a wide range of behaviors has been shown to be feasible (Ness et al., 2019). Advantages include dense sampling across real world environments, automated scoring and data reduction, and appreciation of the range of variability in both symptomatic and adaptive behaviors, including psychomotor activity, circadian rhythms, autonomic reactivity in different settings, language use, and predictions of behavior. Impressive successes have occurred in some areas, such as the prediction of seizures (Poh et al., 2012), aggression by autonomic profiles (Goodwin et al., 2019), and stereotypy (Heathers et al., 2019). More complex multi-method monitoring systems have been developed (Ness et al., 2017), including smartphone applications (Jones et al., 2018). Some tools have turned out to possess limited value (Jones et al., 2019), or demonstrate small to moderate correlations with standard behavioral measures (Ness et al., 2019), making their advantages unclear. More importantly, the extent to which these measures provide enhanced “signal to noise” over standard behavioral

assessments is unknown, as few have been tested in a clinical trial context. Nevertheless, such instruments are hoped to facilitate behavioural phenotyping, increase sensitivity to detect salient behavioral and physiologic effects of treatments, and broaden the appreciation of treatment impact. Challenges include identification of "clinically meaningful" changes, data quality and analytic approaches, and establishing links between digital variables and behavior dimensions of interest.

3.12. Suitable endpoints for clinical investigations

Currently the ASD field lacks consensus on a narrowed set of better validated clinical outcome measures for use in clinical trials (Anagnostou, 2018), and outcome evaluation for young children (McConachie et al., 2015). The knowledge gap for adult measures is woefully greater (Bruhga et al., T.S 2015). The same exists for FXS outcomes (Budimirovic et al., 2017). Weaknesses of available measures include inability to apply across the lifespan, given that many are designed for specific age groups (eg. 0 – 3 years, versus schoolage, and older). Most ASD trials still rely on clinician or caregiver rated measures. Negative trials of targeted compounds for ASD and monogenic syndromes have been blamed on clinical endpoint insensitivity to change, vulnerability to placebo effects (Masi et al., 2015), impact of non-ASD behaviors (Hus et al., 2013; Sturm et al., 2017), and possible age and IQ effects (Jeste and Geschwind, 2016; Anagnostou, 2018). Expert consensus reviews from 2014 to 2015 of endpoint measures concluded that none met the highest standards for endorsement. At that time, several were "appropriate with conditions", namely four measures of social communication (Anagnoustou et al., 2015), five for RRBs (Scahill et al., 2015), and four for anxiety (Lecavlier et al., 2014) had moderate support (or "moderate" quality by evidence grading) by virtue of acceptable to excellent psychometrics, with some data on sensitivity to change. Out of necessity, evaluations heavily weighted reliability and validity. However, at the end of the day, measure sensitivity to change should be a priority.

Since then, a significant amount of new clinical trial data are available. Taking demonstrated "sensitivity to change" from short-term intervention trials as a priority, the ABC-Stereotypy subscale (McCracken et al., 2002; Marcus et al., 2009; Owen et al., 2009; Hardan et al., 2012; Scahill et al., 2015), the Children's Yale-Brown Obsessive-Compulsive Scale-modified for ASD (CY-BOCS-ASD) (Scahill et al., 2016; Politte et al., 2018), and the Repetitive Behavior Scale-Revised (RBS-R) (Chugani et al., 2016; McGough et al., 2019; Parker et al., 2019), have successfully detected change. None of these is perfect—the ABC-Stereotopy subscale focuses only on "lower order" RRBs, and its range is limited due to item number. The CY-BOCS-ASD has been consistent in detecting treatment effects which are modest in absolute change but show limited variability, generating larger effect sizes, even though the meaningfulness of the "Resistance score" is unclear in ASD. The RBS-R broader coverage of RRBs may reduce the sensitivity of its total score, and its optimal scoring (3- versus 5-factor, Miranda et al., 2010; Bishop et al., 2013; Uljarevíc M et al., 2020a), needs additional comparisons from trial data, but the RBS-R-stereotypy subscale generated an equivalent, even slightly larger, estimated effect size than the ABC in one comparison (Hardan et al., 2012). Of note, in the multiple trials that included both the CY-BOCS-ASD and the ABC-Stereotypy subscale, treatment effects have never been discordant across measures, both positive and negative. Such convergence between a parent-report and

clinician-rated measure adds validity to each. Early phase trials may consider choosing between the ABC-S versus the RBS-R depending on targeted mechanism, behavioral dimension, and preclinical effects. Although the US FDA accepted the proposed endpoint of the Children's Yale-Brown Obsessive Compulsive Scale for Pervasive Developmental Disorders (CYBOCS-PDD) for a proposed registration trial (NCT00515320; Herscu et al., 2019), concern exists over the CYBOCS-PDD's consolidation of lower- and higher-order repetitive behaviors in its ratings, as these may have differing neurobiologic foundations. Overall however, these three measures perform well as endpoints.

With new data, anxiety endpoints in ASD have coalesced into stronger support available for two clinician measures, the Pediatric Anxiety Rating Scale (PARS) and the Anxi- ety Disorder Interview Schedule—Clinical Severity Rating (ADIS-CSR) (McNally Keehn et al., 2013; Storch et al., 2015; Wood et al., 2015), both again demonstrating very good psychometrics and sensitivity to change. These are recommended for future studies. By comparison the MASC-Parent performs less well in these new CBT studies. In addition, new psychometrically sound anxiety measures have been developed, although they lack information on sensitivity to change (Carruthers et al., 2018; Scahill et al., 2019).

Given the ubiquity of social skill and interaction deficits in ASD, there is a compelling need for a developmentally based social communication measure, one that captures skill acquisition in the context of developmental level, rather than solely a metric of deficits (Bishop et al., 2019), and is also sensitive to sex and gender effects (Halladay et al., 2015). One approach has been to examine Vineland measures of adaptive behaviors, socialization, and communication scales as endpoints by defining fine-grained clinically meaningful change estimates to apply in clinical trials (Chatham et al., 2018), given observations of some sensitivity to change from early intervention (Dawson et al., 2010) and pharmacologic trials (Williams et al., 2006; Scahill et al., 2012). The situation in ASD is not dissimiliar to that of FXS (Erickson et al., 2017) or other NDDs. ASD clinical trials should also consider borrowing and adapting well-validated functional measures from other related areas to fill gaps, such as cognitive (SCoRS; Keefe et al., 2006) and functional (Patterson et al., 2001) from schizophrenia for adults, or prosocial and deficit social skill measures (BASC-2, SISS; Gresham and Elliott, 2008; E. Anagnostou et al., 2015) from disruptive behavior disorders intervention trials. Too few measures have been subjected to efforts to define "minimum clinically meaningful" change (Jacobson and Truax, 1991; FDA, 2009; Coon and Cappelleri, 2016).

A number of new measures of ASD core domains have been developed that are psychometrically sound, including the Autism Impact Measure (AIM; Kanne et al., 2014; Mazurek et al., 2018; Houghton et al., 2019), the Autism Behavior Inventory (ABI; Bangerter et al., 2019), and the Brief Observation of Social Communication Change (BOSCC)(Grzadzinski et al., 2016). The BOSCC may prove to possess sensitivity to change (Pijl et al., 2018; Kim et al., 2019). The field awaits more data for these measures from older children and treatment sensitivity from controlled trials for evaluation. In addition, data-driven attempts to refine existing clinical endpoints have been encouraging. Applying advanced statistical methods, such as Item Response Theory and machine learning, to large datasets containing common ASD measures, such as the SRS, the Social Communication

Questionnaire (SCQ), and ADOS, has shown promise to increase precision for diagnosis and detection of drug effects (Bone et al., 2016; Sturm et al., 2017; Kuhfeld and Sturm, 2018). With the SRS, multiple short forms and subscales have been derived that have removed items identified that exert confounding effects due to age, language, and non-ASD behaviors (Park et al., 2017; Sturm et al., 2017), increasing precision as measures of social communication and other domains, not global severity including comorbidity. Analysis of SCQ items from multiple datasets suggested RDoC social processes domain to be dimensional (Uljarevíc M et al., 2020b). These deserve application in secondary analyses of trial data for comparison and possible detection of obscured drug effects. Additional measures of circumscribed interests (Turner-Brown et al., 2011) and anxious and depressive symptoms (Uljarevic et al., 2018), also represent serious attempts to improve trial assessments.

In FXS, an interesting measurement approach was the testing of composite scores from the FXS Rating Scale and FXS Domain Specific Concerns measure, which identified a positive treatment effect of NCZ-2566, trofinetidine (NCT01894958), but trial data are not yet available. While the relevance to ASD is uncertain, such composite measure development may enhance sensitivity to overall benefits, but may be misleading (Montori et al., 2005), as the heterogeneity and differing genetic and biologic underpinnings of ASD phenotypic traits suggest the need to declare independent dimensional clinical endpoints. Similarly, the importance of treatments to improve adapative behaviors and reduce disability is of obvious importance, especially for the design of Phase III efficacy trials. A clinically relevant metric is the difference score between IQ and overall adaptive behavior that has been found to increasingly diverge with higher IQ across children and adults (Bal et al., 2015; Duncan and Bishop, 2015). This discrepancy score may serve as a crucial endpoint in longer-term intervention studies of higher-functioning individuals with ASD. Examining the precision of these as endpoints should be a high priority. Such measures provide a potential validation of the meaningfulness of a treatment effect in later-stage clinical efficacy trials.

A fundamental challenge in endpoint selection for targeted treatments in ASD and related disorders relates to differences between the aims of early phase proof of concept or mechanism trials (Phase I and II) versus later stage efficacy studies (Phase III). Early phase studies by necessity are of short duration, built around determinations of target engagement, dose selection, and detection of proximal signals of potential efficacy. With regards to core ASD domains, changes in complex, global, learned behavioral dimensions such as social communication are considered less likely in short duration trials. Determination of efficacy and distal, clinically meaningful improvements in social adaptation and quality of life require trial durations considerably longer than the majority of typical RCTs in ASD, perhaps requiring minimum treatment exposures of 6 months or longer (Erickson et al., 2017), especially given the sensitivity of the most commonly applied adaptive skill measures, such as the Vineland Adaptive Behavior Scales. Therefore, additional efforts are needed to validate and develop consensus around appropriate measurement batteries and endpoints for early phase versus late phase efficacy trials. Lengthening early phase clinical trials would slow drug development progress further, and appears ill-advised, given that circuit or mechanistic based endpoints are available. The desired measurement sensitivities

optimal for ASD early phase trials herein differ from the proposed “shorter” (12 months), or “longer” (>12 months) durations suggested for FXS (Erickson et al., 2017).

As a result, the identification of ASD subdimensions and correlated biomarkers have important implications for targeted drug development efforts, in order to enhance the accuracy and sensitivity of early phase trial results, supporting Go/No-Go decision making for compound selection and reducing negative Phase III trials, thereby de-risking and increasing efficiency of drug development (Grabb et al., 2016; Paul et al., 2010). In addition, the further identification of behavioral subdomains which are heritable, and can be shown to function as quantitative traits, hold promise for the creation of biologically informed targets for drug effects.

3.13. Can trial designs be improved?

A major weakness in extant RCTs for ASD and related disorders, especially early phase trials, is that the vast majority of studies are under-powered to detect moderate, clinically significant effects; rather, such studies defend sample sizes to capture large effects that all too often are unrealistic or not replicated. With respect to ASD core deficits, it is unlikely that longstanding, “trait” functional deficits such as impaired social communication would be amenable to near normalization due to lost learning during sensitive developmental periods, even with targeted treatments (despite “rescues” in animal models). Despite the challenges of recruitment for larger trials, an emphasis on reproducibility demands larger clinical trials, even in early phase studies.

Lessons learned from ASD early behavioral intervention trials can inform studies of potential pharmacotherapies. Comprehensive early intervention programs in very young children showed gains in cognitive measures and adaptive skills, but less improvement in social functioning (Dawson et al., 2010). Modular, shorter duration interventions focused on social communication (with different endpoints) yielded more robust improvements in social domains (Kasari et al., 2006). Given the broad access to a wide range of behavioral and educational interventions, studies of com- bined behavioral and pharmacologic treatments are sorely needed. One rare example suggests that drug therapy may boost longer-term improvement in children undergoing a social skills intervention (Wink et al., 2017). Hypothesis-driven combined treatment trials with targeted pharmacotherapy could reveal synergistic or augmenting effects, substantially enhancing the efficacy of standard behavioral interventions for ASD.

Early phase trials are also taking too long to advance the field by vetting preclinically nominated compounds, frequently taking years to complete. Shortening trials relying on typical clinical efficacy endpoints may be difficult; nevertheless, review of many early phase studies finds the majority of change occurs rapidly enough to detect sooner. Embracing intermediate phenotypic endpoints for early phase trials, such as cognitive endpoints strongly linked to behavior, social reward, eye-tracking, and/or EEG readouts, might facilitate the wider use of single-dose acute challenge or brief repeated dosing designs to establish presumptive efficacy. The addition of modest duration continuation phases could still afford exploring early efficacy signals with linked behavioral outcomes.

Another concern relates to the use of cross-over trial designs in RCTs of ASD and neurodevelopmental disorders. Several issues arise in cross-over designs, including carry-over effects from initial treatment, unblinding due to emergence or resolution of side effects in wash-out phases, and effects of unequal drop-out over time. Systematic or meta-analytic health care quality standards often classify cross-over trials as “low quality” or “high risk for bias” evidence (Schünemann et al., 2006). The time course of response and decay of many behavioral endpoints used in RCTs for ASD and related disorders is unfortunately unknown at present and challenges the use of such designs for future studies testing effects on core deficits.

Recommendations exist to manage expectancy bias in clinical trials, but most ASD trials do not incorporate them (Siafis et al., 2020), such as single-blind lead-in phases, analytic plans separating initial from later blinded periods (McGough et al., 2019), or randomized, discontinuation phases following an acute, blinded phase that can yield data on durability of drug effects (RUPP Autism Network, 2005). A recent RCT of trofinitide in Rett Syndrome utilized a 2-week single-blind placebo phase, which may have reduced placebo confounds. An important, though labor-intensive, tactic to minimize “peeking through the blind” by side effect awareness, is separating efficacy raters from side effect knowledge by using “treating” clinicians for dosing and adverse event monitoring. Contrary to expectations, in a meta-analysis of 26 ASD RCTs, clinician-administered endpoint measures were found more vulnerable to placebo effects than caregiver ratings (Masi et al., 2015), while shorter trial length and more study visits did not moderate expectancy effects. However a more recent meta-regression analysis found clinician measures less subject to expectancy, as well as fixed-dosing schedules, and fewer number of sites (Siafis et al., 2020). In the phase 2 trial of balovaptan versus placebo, symptom measures (SRS-2, ABC, RBS-R) all proved more susceptible to placebo effects that the adaptive functioning measures (Vineland Adaptive Behavior Scales) (Bolognani et al., 2019). The application of objective outcome measures, where possible, is another means to preserve blinding and reduce placebo response. In that vein, intermediate phenotypes such as cognitive tests, eye-tracking, and EEG parameters as primary endpoints have additional advantages in early phase studies.

Additional challenges are encountered in longer-term studies aimed at detecting effects on skill acquisition, changes in adaptive functioning, and quality of life, critical in the determination of the broad impact of a novel intervention on core deficits. Challenges include unclear ability of informant reports to accurately capture separate intervention effects versus developmental gains over time, as well as the sensitivity of measures to changes in adaptive function and/or quality, given that differences in subdomain scores are often driven by few items in some measures, or assume equal opportunities for certain behaviors to be demonstrated. Another problem involves external influences (education and treatment changes over time) on functioning and symptom level independent of experimental treatment.

3.14. Regulatory requirements

In the era of targeted treatments, several challenges arise in the regulatory evaluation of new therapeutics. An especially daunting issue relates to specifying new indications for

a particular treatment. If the biology of ASD's domains or subdimensions differ, global change may be more modest, therefore, determining the significance of an intervention's impact on a single domain is more difficult. For example, would a reduction in "restricted interests" associated with drug exposure meet standards for an indication in ASD? Similarly, if a targeted compound appeared to exert a beneficial effect at a particular age of exposure, should it be required to be examined at earlier ages? Likewise, given the persistence of ASD and its negative impact across the entire lifespan, including excess mortality, how should regulatory bodies assess the risk/benefit ratio of a new treatment? What are the standards for safety determination considering that some interventions may affect long term development, cognition, sexual maturation? What standard of preclinical juvenile toxicity data is necessary prior to testing in pediatric samples? A requirement of extensive, preclinical "juvenile" toxicology testing may represent an insurmountable hurdle for smaller drug development programs and reduce enthusiasm, risking development investments that require such expensive and protracted studies prior to assessment of an agent's promise. Differences between ASD efficacy results between adults and pediatric samples strongly support the importance of early pediatric pharmacokinetic bridging studies. Other hurdles include EMA requirements for randomized withdrawal from maintenance trials to assess duration of treatment effect and impact of withdrawal. If a compound ameliorates a developmental delay, what is the assessment if progress regresses, plateaus, or continues once treatment is withdrawn?

3.15. Incorporating patient/caregiver perspectives: insuring relevance

Attention to the interests of parents and family members are often not considered in the design and choices for intervention targets of promising drug therapies. Such a potential disconnect risks that research findings may be deemed irrelevant to the desires and priorities of parents and stakeholders of individuals with ASD. Substantial efforts have recently been made to appreciate the priorities of individuals involved and their parents (Bal et al., 2018; McConachie et al., 2018). Parents highlight the importance of independence, anxiety, distress, hypersensivity, insomnia, happiness, family relationships, and parent stress as important indices of important outcomes. and have led to the development of an arguably more ecologically valid quality of life scale, the Autism Family Experience Questionnaire (AFEQ; Leadbitter et al., 2018). Caregivers less often rank RRBs as priorities for treatment targets, while highlighting the mood and anxiety symptoms that may contribute to the intensity or severity of RRBs. Parent-nominated problems, rated by parents and clinicians, has been employed to individualize capturing parent perspectives on treatment impact (Scahill et al., 2017). Greater efforts to demonstrate effects on these concerns and impact on overall quality of life are recommended, including possible further measurement development (Varni et al., 1999; Leadbitter et al., 2018).

3.16. Anticipated ethical issues

Disruption of brain development and the roots of later emergence of ASD are well known to begin in fetal development (Muhle et al., 2018). Early intervention, including potential curative drug therapies, is expected to require treatment at younger ages than currently tested, and that brings exposure to unknown risks. Contrary to preclinical studies "rescuing" ASD phenotypes in adult animals with experimental treatments (Dölen et al.,

2007; Henderson et al., 2012), as time goes by, negative trials in ASD, FXS, and other disorders enrolling adolescents and adults challenge the optimism that the disordered brain development and experience generated by these disorders can be promptly reversed. As more targeted drug treatments are identified, there will be a theoretical and clinical argument to intervene at earlier and earlier stages of development than is currently deemed acceptable (Veenstra-VanderWeele and Blakely, 2014), given unknown risks. The field and regulatory agencies must grapple proactively with what represents adequate indication of promise sufficient for research examination and what would demonstrate meaningful standards for efficacy and safety given the high stakes of efforts to modify the impact of ASD and related disorders across the lifespan. Such studies at some point in their development will undoubtedly require major investments necessary to undertake long-range studies to determine the risk/benefit ratios of very early targeted drug therapies, balancing the major need for progress and possible cure against protection from safety risks.

3.17. Are ASD animal models still relevant?

Given the disappointing results of attempts to translate rescues of ASD phenotypes in ASD and FXS animal models to humans, there has been serious debate of the relevance of ASD preclinical models to clinical drug development (Chadman et al., 2019). As rightly pointed out, many of the preclinical behaviors of ASD models do not map as close to the human phenotype as desired (Jeste and Geschwind, 2016). This is perhaps most notable with respect to preclinical ASD social behavior analogues. Hopefully greater refinement of these animal behavioral assessments will increase their translatability to the human phenotype for clinical studies, via such methods as EEG, MR imaging, reward responsivity measures, and the develop- ment of new social behavioral assays and analysis methods for preclinical investigation (Silverman and Crawley, 2014; Howe et al., 2018; M. Sonzogni et al., 2018; Das et al., 2019). Identification of biomarkers, such as neurophysiological signatures, that are comparable across animals and humans may facilitate greater success in translation.

3.18. Recommendations and conclusions

The Work Group debated recommending a menu of “gold standard” ASD clinical trial assessments and endpoints. Ultimately, the conclusion was that more progress in development and validation of clinical trial measures is needed before such a consensus is possible, but common endpoints, rated by sensitivity to change, with proven acceptable psychometrics, are listed in Table 5. Continued research to critically evaluate the precision and ecological validity of measures to include in trials should be a high priority. However, a number of recommendations emerged to enhance standardization, precision, and success of future ASD clinical trials, in the areas of methodologic development, planned clinical trials, and preclinical drug development. The specific recommendations for the field include the following:

3.19. Preclinical

- **a.** Move away from animal models purely based on behavioral phenotypes to more circuit-based approaches to improve translation
- **b.** Favor preclinical measures with direct translation to clinical endpoints

c. Robust demonstration of compound engagement of target mechanism

d. Convergence of effects across multiple preclinical models should be examined

3.20. Clinical

a. Replication of positive findings has high priority

b. Prioritize additional treatment research on ASD co-occuring disorders

c. Better basic characterization of study samples for cognitive ability, core symptom severity, gold standard diagnostic measures, language level, functional ability, and comorbidities

d. Trials should include most commonly employed measures (eg. SRS-2, ABC, RBS-R, CGI-I, Vineland), even as secondary endpoints, to facilitate combined/comparative analyses

e. More outcome measures should be developed to target key domains/constructs such as RDoC systems (eg. positive valence–social motivation)

f. Preferred endpoints should have broader developmental and ability norms, and reliability/stability data

g. Endpoints need demonstrated sensitivity to capture established clinically meaningful change, beyond their sensitivity to identify deficits or differences

h. More outcome measures are needed with independence from confounding influence of cognitive or language ability

i. Hypotheses should drive study design (including sample size, population stratification, etc.); trial length choice based on when changes are expected according to the hypothesis and the outcome measure

j. Differential treatment impact according to cognitive ability needs broader investigation

k. More research on utility of digital approaches with required data on feasibility, reliability, sensitivity to change, and convergent validity with standard behavioral measures

l. Greater incorporation of perspectives of individuals with ASD and their families in the development of measures, nomination of meaningful endpoints, and trial design

m. Pilot studies are still necessary for new compounds to test proof of mechanism/concept hypotheses, but are not sufficient for estimating effect size for repurposing compounds

In summary, among neuropsychiatric and neurodevelopmental disorders, there is perhaps none as complex and etiologically and phenotypically heterogenous as idiopathic ASD. It is not a surprise that ASD drug development challenges our most sophisticated preclinical models and methods for developing precise translational clinical study designs and identifying curative therapeutics. Greater leveraging of genetic and neurobiologic data

with further refinements in our understanding of ASD's phenotypic dimensions should lead to more significant progress in this effort. However, methodologic advances will depend heavily on research investments to refine clinical tools and identify new, biologically based endpoints of key circuits involved in ASD. Following that, it is certain that multiple tests of rational, carefully adjudicated and prioritized drug targets, many of which are expected to fail, must be examined before disorder modifying treatments for ASD and possibly other related disorders are identified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of the founding source

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Table 1

Current Challenges in ASD Clinical Trials.

Managing ASD heterogeneity
Failures of preclinical to clinical translation of targeted treatments
Lack of validated, objective biomarkers for diagnosis, stratification, treatment prediction, early change detection, target mechanism engagement, and relevant neural circuit modulation
Need for improved clinical endpoints
Prioritization of molecular targets
Creating more robust trial designs
Navigating regulatory requirements for new therapeutic indications
Defining priorities for therapeutics directed towards comorbidities
Incorporating participant/caregiver perspectives
Addressing anticipated research ethical issues

Table 2

Molecular Targets Currently in Development.

Clinical Development
• Cannabinoid receptor agonist
• Vasopressin 1A antagonist
• Bumetanide
• NMDA receptor antagonist
• Tyrosine hydroxylase inhibitor
• Oxytocin receptor agonist
• GABA A receptor agonist

Table 3

Biomarkers in ASD Under Examination.

Biomarker	Potential type
Eye Tracking	
multiple paradigms	S,D,M
Resting state electroencephalogram (EEG)	D
alpha power/ coherence/ suppression	D
gamma power	D
beta power	PG
Event Related Potentials (ERPs)	
visual, auditory, multisensory	D
Pupillometry (emotional faces)	D
Facial emotion labeling (pictures)	D
Whole Blood Serotonin (WBS)	
WBS+ *N*- Acetylserotonin + melatonin	D
Cerebrospinal fluid arginine vasppressin	D,M
Legend:	
S: suspectibility/ risk	
D: diagnostic	
M: monitoring	
PG: prognostic	
PR: predictive	
PD: pharmacodynamic response	
SF: safety	
(see BEST-https://www.ncbi.nlm.nih.gov/books/NBK326791/)	

Table 4

Evaluation Criteria for Proposed Compounds and Targets.

Preclinical Data: Are there robust, rigorous preclinical data to understand:
• The proposed target mechanism?
• Whether the proposed compound engages the target mechanism?
Receptor Occupancy/ Pharmacodynamic Readout:
• Is there a PET ligand for target occupancy studies of the proposed compound/target in humans?
• Are there pharmacodynamic readouts to inform clinical dose selection?
• Are there functional measures (e.g., EEG, fMRI) available to validate involvement of the presumed brain area or circuit?
• If no PET ligand is available, are there PET ligands in development?
Clinical Data: If human data is available:
• Is there convincing evidence that the proposed compound engages the target/brain area (e.g., receptor occupancy, functional measure)?
• Is there convincing evidence that engagement of the target produces a promising clinical signal?
• What indications has the compound/target been explored for?
NIMH Research Domain Criteria (RDoC): Does the target/compound affect a circuit relevant to an RDoC domain?
• Negative Valence Systems (i.e., systems for aversive motivation)
• Positive Valence Systems
• Cognitive Systems
• Systems for Social Processes
• Arousal/Regulatory Systems
IND: For a proposed compound, is there an IND in effect for the proposed clinical trial?
• If not, what will be required to enable an IND?
• How long would it take to reach IND stage?

Adapted from National Advisory Mental Health Council (NAMHC) FAST Working Group.

Table 5

Outcome Measures for ASD Clinical Trials Ranked by Sensitivity to Change.

Domain	Instrument	Sensitivity to Change	Informant	Burden	Comments
ASD Severity					
	Social Responsiveness Scale - 2 (SRS-2) Total	++	S, P, T	Low	Many non-ASD covariates
	Brief Observation of Social Communication Change (BOSCC)	+	Ex	Medium	No comparative trial data
(With Conditions)					
	Aberrant Behavior Checklist (ABC) - Total	+	P, T	Low	Multiple non-ASD factors
	Parent Target Problems	+	Ex	Low	
(New/Needs More Data)					
	Autism Behavior Inventory (ABI)	N/A	P, Ex	Low	
	SRS-2 Item Response Theory 16-item Short Form	N/A	S, P, T	Low	
	SRS-2 11-item Factor Analyzed Short Form	N/A	S, P. T	Low	
	Autism Impact Measure (AIM)	N/A	P	Low	
	Autism Diagnostic Observation Schedule-2 Calibrated Severity Metric (CSS) (ADOS-2 CSS)	N/A	Ex	High	
Social/ Communication					
	Vineland Adaptive Behavior Scales (VABS Communication) II	+++	P, Ex	Medium	Requires lengthy trials
	Social Skills Improvement System (SSIS)	++	S, P, T	Low	Used with cognitively able
	Natural Language Sample	++	Ex	Medium	
(With Conditions)					
	ABC Lethargy- Social Withdrawal subscale	++	P, T	Low	Limited range of behaviors
	Behavior Assessment System for Children- 2 (BASC-2)	++	P, T	Low	
	Early Social Communication Scale (ESCS-JAMES)	+	Ex	Medium	Data from < 9 yo
	Communication and Symbolic Behavior Scales (CSBS)	+	Ex	High	Limited to < 6 yo
New/Needs More Data					
	Autism Impact Measure (AIM)	N/A	P	Low	
	Pervasive Developmental Disorder-Behavior Inventory (PDD-BI)	N/A	P	Low	
	Social Communication Interaction Test (SCIT)	N/A	Ex	Medium	Data from > 17 yo
Repetitive Behaviors/Restricted Interests					
	Children's Yale-Brown Obsessive Compulsive Scale-Modified for ASD	+++	Ex	Medium	Limited score range
	Aberrant Behavior Checklist-Stereotypy subscale	+++	P, T	Low	Motor behaviors only

Domain	Instrument	Sensitivity to Change	Informant	Burden	Comments
	Repetitive Behavior Scale-Revised	++	P	Low	Multiple scoring approaches
(With Conditions)					
	Stereotyped Behavior Checklist	N/A	P	Low	
	Repetitive Behavior Questionnaire	N/A	P	Low	
New/Needs More Data					
	Autism Behavior Inventory	N/A	P, Ex	Low	
Anxiety					
	Anxiety Disorders Interview Schedule-Clinician Severity Rating (ADIS-CSR)	+++	Ex	High	
	Pediatric Anxiety Rating Scale (PARS)	+++	Ex	Medium	
(With Conditions)					
	Multi-dimensional Anxiety Scale for Children - Parent (MASC-P)	+	S, P	Low	
	Child and Adolescent Symptom Inventory −4 21-item Anxiety Scale (CASI-4-ANX)	N/A	Ex	Medium	
(New/Needs more data)					
	Parent-Rated Anxiety Scale for ASD (PRAS-ASD)	N/A	P	Low	
	Spence Children's Anxiety Scale Parent (SCAS-P)	N/A	P	Low	

+ - one positive comparative study or mixed S - Self.

+ + - > 1 study showing change to active treatment P - Parent/ Caregiver.

+ + + - multiple studies showing robust, consistent changes EX- examiner T - Teacher.