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Running Head: ASD AND ADHD

An update on the comorbidity of ASD and ADHD: A focus on clinical management

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Abstract

Attention deficit / hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) commonly co-occur. With the DSM-5, clinicians are permitted to make an ASD diagnosis in the context of ADHD. In earlier versions of the DSM, this was not acceptable. Both ASD and ADHD are reported to have had substantial increases in prevalence within the past 10 years. As a function of both the increased prevalence of both disorders as well as the ability to make an ASD diagnosis in ADHD, there has been a significant amount of research focusing on the comorbidity between ADHD and ASD in the past few years. Here, we provide an update on the biological, cognitive and behavioral overlap / distinctiveness between the two neurodevelopmental disorders with a focus on data published in the last four years. Treatment strategies for the comorbid condition as well as future areas of research and clinical need are discussed.

Keywords: ADHD, autism spectrum disorder, ASD, neurodevelopmental disorder, developmental delay, comorbidity, children, adolescent

An Update on the Comorbidity of ASD and ADHD: A Focus on Clinical Management

ADHD is characterized by developmentally inappropriate inattention, impulsiveness, and/or hyperactivity that remain relatively persistent over time and result in impairment across multiple domains of life activities [1]. ASD is characterized by persistent deficits in social interaction and communication (e.g., poor social-emotional reciprocity, deficits in nonverbal communication, deficits in developing relationships) as well as restrictive, repetitive patterns of behavior or interests [1]. In the DSM-IV [2] and previous DSM editions, clinicians were prohibited from making an ASD diagnosis in an individual with ADHD. The prevailing notion was that *most* children with ASD had high levels of inattention and hyperactivity-impulsivity, thus introducing bias into the diagnosis of ADHD. In the DSM-5, this prohibition has been lifted [1] and the result has been largely applauded [3] and supported by data [4, 5]. While some researchers have argued against considering "comorbidity" and instead argue for considering symptom co-occurrence [6], at this time, comorbidity research has largely dominated the field.

A substantial minority of youth with ADHD (15-25%) demonstrate ASD traits and symptoms [7, 8] with 12.4% having an ASD diagnosis [9]. Conversely, ADHD is *the* most common comorbidity in children with ASD with comorbidity rates in the 40-70% range [10-13]. Consistent with these data, some researchers, using latent class analyses, assert that while ADHD symptoms occur without ASD symptoms, ASD symptoms do not occur without ADHD symptoms [14].

To further clarify ASD/ADHD comorbidity, the present review updates our 2012 review. We describe data published within the last four years and offer specific clinical and research recommendations based on extant data.

Genetics and Neurobiology of ASD and ADHD

Genetics. A PubMed search with the key words "ADHD AND (autism OR autistic) AND (genes OR genetics OR genotype) found 322 articles from 1/1/2012 to 11/17/2015. Abstracts were read to retain only studies that examined the shared or different genetic findings between

ADHD and ASD (N=47). ASD and ADHD share genetic risk factors [15]. A large twin study of 53 neurodevelopmental problems identified a single genetic factor accounting for a large proportion of the phenotypic covariation among all the 53 symptoms [16]. Three specific genetic subfactors were identified as 'impulsivity,' 'learning problems,' and 'tics and autism'. Twin studies of children found that communication difficulties showed the strongest genetic overlap with traits of ADHD [17, 18]. Polderman et al. suggested that the attention-related problems are most commonly shared between ADHD and ASD, thus focusing on biological pathways involving attentional control may help to unravel common genetic causes [19].

A large number of copy number variants (CNVs) and chromosome abnormalities confer risks for ADHD and ASD. These include 2q11.2 deletions [20], the 3p26.3 CNVs involving the CNTN6 gene [21], 4p12 13 duplications involving a cluster of four $GABA_A$ receptor subunit genes [22], 7q11.23 duplication (the classic Williams syndrome region) [23], a rare maternal inherited 8q24.3 and a paternally inherited 14q23.3 CNV [24], duplications and deletions at 16p13.11 [25], monosomy of 15q26 [26], duplications of X (XXY Klinefelter syndrome) or Y chromosome (XYY syndrome) [27, 28]. Genome-wide searches for CNVs in ADHD [29] and ASD samples [30] implicated an increased burden of large, rare highly penetrant CNVs. 15q13.3 duplications spanning the CHRNA7 gene was identified as a novel risk factor for ADHD [29]. ASD-CNV loci included gains and losses at 16p11.2, SHANK2, NRXN1, and PTCHD1 [30]. The 22q11.2 deletion [31] confers high risks for ADHD, ASD, anxiety and mood disorders, and schizophrenia/psychotic disorders [31-33]. The 15q11-13 microdeletion causes several disorders including ADHD and ASD [34-36]. Prader-Willi syndrome (PWS) is caused by maternal uniparental disomy 15 (mUPD) or paternal deletion of 15q11-13 (DEL). DEL children do not differ from mUPD children in ASD symptoms. However, in adolescents, mUPD patients showed significantly more autistic symptoms and impulsive behavior than DEL patients [37]. Martin et al. found three common biological processes enriched by large rare CNV hits for

ADHD and ASD, even when the common CNV regions were excluded: nicotinic acetylcholine receptor signaling pathway, cell division, and response to drug [38].

The first cross-disorder genome-wide association studies (GWAS) of five major psychiatric conditions (including ADHD and ASD) provided the first genome-wide evidence for shared genetic risk factors. In particular, two of the four loci localize to voltage-gated calcium channel genes [39]. Cristino and colleagues built integrated genetic networks for ASD, X-linked intellectual disability (XLID), ADHD and schizophrenia risk genes and identified common molecular pathways and functional domains as well as disease-unique patterns of variations, particularly intergenic DNA variations that comprise regulatory sites for transcription factors (TFs) or miRNA [40]. 15 of 180 candidate genes were associated with at least five of six disorders studied. This study also identified two shared genetic components that accounted for 20-30% of the common genetic variance: one implicated nervous system development, neural projections and synaptic transmission and the other implicated cytoplasmic organelles and cellular processes [41].

Genes reported for ADHD and ASD have been found enriched in similar functional pathways such as cell adhesion and neuronal migration [42-49]. These analyses also implicated gene expression and protein translation, which include chromatin modifiers [50], transcription factor genes [51], and the fragile X mental retardation 1 gene (FMR1) [52]. Several other implicated pathways are mitochondrial dysfunction [53]; neuronal membrane trafficking [54-57]; neuropeptide oxytocin related genes [58, 59]; metabotropic glutamate receptor genes [37]; and genes in the catecholamine system [60, 61].

Environmental factors. Many environmental toxins, developmental exposure of alcohol and cigarette smoke, hormonal imbalance and pre-/perinatal risk factors (PPFs) are shared between ADHD and ASD as reviewed previously [62]. However, a recent large study of pre- and perinatal risk factors (PPFs) found that comorbidity of ADHD and ASD is unlikely to be explained by shared PPFs. Maternal infections and suboptimal condition at birth were more

important for ASD [63]. Young parental age, maternal diseases, smoking and stress were associated with increased risk for ADHD [63]. Birth difficulties (cesarean section and induction of labor) were not associated with either ADHD or ASD [64]. A community-based study of 4,000 pairs of 12-year-old twins also found little overlap among the environmental factors associated with ADHD and ASD symptoms [17].

Both genetic and environmental risk factors, and their interaction can alter epigenetic programs including DNA methylation, histone modifications and microRNA expression. The subsequent alterations in gene expression, along with other genetic liabilities, could influence tightly regulated brain development processes such as neuronal and synaptic genesis, maturation and functional specialization. Such changes could subsequently modify the risk (or resilience) to ADHD and ASD [65-67].

Neuroimaging

A PubMed search (using key words “ADHD AND (autism OR autistic) AND (imaging OR MRI) found 67 articles (1/1/2012 to 11/17/2015), of which 12 examined structural or functional imaging findings that are shared or different between ADHD and ASD and reviewed in this section.

Structural imaging. Brain structure studies of ADHD and ASD have found both shared and distinct neural features in gray and white matter structures. Gray matter volume (GM), measured by voxel-based morphometry of MRI data, showed reduction in right posterior cerebellum specific for ADHD and enlargement in left middle/superior temporal gyrus (MTG/STG) specific for ASD [68]. The ADHD-specific reduction of right posterior cerebellum, which is extensively connected with prefrontal cortical and basal ganglia structures, has been consistently observed and suggests that there may be delayed maturation of these regions in ADHD. Such delays could give arise to the deficits in attention, executive function and working memory associated with ADHD [69-72]. The ASD-specific enlargement of the left MTG/STG, a

region important for language and social communications [73] supports the theory of precocious growth and failure to mature and specialize for specific functions in ASD [74].

Similarly, frontal-parietal regions relevant to motor functions were enlarged in ASD children, particularly postcentral gyrus (S1). ASD symptom were associated with greater gray matter volume in ADHD even in the absence of a diagnosis of ASD [75]. In healthy adults, both ADHD and ASD symptoms were correlated with GM variations in many shared and unique brain regions. Both ADHD and ASD symptoms were negatively correlated with the left inferior frontal gyrus, a key area involved in language processing, inhibition and attention control [76, 77]. ADHD was positively correlated with many cortical and basal ganglia regions and ASD was positively associated with the left middle frontal gyrus [78], thought to be of importance for executive functions [79].

Connectivity between the relevant brain regions can be inferred from white matters microstructure measured by fractional anisotropy (FA) and radial diffusivity (RD) in diffusion tensor imaging (DTI) are used to measure white matter microstructure. ASD traits were found to be positively correlated with FA and negatively with RD microstructure signatures in the right posterior limb of the internal capsule/corticospinal tract, right cerebellar peduncle and the midbrain [80]. Although ADHD subjects were not significantly different from controls, ADHD symptoms were positively associated with FA and negatively associated with RD in the left subgenual cingulum [81].

A review of neuroimaging studies concluded that ASD show increased total brain volume and overgrowth of the amygdala, an important part of the limbic system involved in many functions including emotion and motivations; yet ADHD is associated with reduced total brain volume, normal amygdala and reduced white matter FA values in the internal capsule, the large ascending and descending tracts of the brain. Shared features include lower volumes and reduced FA of corpus callosum (the large interhemispheric connection) and cerebellum, and

decreased FA for superior longitudinal fasciculus (the large front and back connections within each hemisphere) [82].

Functional imaging. In functional magnetic resonance imaging (fMRI) studies, ASD boys showed over-activation in left and right inferior frontal cortex, while ADHD boys showed under-activation in orbitofrontal cortex (OFC) and basal ganglia [83]. A single dose of the selective serotonin reuptake inhibitor fluoxetine normalized the opposite frontal lobe dysfunction in both disorders [83]. A functional near-infrared spectroscopy study (NIRS) examined response inhibition during a Go/No-Go task and found reduced activation in the right PFC in children with ASD or ADHD, indicating shared inhibitory dysfunction [84]. Deficits in sustained attention were associated with deficits in fronto-striato-parietal activation and default mode suppression in both ADHD and ASD. However, ADHD had more severe dorsolateral prefrontal cortex dysfunction and ASD had more enhanced cerebellar activation [85].

Brain connectivity. Graph theory and network matrices have been used to assess large scale brain connectivity patterns with integrated anatomical and functional data. Grayson et al described a robust rich-club organization in the human brain, whereby the most highly connected regions of the brain are also highly connected to each other [86]. In the ASD group, higher connectivity was found inside the rich-club networks. The ADHD group exhibited a lower generalized connectivity inside the rich-club networks but a higher number of axonal fibers and correlation coefficient values outside the rich club [87]. Another study used voxel-wise network centrality to measure both local and global connectivity with resting state fMRI; it found a common centrality abnormality in precuneus, the posteromedial portion of the parietal lobe, for both ADHD and ASD. Changes in temporal-limbic area were unique to ASD children regardless of ADHD comorbidity [88].

ASD and ADHD Cognitive Phenotype

A PubMed search (using key words “ADHD AND (autism OR autistic) AND (cognition, behavior, functioning, neuropsychology, treatment, intervention OR therapy) found 1988 articles

(1/1/2012 to 12/01/2015), of which 116 examined findings relevant to ADHD and ASD and are reviewed in this section.

Neurocognition. Executive functioning impairments are associated with both ADHD [89, 90] and ASD [91-93] and much cognitive research on the comorbid state has focused on executive functioning. Some research has indicated executive dysfunction in both conditions is associated with different psychiatric comorbidity patterns. For example, ASD is associated with cognitive inflexibility that predicts to greater internalizing symptoms and increased aggression while ADHD is associated with cognitive disinhibition that predicts to greater externalizing symptoms [94].

In a study of 711 children with ADHD, the impact of ASD symptoms was evaluated [8]. The presence of higher levels of ASD symptoms in those with ADHD predicted a more severe clinical, cognitive and developmental phenotype. Higher levels of ASD traits were associated with having the Combined subtype, more comorbid internalizing and externalizing disorders, lower general cognitive ability and a higher likelihood of developmental delays in language and motor development. No relationship was reported between ASD symptoms and cognitive inflexibility [8].

A study of motor deficits in children (24 with ADHD, 22 with ASD and 20 typically developing control children) [96] found that motor dysfunction was common to both ASD and ADHD. Imitation deficits were unique to ASD. The authors concluded that increased variability and impulsivity in ADHD affects motor control while in ASD, complex sensorimotor integration deficits lead to motor and imitation deficits.

A population-based twin study (N=1312) explored the phenotypic and genetic association between social communication and non-social autistic like traits (ALTs) with ADHD symptoms, reaction time variability and commission errors [18]. The phenotypic and genetic overlap between ADHD symptoms and ALTs was driven by social-communication ALTs. Social Communication ALTs were also phenotypically and genetically correlated with reaction time

variability. Response inhibition was not associated to ALTs, demonstrating that response inhibition does not explain the overlap between ADHD and ALT symptoms. The authors concluded that a modest amount of shared genetic risk factors influence reaction time variability, inattention and social-communication ALTs [18].

Another study explored the relationship between sensory processing, social participation, praxis and nonverbal IQ, severity of autism and the ADHD symptoms in the home and school settings in 41 children with ASD [97]. Nonverbal IQ was not associated with the presence of sensory processing difficulties, social participation impairments or praxis deficits. Both domains of ADHD symptoms associated positively with sensory processing difficulties, social participation impairments and praxis deficits by parent report. Conversely, teacher reports did not find any relationship between hyperactivity-impulsivity symptoms and sensory processing and found that inattention was positively related only to social participation impairments [97]. While this study did not make ADHD diagnoses, others have reported that compared to youth with ADHD, children with ASD+ADHD have more sensory and motor deficits [98].

A study investigated planning in 83 boys with ASD only, ADHD only, ASD+ADHD, and typically developing children [99]. On the Tower of London, youth with ASD+ADHD were more impaired / less accurate at younger ages but comparable to other groups at older ages. This suggests a developmental delay that is more robust in the ASD+ADHD group.

Tye and colleagues [100] investigated attention and inhibition using a flanker cued-continuous performance test administered to 8-13-year-old boys with ASD (n = 19), ADHD (n = 18), co-morbid ASD+ADHD (n = 29) and typically developing controls (n = 26). Youth with ADHD (with and without ASD) made more omission errors and had greater reaction time variability. Youth with ASD demonstrated abnormalities in response preparation and conflict monitoring. Youth with comorbid ASD+ADHD had deficits in all these domains. The authors

concluded that youth with ASD+ADHD had an “additive” profile rather having a qualitatively distinct distinctive pattern of weaknesses.

Verbal working memory using a letter/number sequencing task and a verbal list-learning task was investigated in a sample of children (age 8-17), 38 with ASD, 79 with ADHD and 50 controls [101]. Compared to controls, the ASD and ADHD groups performed less well. No differences emerged between the ASD and ADHD groups. Youth with ASD that had elevated rates of ADHD symptoms were more impaired than both the ASD and ADHD groups on verbal working memory task. The authors concluded that ASD+ADHD symptoms represent an “additive” effect in which ADHD symptoms negatively affect performance in ASD.

Response time intra-subject variability was investigated in 46 children with ASD, 46 with ADHD, and 36 typically developing control participants (aged 7–11.9 years) [102]. Results indicated that ADHD symptoms (regardless of the diagnostic classification of ASD or ADHD) were associated with response time intra-subject variability fluctuations at Slow-2 frequencies (0.20–0.345 Hz, i.e., periods of 3–5 s).

Children age 8- to 10-year-old in four groups (a) ASD+ADHD (*n* = 11), (b) ASD only (*n* = 9), (c) ADHD only (*n* = 38), and (d) no diagnosis controls (*n* = 134) were compared on a continuous performance test (CPT) [103]. Children with ASD+ADHD and ADHD only had more errors of commission and more response variability than ASD only and control participants on the CPT.

Studies of adults with ADHD and ASD are far less plentiful. In adults, problems with attention-switching occur in both ASD and ADHD [104]. One study with adults with ASD, ADHD, and comorbid ASD+ADHD reported that all three groups reduced performance on multiple tests of executive functioning although performance was comparable between the three groups [105].

Social cognition. A study of 92 children found that those with ASD displayed reduced lateral occipito-temporal face-sensitive N170 amplitude across all stimuli while those with ADHD demonstrated reduced modulation of the centro-parietal N400 component (associated with

semantic processing) amplitude for fearful expressions in parietal scalp regions and happy facial expressions in central scalp regions [106]. These data indicate that structural encoding alterations are common to ASD while contextual processing stage abnormalities are common to ADHD. The comorbid ASD+ADHD group had deficits of both conditions.

Another study investigated response inhibition in an emotional Go/No-Go task that required discriminating four emotional facial expressions (angry, fearful, happy, and sad) from neutral ones and the impact that ADHD and ASD symptoms had on performance in youth with ASD (*n* = 28) relative to typically developing children (*n* = 23) [107]. Children with ASD were faster than typically developing peers on all emotional trials and response speed was positively correlated with ASD symptoms. Youth with ASD demonstrated a positive correlation between ADHD symptoms and impulsive responses to emotional and neutral No-Go stimuli. The researchers concluded that the ASD group's impairments on the social-emotional response inhibition task had both social and cognitive control components and each component was associated with ASD symptoms (social) and ADHD symptoms (cognitive).

Facial emotion and affective prosody recognition were tested in 90 children with ASD (43 with and 47 without ADHD), 79 ASD unaffected siblings, and 139 controls [108]. Youth with ASD were slower and less accurate at identifying facial emotions. Youth with ASD+ADHD were more impaired than ASD only on tests of emotion and affective prosody recognition. After controlling for impaired reaction time speed, inhibition and inattention, affective prosody recognition differences remained. The authors concluded that youth with ASD+ADHD were at the highest risk for emotion recognition deficits [108].

In a sample of 37 youth with ASD and 54 age and IQ-matched peers, Jarrold and colleagues [109] used a virtual classroom public speaking paradigm to assess the simultaneous ability to answer self-referenced questions and to attend to avatar peers. Participants with ASD demonstrated atypical social orienting when asked to simultaneously speak and attend to avatar peers in a virtual classroom. Youth with ASD did not demonstrate atypical social attention in the

baseline condition that did not require the dual tasks of regulating attention while speaking. Self-reported symptoms of anxiety, parent reported symptoms of inattention and IQ were moderators of performance in the ASD cohort. Youth with ASD who had both self-reported symptoms of anxiety, parent reported symptoms of inattention were at the highest risk for atypical social attention.

In addition to emotion processing, theory of mind has also been explored in both populations. Children with ADHD are not as impaired as children with ASD on theory of mind tasks [110, 111], although both are more impaired than typically developing children as well as children with obsessive compulsive disorder [111]. Other research indicates that youth with ASD+ADHD also have more severely impaired social awareness, social cognition, social communication, social motivation, and stereotypic behaviors and restricted interests than children with ASD alone [3, 112].

Temporal discounting is the decrease in reinforcement appeal that occurs with increasing delay of reinforcement. It is steeper in children with ADHD [113, 114]. A study of temporal discounting in children with ADHD (n=72), ASD (n=69) and typically developing controls (n=130) [115] found strong correlations between temporal discounting of money and rewarding activities, food and material rewards. Temporal discounting slopes were steeper for transient reinforcers with primary-reinforcing properties (rewarding activities, food and social rewards) relative to money and material rewards. Unlike the other two groups, however, the ASD group discounted material rewards to a greater extent than money, possibly due to the restricted nature of interests that accompanies ASD.

ASD and ADHD Behavioral Phenotype

Symptom overlap. While some research indicates differences in ADHD symptom levels between the disorders (more inattentive symptoms in the ASD group with the ADHD group having higher levels of hyperactivity) [17], the presence of, and number of, ADHD symptoms does not reliably discriminate between ADHD and ASD+ADHD [116-119]. For example,

approximately 60% of children with ASD meet DSM-IV-TR symptoms and impairment criteria for ADHD [116, 120]. Likewise, follow-up data on infants at high risk for ASD (due to having an older sibling with ASD) yet who do not meet ASD criteria themselves indicate that at school-entry, ADHD concerns are three times more likely compared with typically developing youth. These data suggest that ADHD symptoms are common even if the child does not meet ASD criteria, yet has a family history of ASD [121].

Similarly, youth with ADHD have more ASD symptoms / traits than typically developing children [118, 119, 122-125]. A community based study of 164 children with ADHD found that 25% of children had parent-reported ASD symptoms in the clinical range and 40% were in the at-risk range, with higher ASD symptoms being positively correlated ADHD symptoms [126]. Other data indicate that hyperactive / impulsive symptoms, not inattentive symptoms, may be more closely associated with ASD behaviors [127].

In a large study of 1496 children with ASD, 20% received a diagnosis of ADHD *before* ASD [128]. Youth diagnosed with ADHD first were diagnosed with ASD on average 3 years later than those diagnosed with ADHD and ASD concurrently or ASD only. The authors concluded that ASD should be considered in young children who have ADHD symptoms.

Social deficits are characteristic of an ASD diagnosis, but are also common in children with ADHD [129]. Until recently, social problems were frequently interpreted to be the result of ADHD symptoms, but with a high prevalence of co-occurring ASD symptoms in ADHD, it is possible that these impairments suggest deficits in social skills characteristic of ASD [130]. For example, some data suggest that parents reported ASD traits in approximately one-third to one-fifth of 75 children with ADHD and that these symptoms could not be accounted for by symptoms of ADHD [145].

Compared to children and adolescents, studies of ADHD in adults with ASD are scarce. In a sample of adults diagnosed with ADHD in adulthood, over 10% of the sample reported having a current and past diagnosis of ASD [131]. In one of the few studies to assess the

ASD+ADHD comorbidity, Johnston and colleagues [132] compared ADHD symptom reports in 31 adults with ASD and average intellectual function. Results indicated that 36.7% of adults with ASD met DSM-IV symptom thresholds for ADHD. Adults with ASD performed comparably to adults with ADHD on neuropsychological tests of selective attention. However, adults with ASD were significantly slower and more accurate on a task of attentional switching relative to adults with ADHD.

Adaptive behaviors. ADHD and ASD are both associated with adaptive behavioral deficits. A large study of children (N=2990) presenting for early intervention programming, examined socialization and communication deficits in toddlers with ASD, ADHD, and ASD+ADHD [133]. Adaptive functioning behaviors were most impaired in the ADHD+ASD and ASD groups. Children with ASD were rated by parents as being more impaired than both ADHD-only groups on every adaptive domain [133]. Others have similarly reported that ADHD negatively impacts adaptive functioning and quality of life in children with ASD [134].

Other research similarly suggests that children with ASD+ADHD demonstrate more severe impairments in adaptive functioning, with a greater discrepancy noted between IQ and adaptive functioning relative to children with ADHD alone [135]. Children with ADHD+ASD were reported by parents as having more severe impairments in nearly all domains of adaptive functioning [136]. Others have likewise demonstrated that ASD+ADHD is associated with more severe impairments in adaptive behavior when compared to children with ASD alone [112, 137]. These findings provide strong and consistent evidence suggesting that ADHD symptoms exacerbate adaptive functioning impairments in youth with ASD.

Externalizing behaviors. Tantrum behaviors were compared in youth with ASD (*n* = 255), ADHD (*n* = 40) and children with ASD+ADHD (*n* = 47) [138]. All three groups had elevated rates of tantrum behaviors although the ASD+ADHD group had the highest rates. Youth with ADHD only had the lowest rates of tantrums. Other research has likewise suggested that children with ASD+ADHD have more externalizing behavior problems than children with

ASD alone [137, 139].

Another study [95] included 181 children divided into four groups: ADHD only, ASD only, ASD+ADHD and a control group of typically developing youth. The ADHD+ASD group had a significantly lower IQ compared with the ASD and ADHD groups. Compared to controls, all three groups had higher internalizing and externalizing symptoms, while the ADHD and ASD+ADHD group had higher externalizing scores compared to the ASD and control groups. The authors concluded that the ASD+ADHD group and the ADHD only groups have similar behavioral phenotypes. The ASD+ADHD group had the highest levels of ASD symptoms indicating that the presence of ADHD may be associated with a more severe ASD phenotype. There were no differences in adaptive functioning between the ASD+ADHD and the ASD groups; however, both ASD groups had weaker adaptive skills compared to the ADHD and control groups [95].

Data from a large a longitudinal general population study in England indicated that children with ASD+ADHD were more likely to experience harsh parenting and maternal stress than children with ASD who did not have ADHD [140]. Youth with ASD + ADHD were at elevated risk for emotional problems especially if the family had a low socioeconomic status.

While not addressing the comorbid state, a large Swedish twin registry study of 1886 twins found that ASD and ADHD were associated with two different temperament profiles: ADHD was associated with high novelty seeking while ASD was associated with high harm avoidance (worry, pessimism) and low reward dependence (insensitivity to rewards) [141]. Parents of youth with ADHD and ASD both rated their children as being lower on self-directedness (being responsible and resourceful).

Treatments

Behavioral. An open label trial of an 8-week internet-based support and coaching (IBSC) intervention in ten 15 - 26 year old individuals with ASD, ADHD, or ASD+ADHD [142] provided IBSC at a fixed time twice a week for 30 – 60 minutes. This intervention was preceded

by an in-person goal setting meeting to plan session topics (e.g., study techniques, daily routines, skill building). Self-reported sense of coherence, self-esteem, and quality of life were significantly higher after the intervention. However, this study did not target ADHD or ASD symptomology directly and was limited by a small sample size and the non-blinded nature of the trial. Another study used computerized working memory training aimed at ADHD symptom reduction in 121 children with ASD and found no intervention effects compared to mock working memory training [143].

Sleep problems are common in both ASD [144] and ADHD [145] and are especially pronounced in comorbid ASD+ADHD [146]. A randomized controlled trial (RCT) study tested a brief sleep intervention in 61 youth with ASD+ADHD (age 5-13). It comprised two face-to-face sleep consultations and a two-week follow-up phone call with a clinician. The brief intervention led to large reductions in sleep problems and moderate improvements in behavioral problems at 3- and 6-month follow-ups [147].

Pharmacological. Compared with behavioral interventions, more pharmacological interventions have been attempted in the past four years. A within-subject, crossover, placebo-controlled study investigated combining extended-release methylphenidate in the morning with immediate-release methylphenidate in the afternoon in 24 children with ASD that had significant symptoms of ADHD [148]. Both parents and teachers noted improvements (especially in hyperactivity and impulsivity) in youth with ASD as a function of methylphenidate treatment. Parents and teachers both reported the greatest improvements at the highest methylphenidate dose level although both also reported improvements at the medium dose. No significant adverse effects on ASD symptoms were noted.

A meta-analysis reporting on seven trials (n=225 participants) indicated that methylphenidate was effective (ES = 0.67) for reducing ADHD symptoms in ASD [149]. This effect size is lower than that reported for treating ADHD (without ASD) (ES = 1.03) [150]. A higher rate of side-effects was also noted in youth with ASD; compared to placebo,

methylphenidate treatment was associated with a greater likelihood of experiencing social withdrawal, depression and irritability in youth with ASD (more so than in youth with ADHD who do not have ASD).

Atomoxetine (1.2 mg/kg/day) was tested in an open label extension period of 20 weeks as a follow-up to an 8-week double-blind placebo-controlled period in 88 youth 6-17 years of age, with ADHD and ASD [151]. This study reported better efficacy with atomoxetine with limited side effects relative to placebo [152]. The 20-week extension data indicated that a total treatment length of 28 weeks was associated with continued reductions in ADHD symptoms (especially hyperactive-impulsive) in youth with ASD. Approximately 17% of participants discontinued the medication trial due to adverse effects. The authors concluded that in youth with ASD and ADHD, a more prolonged medication trial might need to be conducted prior to attainment of full response.

In a large, multisite study of 128 children with ASD, the efficacy of atomoxetine **(**capped at 1.8 mg/kg/day) and 9-sessions of parent training were investigated for reducing ADHD and oppositional symptoms [153]. Using a 10-week, double blind protocol, children were randomized to atomoxetine only, atomoxetine+parent training, placebo+parent training or placebo. For ADHD symptoms, all three intervention groups were superior to placebo. For oppositional symptoms, only the two atomoxetine groups were superior to placebo. The medication was well tolerated. The authors concluded that atomoxetine might be a viable alternative to stimulant medications for youth with ASD.

Other atomoxetine data suggest that while beneficial effects are noted for hyperactivity and reduced restricted and repetitive behaviors, no beneficial effects were noted for social functioning [154]. Also, similar to youth with ADHD [155], demographic and clinical factors (including ASD severity) do not predict atomoxetine response in youth with ASD+ADHD [156]

In a sample of 62 children with ASD, the efficacy of extended release guanfacine (ELG: modal dose = 3 mg/day) was evaluated using an 8-week RCT design [157]. Compared to

placebo, ELG was well tolerated and associated with a large decline in hyperactivity ratings (*d* = 1.67). Laboratory tests of working memory and motor planning did not improve after the 8-week ELG intervention.

A norepinephrine reuptake inhibitor, reboxetine (maximal dose of 4mg/day), was tested using an open label 12-week trial in 11 youth with ASD [158]. Side effects were common (90% of participants reported at least one). Decreases in the severity of ADHD symptoms and depressive symptoms were noted.

Combined pharmacotherapy is common when treating youth with ASD. One study found that 41% of youth with ASD seen between 2000 and 2008 were treated with combined pharmacotherapy, most often ADHD medications and an antidepressant, antipsychotic, or mood stabilizer [159]. No gender, racial or demographic variables were predictive of combined pharmacotherapy in youth with ASD. This same research group reported that less than half of children (44%) with ASD were adherent to ADHD medications [160].

Data from the multisite Simons Simplex Collection indicated that 41.7% of youth with ASD had ever been treated with pharmacotherapy [161]. ADHD medications were the most commonly used with 28% of youth with ASD having a lifetime history of ADHD medication. Older children and those with intellectual disability were more likely to have a history of pharmacotherapy. Core ASD symptoms (poor social interaction, restricted and repetitive behaviors) were weakly associated with pharmacotherapy (*r's* = < .12) suggesting it is the comorbidities and developmental delays that are driving pharmacotherapy in ASD. Data from the Autism Treatment Network registry [162] indicated that 27% of youth with ASD are prescribed psychotropic medication. Medication rates were higher in adolescents, Caucasians, and those with mood disorder and ADHD diagnoses (82% of those with ADHD were prescribed a medication).

Clinical Management

Clinically, the management strategy for ASD+ADHD depends on a variety of factors

including the intellectual level and language abilities of the individual, the topography of the ASD and ADHD symptoms, and the family and school support systems. More positive outcomes are associated with having supportive parents, an IQ > 70 and receiving intervention at an early age [163]. Thus, the following recommendations will need to be tailored to the individual child and family.

Preschool. Early and intensive intervention for ASD in preschool children should consist of applied behavior analysis (ABA), conducted in home and school settings [164]. Thus, any preschool child with ASD (regardless of ADHD status) should receive ABA. However, given that some data indicate that compared with children with ADHD only, children with ASD+ADHD are less likely to be treated appropriately for their ADHD with evidence based interventions [10], the presence of ADHD symptoms in a young child with ASD should not be overlooked. Moreover, the data reviewed above suggest that ASD+ADHD is a more severe phenotype that is associated with increased functional impairments. In addition, ADHD symptoms moderate the relationship between ASD and depressive and somatic symptoms in young children with ASD [165]. Thus, in addition to ABA, standard evidence based interventions for ADHD including behavioral parent training and teacher training in contingency management [166] should be attempted. Finally, for severe ADHD symptoms, the Preschool ADHD Treatment Study (PATS) reported methylphenidate to be efficacious in decreasing ADHD symptoms in preschool children with severe ADHD [167].

Children. For school-age children, it is imperative to include a school component to effective ASD+ADHD treatment. While none of these have been empirically investigated in ASD+ADHD, the following interventions are evidence based elementary school interventions for managing ADHD: proactive strategies (e.g., systematic teaching of classroom rules), teacher attention contingent on appropriate behavior, token reinforcement and response cost systems, and daily report cards. Academic skill interventions include explicit instruction, computer-

assisted instruction, and peer tutoring. Finally, self-regulation strategies train elementary school children to monitor, evaluate, and/or reinforce their own behavior [168].

In addition to these school-based strategies, pharmacotherapy for ADHD should also be considered. In November 2012, the Autism Speaks Autism Treatment Network Psychopharmacology Committee issued the *Clinical Practice Pathways for Evaluation and Medication Choice for ADHD symptoms in ASD* [169]. In this publication, the Committee recommended that primary care physicians of youth with ASD follow routine screening guidelines from the American Academy of Pediatrics [170]. If the child shows discrepancy in ADHD symptoms across settings, educational or behavioural interventions should be considered. Parents are encouraged to request a Section 504 plan or Individualized Educational Program (IEP). A comprehensive psychoeducational evaluation is recommended to help design an appropriate IEP. The Committee recommends if the child's ADHD symptoms continue after the above steps, a medication trial can then be considered and the Committee recommended the use of methylphenidate as the first line agent. Other agents can be then tried if the child does not have a positive methylphenidate response. Close and ongoing monitoring of efficacy and side effects is recommended.

Likewise, behavioral parent training (BPT) is an evidence based intervention and (a) provides psychoeducation about ADHD, (b) teaches effective parenting skills by managing antecedents and consequences and (c) provides practice opportunities for parents [171]. Although not specifically targeting ADHD, several BPT programs have recently been modified for use with ASD and each has reported positive findings [172-175]. For example, efforts to increase maternal warmth may be an important intervention target, especially for low SES families of children with ASD [176]

Children with ASD+ADHD are especially likely to have externalizing symptoms. A study of 216 youth with ASD investigated the validity of the DSM-5 tripartite model of oppositional defiant disorder (1) angry, irritable symptoms; (2) argumentative and defiant behavior; and (3)

vindictiveness in ASD [177]. Results generally provided support for the DSM-5 tripartite oppositional defiant disorder model in ASD, indicating that oppositional defiant disorder in ASD presents very similarly to oppositional defiant disorder in non-ASD populations. Angry, irritable symptoms were associated with internalizing problems, argumentative and defiant behavior was associated with ADHD and vindictiveness was associated with conduct disorder symptoms. The authors concluded that there is a great need for developing effective oppositional defiant disorder interventions for children with ASD and recommended testing existing evidence-based treatments, like BPT, for oppositional defiant disorder in ASD [177].

The burden on caregivers in both ASD and ADHD is significant, although the burden may be greater in ASD [178]. Relative to ADHD and ASD, parenting stress levels are the highest in ASD+ADHD and parental depressive symptoms are the most elevated in ASD+ADHD. Paternal ASD symptoms and maternal ADHD symptoms are especially associated with increased parenting stress [179]. Compared to siblings who do not have ASD or ADHD, youth with ASD+ADHD perceive that their parents have weak conflict resolution skills and are less accepting of them [180]. All of the above suggests that a family component to intervention may be beneficial to consider.

Complementary and alternative medicine (CAM) is relatively common in ADHD (19%) and near ubiquitous in ASD (82%) [181]. Parents of youth with ASD are also more likely to express satisfaction with CAM [181, 182] yet simultaneously report that their primary care physician is not knowledgeable in CAM [181, 183]. Thus, any intervention for children with ASD+ADHD should include inquiring with parents about what CAM interventions they are utilizing. Mental health clinicians are encouraged to develop a working knowledge of the CAM evidence base.

Finally, given that data indicate that bedroom access to media (television, computer, and video games) is associated with less hours sleeping per night in all children, yet especially in those with ASD [184], it seems prudent to recommend sleep hygiene practices that reduce

media exposure in the bedroom. This same study indicated that videogames were particularly problematic for sleep in ASD.

Adolescents. Most of the child interventions recommended above for managing ASD+ADHD also apply to adolescents. The Challenging Horizons program is an effective adolescent ADHD psychosocial intervention that occurs twice a week for 2 hours, 15 minutes each day during an entire 9-month academic year [185]. Intervention components include meeting with a primary counselor, a social group intervention targeting social functioning, recreation time, a study skills group and individual homework completion time. The intervention uses a behavioral management strategy based upon contingency management. In addition to the intensive school based intervention, directly teaching organizational and planning skills has also been demonstrated to have efficacy for adolescents with ADHD [186-188]. While all of the above make intuitive sense to attempt with adolescents with ASD+ADHD, none have been empirically tested in that population. In fact, in most of these efficacy trials, ASD was an exclusionary criterion.

Also more specific to adolescence, youth with ASD+ADHD are especially likely to be bullied and victimized by their peers [189, 190]. Moreover, there is evidence to suggest that the presence of ADHD negatively impacts social skills training outcomes in ASD [191]. Thus, future research should focus on developing interventions, most likely school based [192] that simultaneously reduce victimization (including cyberbullying) of youth with ASD+ADHD as well as improve adolescents with ASD+ADHD abilities to navigate the social milieu.

Pharmacological. Between 25 - 40% of children with ASD have ever been treated with pharmacotherapy [161, 162], especially those with comorbid ADHD [162]. Methylphenidate has been studied most extensively in the ASD+ADHD population and appears to be efficacious for managing ADHD symptoms, especially hyperactivity and impulsivity [148]. While efficacious, the use of methylphenidate is associated with a less significant effect size and more side effects such as social withdrawal, depression and irritability [149] than typically observed in the non-

ASD ADHD population who do not have ASD. Atomoxetine [151-153] and guanfacine [157] have also been demonstrated to be efficacious in children and adolescents with ASD+ADHD. Thus, for children and adolescents with ASD+ADHD, the standard ADHD medications appear efficacious.

Expert Commentary

ADHD and ASD share environmental and biological risk factors. Those with both disorders are more severely impaired than those with only one. Within the past four years, there has been an impressive amount of research study of ADHD/ASD comorbidity. This work coheres with a larger body of cross disorder research, which is challenging the idea that DSM diagnostic classes are distinct disorders. The strong evidence for genetic overlap between ADHD and ASD shows that, rather than being an artifact of diagnosis, comorbidity is rooted in shared genetic risk factors.

Relative to this large etiological and descriptive literature, there has been far less published on *treating* the comorbid state. This is likely a function of the relative fiefdoms of research; ADHD researchers generally exclude ASD from ADHD intervention trials while ASD researchers are generally not focused on ADHD symptoms in their interventions. The DSM-5 allows for diagnosing ASD in a child with ADHD and this will hopefully facilitate more intervention research, especially non-pharmacological studies. ASD and ADHD are two of the most costly (both in terms of impairment but also financial dollars) childhood conditions [193]. As noted above, the comorbid state is almost universally found to be more impairing than ADHD or ASD in isolation. This additionally points to a critical public health need to develop effective interventions to lessen the burden associated with ASD+ADHD.

The base rate of ADHD symptoms for children, adolescents and adults with ASD has never been firmly established. The extent to which those symptoms are inherent to ASD is therefore not clear. Some have opined that when ASD and ADHD co-occur, each becomes more difficult to diagnose than when they occur in isolation [194]. Establishing symptom profiles

and cutoffs for making a diagnosis of ADHD in individuals with ASD remains an important area of future research. Without base rate data on ADHD symptoms in ASD, we still do not know which ADHD symptoms and thresholds may enhance the predictive and discriminant validity of our ADHD diagnostic instruments.

Executive functioning deficits are prominent in theoretical models of ADHD [90] and ASD [195]. Nonetheless, components of executive functioning that are disrupted in ADHD and ASD are quite different; as noted above, children with ADHD have difficulties with inhibition and sustaining attention while children with ASD have difficulties in planning and shifting attention. Future work should consider these executive functioning profiles as a potential double dissociation that could aid diagnostic and treatment practices.

Finally, relative to children and adolescents with ASD+ADHD, we know far less about adults with ASD+ADHD. Adopting a lifespan approach to understanding ASD+ADHD will be of great benefit, particularly as the number of children with these diagnoses enters adulthood.

Five-year view

While some data indicate that the true prevalence of neither ADHD [196] nor ASD [197] is increasing, it is unmistakable that both conditions are being identified and diagnosed most often than in the past (increased incidence). In the coming five years, it is quite likely that the increased identification of both conditions will present a major challenge to the nation's special education service delivery systems. Compared to the present state of affairs, more treatment for the comorbid condition will likely be occurring either in schools directly or include a significant school-based component.

In addition to more school-based interventions for the comorbid state, the coming years are also likely to see more interventions integrate and utilize the Internet and social media more robustly. The use of these technologies in mental health treatment has significantly increased in the past 10 years [198] although this trend has not been observed in the ASD or ADHD fields.

The next five years is also likely to see a refinement of our understanding of the great clinical heterogeneity that exists in the ASD+ADHD domain. Examining mediators and moderators of treatment outcome is especially likely to occur. Large sample sizes (and therefore more multi-site studies) are needed to enable these variables to be explored.

The new DSM-5 condition, Social (Pragmatic) Communication Disorder (SCD) is defined by a primary deficit in the social use of verbal and nonverbal communication and cannot be diagnosed in the presence of ASD. This new condition is likely to capture individuals that met DSM-IV criteria for Pervasive Developmental Disorder, Not Otherwise Specified [199]. Presently, there are no studies that have assessed the comorbidity between SCD and ADHD although this is likely to change in the next five years.

Animal models of ASD have also been developed and this pre-clinical research is likely to continue in the next five years. For example, prenatal exposure to valproic acid (VPA) in rodents produces a behavioral and neuroanatomical phenotype consistent with ASD [200]. Likewise, mouse models with genetic mutations in neuroligin, neurexin, shank, Mecp2, Foxp, Cntnap2, Ube3a and Tsc1/Tsc2 have all been developed [201]. This pre-clinical research is likely to continue to focus on cell transplantation of cells capable of producing neurotrophic factors or stem cells as a way to provide insight into developing more specific ASD+ADHD treatments. For example, some research suggests that methylphenidate and atomoxetine, both FDA approved medications for ADHD, increase prefrontal dopamine and noradrenaline release in VPA-treated mice leading to behavior and neuroanatomical improvements [202].

Finally, given the National Institute of Mental Health (NIMH) RDoC initiative [203], future studies of ASD+ADHD may move away from categorical diagnoses to instead using dimensional measures of functioning and severity assessments. As noted above, genetic and environmental risk factors do not map onto specific DSM-5 define categories well. We expect that genetics studies will begin to clarify the genes and regulatory elements that are shared and unique for these two disorders. Likewise, neuroimaging studies will clarify the dimensions of

pathology that lead to these disorders and their comorbid state. Thus, future ASD+ADHD research may not even use this diagnostic label; instead, this line of research may investigate, dimensional measures of neurocognitive performance and brain abnormalities in a manner that facilitates the discovery of new treatment targets and allows for a more objective approach to describing psychopathology in youth.

Key issues

- In the DSM-5, ADHD is now permitted to be diagnosed in an individual with ASD. Prior to the DSM-5, this practice was not sanctioned.
- The majority of individuals with ASD have ADHD symptoms. A substantial minority of individuals with ADHD (15-25%) demonstrates ASD symptoms.
- Executive functioning impairments are associated with both ADHD and ASD and much of the recent cognitive research on the comorbid state has focused on executive functioning.
- Brain structure studies of ADHD and ASD have found both shared and distinct neural features in gray and white matter structures.
- ASD+ADHD is associated with more severe impairments in adaptive behavior when compared to children with ASD alone.
- Compared to children and adolescents, far less recent research has considered ADHD in adults with ASD.
- Methylphenidate and atomoxetine have been researched the most in ASD+ADHD. Both have demonstrated efficacy although with lower effect sizes and increase side effects relative to what is reported in ADHD (without ASD).
- Despite knowing much about what is an effective nonpharmacological intervention for ADHD and ASD in isolation, we presently know very little about what constitutes effective nonpharmacological interventions for the comorbid state.

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Reference annotations

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*** Of considerable interest*

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