Recent Advances in the Diagnosis and Treatment of Attention-Deficit/Hyperactivity Disorder in Individuals With Intellectual Disability

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An extensive review of the literature supports that attention-deficit/hyperactivity disorder (ADHD) is a common and valid co-morbid diagnosis in individuals with intellectual disability. Two recently published diagnostic manuals, the Diagnostic Criteria-Learning Disability (DC-LD) and Diagnostic Manual–Intellectual Disability (DM-ID), support this assertion, and should improve diagnostic accuracy. However, standards are still urgently needed to establish the symptomatic thresholds, above which an individual with intellectual disability who demonstrates inattentive or hyperactive behavior, can be diagnosed as having co-morbid ADHD. Similar to neurotypical persons with ADHD, stimulants are the primary pharmacological treatment in for individuals with ADHD and intellectual disability, but expected treatment response may be less robust. Future research should attempt to refine symptomatic thresholds for ADHD diagnosis, and further characterize ADHD as a behavioral phenotype of intellectual disability etiologies.

Keywords: ADHD, behavioral phenotypes, intellectual disability, mental retardation, psychiatric, stimulants

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. When first characterized in the early 1900s, “hyperactive syndrome” was identified in a group of impulsive, disinhibited and hyperactive children, many of whom had neurological deficits caused by encephalitis. At that time, most reports on ADHD focused on the motor hyperactivity seen in affected patients. Beginning in the 1970s, deficits in attention span and distractibility have supplanted motor overactivity, and they have become the defining feature of the disorder.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria, ADHD is characterized by a persistent pattern of inattentiveness and/or hyperactivity and impulsive behavior, which is in excess of that expected for a child’s development level. In their 1996 DSM-PC (The Classification of Child and Adolescent Mental Diagnoses in Primary Care: Diagnostic and Statistical Manual for Primary Care Child and Adolescent Version), the American Academy of Pediatrics offered definitions for expected and appropriate activity levels for different childhood developmental stages. In the DSM-IV criteria, some of the symptoms must be present before age 7. The impairment from inattention and/or hyperactivity and impulsivity must be pervasive and clinically significant. Pervasive development disorders, psychotic disorders and other major mental disorders must be excluded before the diagnosis of ADHD can be made.

Three subtypes of ADHD are currently classified: predominantly inattentive type, predominantly hyperactive/impulsive type, and a subtype combining inattention and hyperactivity. The combined subtype is the most prevalent subgroup, accounting for 50-75% of all individuals with ADHD, followed by the inattentive subtype (20%-30%), and the hyperactive/impulsive subtype (less than 15%).

Reports on the general prevalence of ADHD vary substantially, partly due to changing conceptions of the illness and evolving diagnostic criteria over time, as well as variations in clinical assessment in different settings and with various sample populations. In the United States, it is currently estimated that the prevalence rate for ADHD in school-aged community samples is 8-10%. ADHD is more prevalent in boys than girls, with the gender ratio ranging from 2-1 to as much as 9-1. Most females with the disorder have been diagnosed with predominantly the inattentive subtype, which may account for a hypothesized under-diagnosis of ADHD among girls, who are less likely to demonstrate the disruptive hyperactive/impulsive behaviors seen in boys.
In neurotypical samples, ADHD commonly occurs in association with oppositional defiant disorder, conduct disorder, mood disorder, anxiety disorder, and a variety of substance use disorders. It is also thought to co-occur with many developmental disorders, such as speech and language delays, and learning disabilities. Co-morbidity with intellectual disability is probably common, although controversial.

In spite of some evolution in its diagnostic conceptualization, ADHD is thought to be one of the more highly inheritable mental disorders. Family studies have demonstrated a two- to eight-fold increase in the risk for ADHD in parents and siblings of children with ADHD. A number of twin studies collectively determined that the mean heritability (the degree to which the disorder is affected by genetic factors) for ADHD is 77%. To date, seven genes involved in central nervous system (CNS) catecholamine pathways have been implicated in the etiology of ADHD through candidate gene studies. Proposed candidate genes include the dopamine D4 receptor gene (DRD4), dopamine D5 receptor gene (DRD5), the dopamine transporter gene (DAT), the dopamine beta-hydroxylase gene (DBH), the serotonin transporter gene (5-HTT), the serotonin receptor 1B gene (HTR1B), and the synaptosomal-associated protein 25 gene (SNAP25). These genes are involved at multiple levels of catecholamine synthesis and metabolism, and affect multiple CNS neural pathways. It is hypothesized that optimal activity of norepinephrine and dopamine in the prefrontal cortex improves the signal-to-noise ratio, providing for prefrontal cortex regulation of attention and behavior.

Neuropsychological and brain imaging studies have shown that ADHD is associated with alterations in neuronal function in areas of the prefrontal cortex, and its connections to the striatum and cerebellum. When this balance is disturbed, individuals with ADHD show poor performance on neuropsychological tests of attention and executive functions, which presumably reflects this prefrontal cortical dysfunction. Among the sub-categories of executive functions, persons with ADHD exhibit severe deficits in inhibitory control, and working memory; and moderate deficits in planning, organization, set-shifting, and impulse-control. These neuropsychological difficulties appear to translate into the typical symptoms demonstrated by individuals with ADHD—difficulty controlling impulses, reasoning through complex decision-making, maintaining attention (resulting in distractibility), and planning ahead.

The Co-Occurrence of ADHD and Intellectual Disability

Any review regarding the incidence or prevalence of ADHD in persons with intellectual disability must begin with discussion of the diagnostic system utilized in identifying the ADHD diagnosis. As diagnostic schema for ADHD have evolved, so, too, has the determination of its form in individuals with intellectual disability. Most early reports of ADHD prevalence have employed standard criteria from the DSM’s (III, III-R, IV) or ICD’s. However, within the last six years, two separate diagnostic systems specifically oriented toward persons with intellectual disability have been outlined. With these novel systems, it may be possible to more accurately diagnose ADHD in affected individuals.

Most studies of ADHD in persons with intellectual disability report greater prevalence, compared to rates of ADHD in neurotypical children or adults. In the mid 1980s, Epstein et al. reported that nearly 20% of 6-18 year old boys with intellectual disability in their sample of 245 children also had ADHD, based on teacher ratings of behavior with the Conner’s Rating Scale. Fox and Wade found that 15% of 86 adults with severe/profound intellectual disability met “conservative” criteria for ADHD, using the DSM-IV and Conner’s Hyperactivity Scale. Reversing the primary and secondary conditions, Ishii et al. reported on several features of ADHD in individuals with intellectual disability. Hastings et al. reported on several features of the co-morbidity of ADHD and intellectual disability. In their sample, younger children and those with autism were more likely to have ADHD symptoms, and 60% of one intellectual disability sample scored above the cut-off for ADHD, compared to only 2.7% of their siblings without intellectual disability.

In a well-considered recent paper, Antshel et al. comprehensively examined the question of ADHD and intellectual disability co-morbidity, utilizing a methodology established by two well-known biological psychiatry researchers for determining the validity of a psychiatric
disorder. This methodology involves seeking evidence for a combination of clinical correlates, family history, treatment response, laboratory studies, course, and outcome. The authors describe the relative lack of research into the comorbidity of ADHD and intellectual disability, including the lack of ADHD instruments which have been validated in children with intellectual disability. Miller et al. agreed, noting that in their sample of 48 children with intellectual disability, only the Aberrant Behavior Checklist, among several possible ADHD instruments, demonstrated sufficient inter-rater reliability to be of clinical use in children with intellectual disability. They also importantly note that both ADHD and intellectual disability cause functional impairment in affected individuals, and conclude that, if ADHD is a valid co-morbid diagnosis in children with intellectual disability, one would expect to see more functional impairment in those with ADHD and intellectual disability than in those with intellectual disability alone.

As noted above, two recent novel diagnostic systems are attempting to provide specific criteria sets for identifying psychiatric disorders in persons with intellectual disability. The first of these is the Diagnostic Criteria for Learning Disabilities/Mental Retardation (DC-LD), formulated by the Royal College of Psychiatrists in the United Kingdom in 2001. The newest is the Diagnostic Manual for Intellectual Disability (DM-ID), published by the National Association for Dual Diagnosis (NADD) in 2007. Both offer diagnostic criteria for ADHD applicable to persons with intellectual disability.

The DC-LD criteria for “attention deficit hyperactivity disorder of adults” require symptoms of inattention, distractibility, impulsiveness, hyperactivity, and restlessness, all of which are more than would be expected on the basis of the intellectual disability alone. Onset must precede age 6, and the symptoms of the disorder must persist over time and across multiple environments. NADD’s DM-ID criteria for ADHD are largely identical to those for ADHD found in the DSM-IV, with several additional recommendations and common clinical examples of inattention and hyperactivity.

Seager and O’Brien, in discussing the DC-LD view of ADHD, quoted the introductory section on ADHD in addressing this “threshold” approach. “In adults with learning disabilities (intellectual disability), the disorder (ADHD) may be easily overlooked, because the combination of poor attention; impulsive, disorganized behavior; and difficulty in initiating and maintaining purposeful behavior is common among people with learning disabilities (intellectual disability). The diagnosis is only to be applied where the overall picture is in excess of that which might be expected on the basis of general intelligence or severity of learning disabilities (intellectual disability).” Similarly, the DM-ID requirement is that hyperactive or impulsive behavior should be in excess of that seen in peers of comparable developmental and chronological age.

The obvious difficulty with both of these approaches is that there are few standardized norms or guidelines for determining what is a “normal” or “usual” amount of inattention, motor overactivity, or impulsivity associated with, or expected in, persons with intellectual disability. Burack et al. have even questioned the widely held belief that attentional deficits are inherent to intellectual disability. And, neither the DC-LD nor the DM-ID (or other diagnostic systems such as the DSM-IV and ICD-10) offer guidelines for determining this symptomatic threshold, above which an individual with intellectual disability would be thought to also have co-morbid ADHD.

In a massive comorbidity study, Cooper et al. examined 1,023 adults with intellectual disability, with the purpose of identifying co-morbid psychiatric illness using the ICD-10, DSM-IV, and DC-LD. Following identification by a nurse clinician, each individual underwent a comprehensive psychiatric assessment by a psychiatrist, which included both an interview as well as a battery of rating scales. The researchers found that the DC-LD more commonly identified the point prevalence of mental illness (35% of the cohort), compared to the ICD-10 (16%) or DSM-IV (15.7%). However, regarding ADHD, the numbers were surprisingly low. Only 1.5% of the sample of 1,023 had the clinical diagnosis of ADHD at the time of assessment, and point prevalence was even lower (DC-LD 1.2%; ICD-10 0.5%; DSM-IV 0.4%). Historically, the reported prevalence of ADHD has been consistently lower in Great Britain than the United States.

One further source of diagnostic difficulty in this area has been the mutual exclusivity recommended by both DSM-IV and ICD-10 between the diagnoses of pervasive developmental disorders (PDD) (including autistic disorder), and ADHD. In these systems, if PDD was present,
the clinician was not to make a co-morbid ADHD diagnosis. Abanilla et al. have reviewed this diagnostic exclusion, and concluded that the current diagnostic and therapeutic literature no longer supports it. The two newer systems described above (DC-LD and DM-ID) do not include this prohibition regarding PDD-ADHD co-morbidity. Indeed, most recent literature has largely ignored the DSM-IV and ICD-10 prohibition, and reported subsets of children and adults with both PDD and ADHD diagnoses. However, this previous diagnostic prescription would have likely influenced older epidemiological studies regarding overall ADHD and intellectual disability co-occurrence.

ADHD Co-Morbidity With Intellectual Disability of Known Etiology

Even though the etiology of intellectual disability is unknown for approximately one-third of patients with intellectual disability (previously known as cultural-familial intellectual disability), at least 25% of persons with intellectual disability have known genetic or prenatal conditions often associated with intellectual disability (previously known as biological intellectual disability). An alternate or overlapping approach to this “two-group” dichotomy has been a multifactorial approach to etiology, in which both biological and cultural-familial factors combine to produce risk for development of intellectual disability. However, with recent advances in the human genome project and neurosciences, there has been an explosion of knowledge in the area of prenatal etiological factors in intellectual disability. A recent search in Online Mendelian Inheritance in Man (OMIM) has identified 1,401 genetic syndromes which may be associated with intellectual disability (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed).

Other authors have formulated the concept of Behavioral Phenotypes, in which particular etiologies of intellectual disability may predict the risk of psychiatric disorders and expectations of functioning. Although progress in discerning behavioral phenotypes has greatly advanced the study of psychopathology in persons with intellectual disability, it may also carry with it the possible risk of bias, which can lead to the anticipation or even encouragement of certain types of “expected” behavior in specific etiologic diagnoses, based on a reductionistic and fixed view of the genotype-phenotype relationship.

Most of the time, individuals with similar genetic predispositions will not express the phenotype to the same extent, which has been called variability of expression. In fact, current constructs regarding causality of mental disorders emphasizes that genetic susceptibility combined with environmental pathogens acting upon particular CNS substrates will eventually determine the clinical outcome, i.e., whether there will be a mental disorder, and how severe it will be. This updated understanding should make mental health caregivers more confident in offering treatment and avoiding therapeutic nihilism, which assumes genetic defects inevitably lead to mental disorders which are not preventable or necessarily amenable to intervention.

Individual signs and symptoms of ADHD, or the complete diagnostic presentation (as a possible behavioral phenotype), have been widely documented in several genetic syndromes resulting in intellectual disability. Both the prevalence and severity of ADHD symptoms varies among different genetic syndromes. In two separate studies of 193 and 261 individuals with Down syndrome, the prevalence of ADHD was estimated to be 6 and 9%, respectively, similar to that seen in neurotypical groups. Conversely, Sullivan et al. reported that 54-59% of 63 boys with fragile-X syndrome met diagnostic criteria for ADHD based on parent or teacher report, and 25% of 58 patients with Prader-Willi syndrome showed clinical evidence of ADHD. Of 62 patients with genetically-confirmed Angelman syndrome (and 29 persons with presumed Angelman syndrome), hyperactivity appeared to be more prominent when compared to inattention or impulsivity. In 19 children and adolescents with Williams syndrome ages 4-16, 65% were diagnosed with ADHD, making ADHD the most prevalent co-morbid diagnosis in these patients. In 84 patients with velocardiofacial syndrome (VCF). ADHD affected 43% of individuals. Finally, high percentages of patients with Smith-Magenis syndrome demonstrated ADHD spectrum behaviors, such as impulsivity (86%), distractibility (89%) and hyperactivity (94%).

The Treatment of ADHD in Individuals With Intellectual Disability

The approach to recognizing ADHD in persons with intellectual disability has largely been extrapolated from that utilized in neurotypical
persons, so it is no surprise that treatment approaches similarly mirror those found for ADHD in general. Although this has primarily involved stimulant medications, several other agents have also been studied. There are few reports of non-pharmacological treatments for ADHD symptoms specific to persons with intellectual disability.

Initial reports of stimulant treatment in persons with intellectual disability were mostly negative, perhaps attributable to heterogenous samples containing many individuals without hyperactivity.\(^{19}\) Subsequent studies reported more benefit, although the rate of positive response to stimulants was thought to be less robust in children with intellectual disability compared to neurotypical peers.\(^{4,5}\) Handen et al.\(^{34}\) re-contacted 52 children with borderline-moderate intellectual disability and ADHD who had participated in a controlled methylphenidate (MPH) trial, and found that 69% of the children were still taking stimulants 1-5 years after the trial. Although 72% of the children were rated as improved with treatment, a similar percentage continued to rate very highly on the hyperactivity index on the Conners Parent Rating Scale. Aman et al.\(^3\) combined three independent, placebo-controlled studies of children with intellectual disability treated with the same dose of MPH (combined N=90), and reported the children were consistently improved in attention, overactivity, and conduct, as rated by both parents and teachers on standardized scales. In these children, lower functional level seemed associated with less favorable response to MPH.

In an interesting report, DiMartino et al.\(^{23}\) gave a single dose of MPH (0.4mg/kg) to 13 children with PDD and moderate-severe hyperactivity and impulsivity. Five of 13 appeared to worsen with the “test dose,” and were excluded from further study. The remaining 8/13 were entered into an open 12 week trial of MPH. Although two more children dropped out surrounding lack of benefit, the group as a whole showed significant improvement in hyperactivity and impulsivity, without any significant adverse effects. Jou et al.\(^{39}\) retrospectively reviewed 10 adults with intellectual disability and ADHD, and found five of the ten were responders, utilizing the hyperactivity and irritability subscales of the Aberrant Behavior Checklist. Gothelf et al.\(^{32}\) treated 12 children with VCF syndrome and ADHD in open label fashion with MPH, and reported benefit, without significant side effects, and notably no exacerbation of psychotic symptoms common in VCF individuals.

Demb and Chang\(^{23}\) reported on a group of 26 children with ADHD and intellectual disability who were part of a larger sample of 115 children treated with stimulants (MPH or dextroamphetamine). In their retrospective review, 73% of the children with intellectual disability improved, compared to 80% of the sample without intellectual disability. Children with severe-profound intellectual disability were less likely to be responders, compared to those with mild-moderate intellectual disability. Nine of the 26 children with ADHD and intellectual disability received at least one additional medication besides the stimulant, usually the alpha-adrenergic agonist clonidine, given usually for sleep disturbance associated with stimulant therapy. Only 17% of the total sample had any side effect necessitating a drug or dose change.

Pearson et al.\(^{49,50}\) studied 24 children with intellectual disability and ADHD, each of whom was given three separate doses of MPH, in double-blinded comparison to placebo. Most of the children improved with MPH, with 55% of children showing substantial behavioral gains, and 46% cognitive task performance improvement, compared to placebo. Of significant interest was the finding that the greatest cognitive performance improvement was seen at the maximum MPH dose (0.60mg/kg bid). The authors noted that, based on this finding, cognitive assessment may be one additional method of determining response to stimulant medication in children with intellectual disability.

Finally, the Research Units in Pediatric Psychopharmacology (RUPP) group described a double-blind, placebo-controlled trial of MPH involving 66 children, ages 5-14, with PDD and hyperactivity.\(^{32}\) Using the teacher-rated hyperactivity subscale of the Aberrant Behavior Checklist, the authors reported that MPH was superior to placebo at three different dose ranges, with 49% of participants classified as MPH responders. However, 18% of those treated had treatment interrupted by side effects.

In a comprehensive review of the use of psychostimulants in children with pervasive developmental disorders,\(^1\) Abanilla et al.\(^1\) concluded that stimulants appear to benefit children with ADHD and PDD, even in the presence of intellectual disability, with more
recent controlled studies revealing more positive effects.

Although most of the treatment literature has focused on stimulants, there are a few reports of other medication utilization for ADHD in persons with intellectual disability. Agarwal et al.\(^2\) performed a 12-week double-blind, placebo-controlled crossover trial of clonidine at three dose strengths, in 10 children with co-morbid hyperkinetic disorder and intellectual disability. On both parents’ and clinicians’ ratings, there was a significant, and dose-related response to clonidine, with benefit in overactivity, impulsivity, and inattention. Initial drowsiness decreased with continued treatment, and the authors concluded that clonidine was safe and effective.\(^2\)

In a retrospective study, Posey et al.\(^51\) reported on 80 children with PDDs who were treated with guanfacine in open label fashion. Guanfacine appeared to improve only 24% of the children with hyperactivity and impulsivity; those children with co-morbid intellectual disability did not respond as well as those with PDD alone. Finally, Reyes et al.\(^53\) followed a cohort of 48 children with an IQ under 84 and disruptive behavior disorders, who were treated with risperidone, in an open label fashion for two years. The authors utilized the conduct problem subscale of the Nisonger Child Behavior Rating Form (N-CBRF), and reported that improvement was maintained over the second year of treatment. Although the children did not have a formal diagnosis of ADHD, the hyperactivity subscale of the N-CBRF showed significant improvement.

**DISCUSSION**

In summary, most authors continue to view the stimulants as the most efficacious approach to the treatment of ADHD in individuals with intellectual disability. As might be expected, the literature has focused mostly on children, with only a single report describing the treatment of adults.\(^39\) As ADHD becomes more accepted as a life-long disorder which persists into adulthood, it would be expected that treatment reports of this group of patients will follow.

Even though pharmacological approaches have dominated the treatment options for ADHD in persons with intellectual disability, psychosocial therapies, especially managing disruptive behaviors in the intellectually disabled population, is still a critical component to mental health treatment.\(^6\)

**SUMMARY**

It is now clear that ADHD and intellectual disability are common co-morbid conditions. Although the literature in this area is limited by changing definitions of ADHD itself, and the difficulty with diagnosis in persons with intellectual disability, several themes seem to emerge. In any patient with intellectual disability, with symptoms of motor overactivity, impulsivity, and inattention, consideration should be made for a co-morbid diagnosis of ADHD. The previous exclusion of ADHD in the context of PDD is probably outmoded, and should be dropped. It is not found in the diagnostic criteria for ADHD offered in the *DC-LD* or *DM-ID*.

It appears that ADHD is found to a greater extent in persons with more severe intellectual disability, compared to peers with mild or moderate intellectual disability. Future research utilizing the new diagnostic systems for persons with intellectual disability, with larger samples, should attempt to confirm this impression.

Treatment approaches to ADHD in persons with intellectual disability should follow the same general guidelines as that in neurotypical children and adults, utilizing primarily stimulant medications. Psychopharmacological treatments for individuals with ADHD and intellectual disability, when utilized, provide benefits, although treatment response seems less robust in persons with intellectual disability compared to neurotypical peers.

There are a number of areas needing future research, both diagnostic and therapeutic. Both should utilize the newer diagnostic systems. Because both new diagnostic systems have maintained the requirement for symptoms in excess of that expected for developmental stage, attempts should be made to determine these norms for persons with intellectual disability. The lack of recognized norms in this area is even more apparent when assessing adults with intellectual disability.

**REFERENCES**


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