The relationship between autism spectrum disorder and attention-deficit hyperactivity disorder: A critical review of the effects of DSM 5 criteria and the implications for treatment

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Abstract
Introduction
Autism Spectrum Disorder (ASD) and Attention Deficit/Hyperactivity Disorder (ADHD) are both severely impairing neurodevelopmental disorders. Interest in the co-occurrence of Attention deficit/hyperactivity disorder (ADHD)-like symptoms and Autism spectrum disorder (ASD) has grown in the last decade. Children with autism spectrum disorder (ASD) are frequently found to manifest symptoms of hyperactivity, inattention and impulsiveness, which are the cardinal symptoms of attention deficit/hyperactivity disorder (ADHD). The purpose of the present work is to review and critically discuss the studies reporting the co-occurrence of ADHD-like symptoms in individuals with formal diagnosis of ASD and the effectiveness of medications for ADHD symptoms in the ASD.

Materials and methods
We carried out a literature research and study selection by searching for published biomedical literature in PubMed.

Results
From a pool of 321 potentially relevant references we selected only reviews published during the past five years, focusing on co-occurrence of ASD and ADHD and their treatment. Our search yielded a total of 64 reviews that matched our search criteria.

Conclusion
DSM 5 currently permits co-diagnosis of ASD and ADHD. This option will facilitate new research approaches and will also have therapeutic implications. As shown in our review further research is needed to understand about developmental trajectories of the co-occurring disorders and to understand how severity of symptoms in one disorder may influence the emergence of symptoms in the other disorder. Individuals with ASD plus ADHD are more impaired than individuals with only ASD. This finding suggests that individuals with co-occurrence of the two disorders may need different treatment methods or intensities than those with only ASD. There is no consensus on the use drugs for individuals with ASD plus ADHD. The limited number of studies and the heterogeneity of results require further and larger RCTs for the assessment of the efficacy and tolerability of psychostimulants.

Introduction
Autism Spectrum Disorder (ASD) and Attention Deficit/Hyperactivity Disorder (ADHD) are both severely impairing neurodevelopmental disorders.

Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text-revision (DSM-IV-TR) outlines Pervasive Developmental Disorders (PDDs) as a triad of qualitative impairments in social interaction, communication and restricted, repetitive and stereotyped behaviours.

Delays or abnormal functioning must be evident in at least one area associated with autism before the age of three. PDDs include the categorical diagnoses of Autistic Disorder (AD), Asperger’s Syndrome (AS), Childhood Disintegrative Disorder and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). The worldwide prevalence of all ASDs has been estimated at approximately 60–70 out of every 10,000 individuals. The CDC estimated the prevalence of Autism Spectrum Disorders (ASD) at approximately 0.9% of the population in the USA.

The term ‘autism spectrum disorders’ (ASDs) is a proposed revision of the current ‘pervasive developmental disorders’ (PDDs) defined by the DSM-IV-TR criteria. Distinctions among ASD subtypes have been found to be inconsistent over time, variable across sites, and often associated with severity of language deficits and intellectual impairment rather than a different manifestation of inherent ASD features, such as social communication deficits and fixed interests and repetitive behaviours symptoms. Thus DSM 5 proposed a significant shift in the diagnostic conceptualization of ASD introducing the construct of a ‘spectrum’ of autistic disorders. This construct aims to produce a clear diagnostic system that identifies the common characteristics of ASDs across all ages and ability levels.

To describe this single category, the triad of impairments has been merged into a dyad: social/communication and restrictive and repetitive behaviours. The dyad has been proposed to embrace AD, AS and PDD-NOS in a dimensional approach.

Attention Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent childhood-onset neuropsychiatric condition, with an estimated worldwide pooled prevalence of approximately 5% in school-age children. The major
changes in DSM 5 classification of the disorder include increases in the amount of descriptive information for each symptom, changes in the way that information is gathered, changes in the way that the criteria are used for different age groups, clarification of the impact of current activity on symptoms, the nature of the disorder (neurodevelopmental) and the relationship between both autism and mood lability and ADHD. In the last decade, studies have reported increased prevalence of both attention deficit/ hyperactivity disorder and autism spectrum disorder, as well as more cases of co-occurring ADHD and ASD symptoms.

The preclusion of a comorbid diagnosis of ADHD when the symptoms occur during the course of a PDD in DSM – IV-TR fails to account for the many individuals with ASD who also meet full criteria for ADHD. Furthermore, many individuals with milder forms of ASD, such as Asperger’s syndrome, may present clinically with initial concerns of ADHD symptoms.

Since the clinician faces the challenges of managing ADHD symptoms (impairing inattention and/or hyperactivity-impulsivity) in day-to-day clinical practice with individuals with ASDs, the aim of the present work is to review and critically discuss the studies reporting the co-occurrence of ADHD-like symptoms in individuals with formal diagnosis of ASD and the effectiveness of medications for ADHD symptoms in the ASD.

Materials and methods

We included studies assessing co-occurrence of ADHD-like symptoms (i.e., inattention and/or hyperactivity and/or impulsivity) in day-to-day clinical practice with individuals with ASDs, the aim of the present work is to review and critically discuss the studies reporting the co-occurrence of ADHD-like symptoms in individuals with formal diagnosis of ASD and the effectiveness of medications for ADHD symptoms in the ASD.

Results

Through a first research on PubMed, we have found 321 results that included some articles focusing on the characteristics of single disorders that have autistic traits in their clinical presentation or associated symptoms of inattention, some others on pharmacological treatments of single disorder (ADHD or ASD), their effectiveness and safety as well as several reviews that dealt with type of treatments other than drug therapy.

On the basis of search criteria developed for this review, we selected only those reviews published during the past five years, excluding all articles focusing on a single disorder. Finally, we selected a total of 64 reviews that focused on the co-occurrence of ASD and ADHD and their treatment. During the analysis, we picked 30 reviews that we found more suitable for our study.

The remaining 34 reviews were excluded, since some of them regard neurodevelopmental disorders and their conceptual issues, some others described genetic aetiology or genetic – environmental interactions in aetiology-genetic pathogenesis of neurodevelopmental disorders and still others discussed new therapeutic targets undergoing clinical trials.

Discussion

Co-occurrence of ASD and ADHD

DSM-IV-TR stated that to meet criteria for ADHD, symptoms could not occur exclusively during the course of a PDD. However, a substantial literature has emerged refuting that idea. As summarized by Grzadzinski et al. the prevalence of ADHD symptoms in individuals with a primary clinical diagnosis of ASD has been reported to be between 13 and 50% in the general population and community-based studies, and between 20 and 85% in clinical samples. Conversely, autistic symptoms are often found in children with ADHD. Santosh et al. described two types of social impairment in ADHD: relationship difficulty related to environmental stressors and social communication deficits which related to symptoms of PDD. It has been shown that children with ADHD have similar difficulties in communication and restrictive repetitive behaviour as children with PDD.

Symptoms of autism in children with ADHD appear to exceed those of the general population and significant correlations between symptoms of ADHD and symptoms of autism spectrum disorder have been shown in the general population.

Recently St. Pourcain et al. explored the interrelationship between trajectories of co-occurring symptoms of ASD and ADHD examining the longitudinal pattern of association between social-communication deficits and hyperactive-inattentive symptoms in the general population, from childhood through adolescence. The study revealed various patterns of association between ASD and ADHD, with children with persistent hyperactive-inattentive symptoms also showing persistent social-communication deficits.

The co-occurrence of ASD and ADHD has significant implications for level of functioning and treatment planning. Accumulating research comparing individuals with both ADHD and ASD to individuals with a single diagnosis (i.e., ADHD or ASD) suggests that co-occurring symptoms are associated with more impairment than single diagnoses, and children with ADHD and ASD experience more difficulty in daily situations, as compared to those with only one disorder, and have...
higher levels of additional psychopathology.\textsuperscript{17}

Furthermore, recent work by Frazier et al. examined the prevalence of psychotropic medication use compared across individuals with ASD-only, ADHD-only, and an ASD with co-morbid ADHD.

Youth characterized as having both ADHD and ASD are more likely to be taking psychiatric medication (58.2\%) than youth with ADHD (49\%) or ASD (34.3\%) alone.\textsuperscript{18}

In other studies co-occurring ADHD and ASD seem to be less responsive to standard treatments for either disorder than individuals with “pure” forms of the disorders.\textsuperscript{19}

While it seems clear that children suffering from both disorders are faced with a more severe condition and a higher degree of psychosocial problems, it remains unclear whether ADHD symptoms influence autistic psychopathology in particular.

Recently Sprenger et al. conducted a large sample study\textsuperscript{15} aiming to investigate the potential influence of ADHD symptoms on ASD psychopathology. The study included 126 patients with the diagnoses high-functioning autism (HFA), atypical autism (AA) or Asperger’s syndrome (AS), 70 ASD plus ADHD symptoms (ASD+) and 56 ASD without ADHD Symptoms (ASD-). Findings are in line with a study hypothesis that ASD+ participants would exhibit more autistic symptoms than ASD-participants.

The mechanisms underlying this phenotypic overlap between ADHD and ASD are poorly understood. A number of studies have been published noting that ADHD and ASD are distinct conditions that have several common cognitive and behavioural symptoms.

Recent findings may indicate commonly shared genetic and neurobiological correlates.\textsuperscript{20,21,22}

**Pharmacological Treatment for co-occurring ASD and ADHD**

The new criteria in DSM 5 state that a diagnosis of ADHD should be allowed in the presence of ASD. This proposal, if implemented, would have an impact on a large number of individuals with ASD who would be more able to receive treatment for their ADHD symptoms.

Pharmacological treatments constitute an important part of the comprehensive multimodal therapeutic strategy for ADHD. Drugs used to treat ADHD include stimulants (methylphenidate [MPH], dexameth-phenidate, dextroamphetamine, mixed amphetamine salts, dextromethamphetamine and lysdexamphetamine), as well as nonstimulant medications such as atomoxetine and a-2a adrenergic receptor agonists (clonidine and guanfacine). Psychostimulants are considered the first pharmacological choice in the management of ADHD.\textsuperscript{23}

For ASD, current pharmacological treatments primarily target comorbid symptoms (e.g. irritability, aggression, hyperactivity) rather than core social and communication impairments.

Atypical antipsychotics are currently first-line pharmacological agents used in treating irritability and associated behaviours in children with ASD. However, there is no consensus on the use of psychopharmacological treatments for autism.

Cortese et al. conducted a comprehensive review of studies assessing the efficacy and tolerability of psychostimulants for ADHD-like symptoms in individuals with autism spectrum disorder. Despite the limited amount of available research, the review highlights that empirical evidence from the controlled studies suggests that methylphenidate may be effective for ADHD-like symptoms in individuals with PDD/ASD.\textsuperscript{24} However the heterogeneity of the design and measures used in the reviewed studies cannot determine both the extent to which psychostimulants are effective and the proportion of ASD plus ADHD individuals who may benefit from this class of drugs.

The largest controlled study of the efficacy and tolerability of MPH immediate release in children with ADHD is the RUPP Autism Network one. This study conducted a randomized, placebo controlled, crossover trial of methylphenidate with 72 children (ages, 5–14 years) who were diagnosed with autism who were also characterized with moderate-to-severe hyperactivity. Results indicated that stimulant medication was effective at reducing hyperactivity and impulsivity in approximately half of the participants, a response rate that is considerably lower than the rates of 70 to 80\% found in studies of methylphenidate for children with ADHD only.\textsuperscript{24}

More adverse effects were reported in the children with ASD, and the highest tolerated dose was lower than that tolerated in children without ASD.\textsuperscript{24} Only one study to date has directly compared methylphenidate treatment response between children with ADHD and children characterized by ASD plus ADHD. This study reported overall improvement in ADHD symptoms, with few differences in treatment response between the groups.\textsuperscript{25}

Some studies have assessed the moderating effect of clinically relevant variables and some of them have pointed to possible differential effects based on level of functioning (e.g., cognitive level, ASD severity). However there are contrast findings and recent works report that IQ may not affect the response to psychostimulants. This issue needs further standardized systematic research.\textsuperscript{23}

Although these findings support the use of methylphenidate in children with both ADHD and ASD, the results were also consistent with prior studies that have suggested a greater need for side effect monitoring and lower dosing in the context of ASD. Other nonstimulant medications have been investigated for co-occurring...
ADHD and ASD symptoms. Atomoxetine, has demonstrated better tolerability than stimulant medications in individuals with co-occurring ADHD and ASD\(^7\). A small placebo-controlled efficacy trial indicated positive effects in terms of the reduction of hyperactivity and impulsivity, but not inattention in youth with ASD, with fewer adverse events as compared to stimulant trials\(^{20}\). Additional research using parents and teachers as informants showed significant reductions in ADHD symptoms among children with ADHD and ASD and side effects were rated as “minimally present”\(^{19}\).

Despite these promising findings, atomoxetine effectiveness may vary as a function of level of impairment: positive results for atomoxetine are more evident among children with ASD who are cognitively higher functioning (defined as IQ >70)\(^{19,23}\).

In a separate investigation, atomoxetine treatment yielded no observed symptom reduction in a sample of children with high ASD symptom severity.

Guanfacine is an alpha-2 adrenergic agonist recently approved for use with ADHD in an extended release formulation. Positive effects have been found in several studies using guanfacine for treatment of children with co-occurring ADHD and ASD symptoms. A retrospective analysis of 80 patients in the clinic indicated reduction in hyperactivity and inattention among children with ASD who were higher cognitively functioning (i.e., not in the cognitively impaired range)\(^{19,23}\).

Similarly, positive effects on parent- and teacher-rated hyperactivity were also observed in an open trial examining children who had previously demonstrated lack of success with methylphenidate\(^{27}\).

**Psycho-educational approach**

Limited work has examined psychosocial interventions for co-occurring ADHD and ASD. Multiple studies have demonstrated that combination pharmacological and psychosocial treatments are particularly effective for ADHD symptom management\(^{20}\).

This approach may also be indicated for children with co-occurring ADHD and ASD symptoms.

**Conclusion**

DSM 5 currently permits co-diagnosis of ASD and ADHD. Given that clinicians are routinely observing and treating individuals with co-occurring symptoms, DSM-5 changes will provide diagnostic clarification and will facilitate treatment studies to guide care.

However, research specifically focusing on co-occurring ADHD and ASD has only emerged recently, and many studies have focused primarily on questions of aetiology and phenomenology. As shown in our review little is known about developmental trajectories of the co-occurring disorders. Unlike the longitudinal research by St. Pourcain et al., most current understanding of co-occurring ADHD and ASD stems from cross-sectional studies. Further research is needed to understand how severity of symptoms in one disorder may influence the emergence of symptoms in the other disorder.

In addition to this and perhaps more important, we know that red flags associated with ASD can be observed prior to two years of age, whereas identifying atypical behaviours in the context of ADHD may be more difficult at very young ages.

Multiple studies have found that early intensive ASD interventions can have a substantial impact on ASD symptoms therefore it will be important to determine whether these early interventions can also mitigate the later development of impairing ADHD symptoms.

Prospective longitudinal studies of attention, social, communication and cognitive functioning are needed from the time that red flags of ASD are identified, so that the earlier this subset of children can be identified the earlier tailored intervention can be designed.

In the matter of pharmacological treatment there is no consensus on the use of these psychostimulants for individuals with ASD plus ADHD. The limited number of studies and the heterogeneity of results require further and larger RCTs for the assessment of the efficacy and tolerability of these drugs, both immediate and extended release formulas.

In summary research suggests that there is a psychopathological difference between ASD patients with and without additional ADHD symptoms, which may be rooted in neurobiological underpinnings. Our understanding of this topic and how etiological commonalities affect those with either diagnosis will surely improve with continued research. The option to diagnose comorbid ADHD and ASD in the DSM 5 will facilitate new research approaches and new therapeutic strategies.

**References**


