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Addiction Biology. 2016 Jul;21:915-23.

DOPAMINE AND SEROTONIN GENETIC RISK SCORES PREDICTING SUBSTANCE AND NICOTINE USE IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Groenman AP, Greven CU, van Donkelaar MMJ, et al.

Individuals with attention deficit/hyperactivity disorder (ADHD) are at increased risk of developing substance use disorders (SUDs) and nicotine dependence. The co-occurrence of ADHD and SUDs/nicotine dependence may in part be mediated by shared genetic liability. Several neurobiological pathways have been implicated in both ADHD and SUDs, including dopamine and serotonin pathways. We hypothesized that variations in dopamine and serotonin neurotransmission genes were involved in the genetic liability to develop SUDs/nicotine dependence in ADHD. The current study included participants with ADHD (n = 280) who were originally part of the Dutch International Multicenter ADHD Genetics study. Participants were aged 5–15 years and attending outpatient clinics at enrollment in the study. Diagnoses of ADHD, SUDs, nicotine dependence, age of first nicotine and substance use, and alcohol use severity were based on semi-structured interviews and questionnaires. Genetic risk scores were created for both serotonergic and dopaminergic risk genes previously shown to be associated with ADHD and SUDs and/or nicotine dependence. The serotonin genetic risk score significantly predicted alcohol use severity. No significant serotonin x dopamine risk score or effect of stimulant medication was found. The current study adds to the literature by providing insight into genetic underpinnings of the co-morbidity of ADHD and SUDs. While the focus of the literature so far has been mostly on dopamine, our study suggests that serotonin may also play a role in the relationship between these disorders

Adolesc Med State Art Rev. 2014 Aug;25:502-19.

UPDATE ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Soileau EJ, Jr.

Per la ricerca degli articoli pubblicati nella letteratura scientifica nel mese in esame sono state consultate le banche dati Medline, Embase, PsycINFO e PsycArticle utilizzando le seguenti parole chiave (o i loro sinonimi): 'Attention deficit disorder', 'Attention deficit hyperactivity disorder', 'Infant', 'Child', 'Adolescent', 'Human'. Sono qui riportate le referenze considerate rilevanti e pertinenti.

Adolesc Med State Art Rev. 2014 Aug;25:398-408.

PEDIATRIC BIPOLAR DISORDER AND MOOD DYSREGULATION: DIAGNOSTIC CONTROVERSIES.

Shain BN.

Pediatric bipolar disorder, once thought rare, has gone through stages of conceptualization. DSM criteria were reinterpreted such that children and adolescents, particularly those with ADHD, were commonly diagnosed with bipolar disorder and thought to be atypical by adult standards. Research criteria separated pediatric bipolar patients into 3 phenotypes, including a research diagnosis of "severe mood dysregulation." DSM-5 largely maintained previous criteria for bipolar disorder at all ages and created a new diagnosis called "disruptive mood dysregulation disorder," categorized as a depressive disorder, for persistently angry or irritable patients with symptoms of childhood onset. However, the controversy regarding the diagnosis of pediatric bipolar disorder continues. Progress has been made in the classification of children and adolescents with mood symptoms who are predominantly irritable or angry, but lack of clarity remains regarding classification of children and adolescents with "symptoms characteristic of bipolar disorder" who do not meet criteria for bipolar I disorder, bipolar II disorder, or cyclothymia

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Am J Intellect Dev Disabil. 2016 Mar;121:79-94.

DEVELOPMENT AND STANDARDIZATION OF THE DIAGNOSTIC ADAPTIVE BEHAVIOR SCALE: APPLICATION OF ITEM RESPONSE THEORY TO THE ASSESSMENT OF ADAPTIVE BEHAVIOR.

Tasse MJ, Schalock RL, Thissen D, et al.

The Diagnostic Adaptive Behavior Scale (DABS) was developed using item response theory (IRT) methods and was constructed to provide the most precise and valid adaptive behavior information at or near the cutoff point of making a decision regarding a diagnosis of intellectual disability. The DABS initial item pool consisted of 260 items. Using IRT modeling and a nationally representative standardization sample, the item set was reduced to 75 items that provide the most precise adaptive behavior information at the cutoff area determining the presence or not of significant adaptive behavior deficits across conceptual, social, and practical skills. The standardization of the DABS is described and discussed

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Am J Occup Ther. 2016 Mar;70:7002250010p1-p9.

COMPARING AND EXPLORING THE SENSORY PROCESSING PATTERNS OF HIGHER EDUCATION STUDENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER.

Clince M, Connolly L, Nolan C.

OBJECTIVE: Research regarding sensory processing and adults with attention deficit hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) is limited. This study aimed to compare sensory processing patterns of groups of higher education students with ADHD or ASD and to explore the implications of these disorders for their college life.

METHOD: The Adolescent/Adult Sensory Profile was administered to 28 students with ADHD and 27 students with ASD. Students and professionals were interviewed.

RESULTS: The majority of students received scores that differed from those of the general population. Students with ADHD received significantly higher scores than students with ASD in relation to sensation seeking; however, there were no other major differences.

CONCLUSION: Few differences exist between the sensory processing patterns of students with ADHD and ASD; however, both groups differ significantly from the general population. Occupational therapists should consider sensory processing patterns when designing supports for these groups

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American Journal of Dance Therapy. 2016 Jun;38:41-62.

AESTHETICS OF HYPERACTIVITY: A STUDY OF THE ROLE OF EXPRESSIVE MOVEMENT IN ADHD AND CAPOEIRA.

Levin K.

In the established classification of attention-deficit/hyperactivity disorder (ADHD), the symptoms of inattention and hyperactivity are primarily interpreted as neurodevelopmental disorders connected to a set of behavioral symptoms or traits. In this construction, behaviors or actions are understood in terms of a fundamental dualism between the acting body and the regulating or executing mind, which expresses a representational model of the mind. As an effort to challenge the representational description, this article addresses the expressive aspects of movement and behavior in ADHD. Based on a qualitative study combining ethnographic and phenomenological methods, the article focuses on a relationship between aesthetic or expressive bodily movement and behavioral awareness in children diagnosed with ADHD, and draws on the experimental and expressive aesthetics of capoeira to propose a rethinking of the role of movement in ADHD behavior. Capoeira's perpetual movement is shown to transform the general traits of hyperactivity into a medium for expression and experimentation. When practiced by diagnosed children, capoeira helped them to gain expressive release, rather than to feel imprisoned, victimized, or even categorized by the hyperactive events that happen to them. Capoeira thus seems to afford a therapeutic potential for change immanent to the hyperactive movements associated with ADHD

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Brain Imaging Behav. 2016 Jun;10:387-407.

A PRELIMINARY STUDY OF THE EFFECTS OF WORKING MEMORY TRAINING ON BRAIN FUNCTION.

Stevens MC, Gaynor A, Bessette KL, et al.

Working memory (WM) training improves WM ability in Attention-Deficit/Hyperactivity Disorder (ADHD), but its efficacy for non-cognitive ADHD impairments ADHD has been sharply debated. The purpose of this preliminary study was to characterize WM training-related changes in ADHD brain function and see if they were linked to clinical improvement. We examined 18 adolescents diagnosed with DSM-IV Combined-subtype ADHD before and after 25 sessions of WM training using a frequently employed approach (Cogmed™) using a nonverbal Sternberg WM fMRI task, neuropsychological tests, and participant- and parent-reports of ADHD symptom severity and associated functional impairment. Whole brain SPM8 analyses identified ADHD activation deficits compared to 18 non-ADHD control participants, then tested whether impaired ADHD frontoparietal brain activation would increase following WM training. Post hoc tests examined the relationships between neural changes and neurocognitive or clinical improvements. As predicted, WM training increased WM performance, ADHD clinical functioning, and WM-related ADHD brain activity in several frontal, parietal and temporal lobe regions. Increased left inferior frontal sulcus region activity was seen in all Encoding, Maintenance, and Retrieval Sternberg task phases. ADHD symptom severity improvements were most often positively correlated with activation gains in brain regions known to be engaged for WM-related executive processing; improvement of different symptom types had different neural correlates. The responsiveness of both amodal WM frontoparietal circuits and executive process-specific WM brain regions was altered by WM training. The latter might represent a promising, relatively unexplored treatment target for researchers seeking to optimize clinical response in ongoing ADHD WM training development efforts

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Child Neuropsychol. 2016 Jul;22:618-26.

A TRIAL-BY-TRIAL ANALYSIS REVEALS MORE INTENSE PHYSICAL ACTIVITY IS ASSOCIATED WITH BETTER COGNITIVE CONTROL PERFORMANCE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hartanto TA, Krafft CE, Iosif AM, et al.

Hyperactivity is a key symptom and the most observable manifestation of attention-deficit/hyperactivity disorder (ADHD). The over-activity associated with ADHD can cause specific challenges in academic settings, extracurricular activities and social relationships. Cognitive control challenges are also well established in ADHD. The current study included 44 children between the ages of 10 and 17 diagnosed with

ADHD or who were typically developing (TD), all of whom had no psychiatric co-morbidity or significant learning disorders. Participants wore an actometer on their ankle while performing a flanker paradigm in order to objectively measure their rates of activity in association with cognitive control. Analyses assessed the relationship between frequency and intensity of activity to task accuracy on a trial-by-trial basis. A significant interaction effect between group and performance revealed that more intense movement was associated with better performance in the ADHD group but not in the TD group. The ADHD group demonstrated more intense activity than the TD group during correct (but not error) trials. Within-group, children with ADHD generated higher intensity movements in their correct trials compared to their error trials, whereas the TD group did not demonstrate any within-group differences. These findings suggest that excessive motoric activity associated with clinically significant ADHD symptoms may reflect compensatory efforts to modulate attention and alertness. Future research should systematically explore the relationship between motion in ADHD and how it might be used to improve cognitive performance.

Child Care Health Dev. 2016 Jul;42:521-33.

EFFECTIVENESS AND COST-EFFECTIVENESS OF A BRIEF SCHOOL-BASED GROUP PROGRAMME FOR PARENTS OF CHILDREN AT RISK OF ADHD: A CLUSTER RANDOMISED CONTROLLED TRIAL.

Sayal K, Taylor JA, Valentine A, et al.

Background: National Institute for Health and Care Excellence guidelines recommend a stepped care approach for the identification and management of children with, or at risk of, attention-deficit/hyperactivity disorder (ADHD). We investigated the effectiveness, cost-effectiveness and acceptability of a group parenting intervention programme (+/- a teacher session) for children at risk of ADHD.

Methods: In a three-arm cluster randomised controlled trial, 12 primary schools were randomly assigned to control, parent-only and combined (parent + teacher) intervention arms. Eligible children had high levels of parent-rated hyperactivity/inattention ($n = 199$). At 6 month follow-up, the primary outcome measure was the parent-completed Conners' Rating Scale—Revised (ADHD index). Secondary outcomes included the Conners' sub-scales (hyperactivity, cognitive problems/inattention and oppositional behaviour), the teacher-completed Conners' Rating Scale—Revised, child health-related quality of life, parental burden and parental mental health. The cost-effectiveness analyses reflected a health and personal social services perspective.

Trial Registration: ISRCTN87634685.

Results: Follow-up data were obtained from 76 parents and 169 teachers. There was no effect of the parent-only (mean difference = -1.1, 95% CI -5.1,2.9; $p = 0.57$) or combined interventions (mean difference = -2.1, 95% CI -6.4,2.1; $p = 0.31$) on the ADHD index. The combined intervention was associated with reduced parent-reported hyperactivity symptoms (mean difference = -5.3; 95% CI -10.5,-0.01; $p = 0.05$) and the parent-only intervention with improved parental mental health (mean difference = -1.9; 95% CI -3.2,-0.5; $p = 0.009$). The incremental costs of the parent-only and the combined interventions were £73 and £123, respectively. Above a willingness-to-pay of £31 per one-point improvement in the ADHD index, the parent-only programme had the highest probability of cost-effectiveness. Participants found the interventions acceptable.

Conclusions: For children at risk of ADHD, this school-based parenting programme was not associated with improvement in core ADHD symptoms. Secondary analyses suggested a possible reduction in parent-reported hyperactivity and parental mental health problems. Future research should compare targeted interventions against watchful waiting and specialist referral

Cochrane Database Syst Rev. 2016;CD005041.

WITHDRAWN: IMMEDIATE-RELEASE METHYLPHENIDATE FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS.

Epstein T, Patsopoulos NA, Weiser M.

F1000Research. 2015;3.

"ADHD TRAINER": THE MOBILE APPLICATION THAT ENHANCES COGNITIVE SKILLS IN ADHD PATIENTS.

Tajima-Pozo K, Ruiz-Manrique G, Montañes-Rada F.

We report the case of a 10 year old patient diagnosed with attention deficit hyperactivity disorder (ADHD) and comorbid video game addiction, who was treated with medication combined with a novel cognitive training method based on video games called TCT method. A great risk of developing video game or internet addiction has been reported in children, especially in children with ADHD. Despite this risk, we hypothesize that the good use of these new technologies might be useful to develop new methods of cognitive training. The cognitive areas in which a greater improvement was observed through the use of video games were visuospatial working memory and fine motor skills. TCT method is a cognitive training method that enhances cognitive skills such as attention, working memory, processing speed, calculation ability, reasoning, and visuomotor coordination. The purpose of reviewing this case is to highlight that regular cognitive computerized training in ADHD patients may improve some of their cognitive symptoms and might be helpful for treating video game addiction

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Frontiers in Psychology. 2016 May;7.

EMOTIONAL PROCESSING AND ATTENTION CONTROL IMPAIRMENTS IN CHILDREN WITH ANXIETY: AN INTEGRATIVE REVIEW OF EVENT-RELATED POTENTIALS FINDINGS.

Wauthia E, Rossignol M.

Anxiety disorders in adults have been associated with biased processing of emotional information which may be due to a deficit in attentional control. This deficit leads to an hypervigilance and a selective attention toward threatening information. Event-related potentials (ERPs) have been used to study this topic in anxious adults. Similar biases have been reported in children with anxiety but researches investigating the ERPs components underpinning these biases are more scarce. However, the understanding of the neural correlates of attentional biases in anxious children seem quite important since they could play a role in the etiology and the maintenance of this disorder. This review summarizes the results of researches having used ERPs to index emotional processing and attention control in children suffering from anxiety. We will focus on the P1, indexing basic visual perceptual processing, the N2, thought to reflect cognitive control process, the P3 typically associated with response inhibition, and the late positive potential (LPP) that indicates sustained attention toward motivationally salient stimuli. We will also examine the error-related negativity (ERN) that indexes monitoring system for detecting errors. Electro-physiological studies generally reported increased amplitudes of these components in anxious children, even when they did not differ from typically developing children at a behavioral level. These results suggest diminished cognitive control that influences children's selective attention mechanisms toward threatening information. Theoretical perspectives and implications for future researches will be discussed in the framework of current models of childhood anxiety

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J Abnorm Child Psychol. 2016 Jul;44:923-35.

IDENTIFYING UNIQUE VERSUS SHARED PRE- AND PERINATAL RISK FACTORS FOR ASD AND ADHD USING A SIMPLEX-MULTIPLEX STRATIFICATION.

Oerlemans AM, Burmanje MJ, Franke B, et al.

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) frequently co-occur. Besides shared genetic factors, pre- and perinatal risk factors (PPFs) may determine if ASD, ADHD, or the combination of both disorders becomes manifest. This study aimed to test shared and unique involvement of PPFs for ASD and ADHD, using an approach that stratifies the sample into affected/unaffected offspring and single-incidence (SPX) versus multi-incidence (MPX) families. Pre- perinatal data based on retrospective parent-report were collected in 288 children (71 % males) from 31 SPX and 59 MPX ASD families, 476 children (65 % males) from 31 SPX and 171 MPX ADHD families, and 408 control children (42 % males). Except for large family size and more firstborns amongst affected offspring, no shared PPFs were identified for ASD and ADHD. PPFs predominantly related to ASD (maternal infections and suboptimal condition at

birth) were more often reported in affected than unaffected siblings. PPFs associated with ADHD (low parental age, maternal diseases, smoking and stress) were shared between affected and unaffected siblings. Firstborn-ship was more frequent in SPX than MPX ASD probands. Our results suggest that the co-morbidity of ASD and ADHD is not likely explained by shared PPFs. Instead, PPFs might play a crucial role in the developmental pathways leading up to either disorder. PPFs in ADHD appear to index an increased shared risk, whereas in ASD PPFs possibly have a more determining role in the disorder. SPX-MPX stratification detected possible etiological differences in ASD families, but provided no deeper insight in the role of PPFs in ADHD

J Abnorm Child Psychol. 2016 Jul;44:1023-32.

IMPAIRED SOCIAL DECISION-MAKING MEDIATES THE ASSOCIATION BETWEEN ADHD AND SOCIAL PROBLEMS.

Humphreys KL, Galán CA, Tottenham N, et al.

Attention-deficit/hyperactivity disorder (ADHD) reliably predicts social dysfunction, ranging from poor social competence and elevated peer rejection to inadequate social skills. Yet, the factors mediating predictions of social problems from childhood ADHD are not well understood. In the present study, we investigated social functioning in 186 (69 % male) 6 to 10 year-old ($M = 7.88$, $SD = 1.17$) children with ($n = 98$) and without ($n = 87$) ADHD who were followed prospectively for two years. We implemented a well-validated measure of social problems as well as a novel social decision-making task assessing dynamic response to changing affective cues at the two-year follow-up. According to separate parent and teacher report, baseline ADHD symptoms positively predicted social problems at the two-year follow-up; individual differences on the social decision-making task mediated this association. This finding was replicated when ADHD dimensions (i.e., inattention and hyperactivity/impulsivity) were separately examined. These findings suggest that the deficient use of affective cues to effectively guide behavior may partially underlie poor social functioning among children with ADHD. If replicated, these preliminary findings suggest that social skills interventions that target interpretation of affective cues to aid in social decision-making behavior may improve social outcomes negatively affected by early ADHD symptoms

Journal of Attention Disorders. 2016 Jul;20:617-26.

HOARDING IN CHILDREN WITH ADHD.

Hacker LE, Park JM, Timpano KR, et al.

Objective: Although evidence suggests that hoarding may be associated with symptoms of ADHD, no study has examined this relationship in children.

Method: Participants included 99 youth diagnosed with ADHD (and a parent) seen in a general outpatient psychiatry clinic. Children completed the Obsessive-Compulsive Inventory–Child Version, the Revised Child Anxiety and Depression Scale, and the Rosenberg Self-Esteem Scale. Parents completed the Children's Saving Inventory and Vanderbilt ADHD Diagnostic Rating Scale–Parent Version.

Results: Inattentive and hyperactive/impulsive symptoms were the only indicator that differentiated those with and without clinically significant hoarding. Symptoms of ADHD, but not nonhoarding obsessive-compulsive symptoms, significantly predicted hoarding. Inattention and hyperactivity/impulsivity were uniquely associated with individual hoarding features. Hoarding symptoms mediated the relationship between ADHD and oppositionality.

Conclusion: These findings contribute to the growing literature about the association between hoarding and ADHD

Journal of Attention Disorders. 2016 Jul;20:636-44.

CHARACTERISTICS OF CHILDREN WITH ADHD AND COMORBID ANXIETY.

Jarrett MA, Wolff JC, Davis TEI, et al.

Objective: The following comorbid subgroups of ADHD have been proposed: ADHD Only, ADHD + anxiety disorders (ANX), ADHD + oppositional defiant disorder/conduct disorder (ODD/CD), and ADHD + ODD/CD + ANX. The current study examined a subset of these groups.

Method: A total of 134 children and adolescents (M age = 9.92; range = 6-17) from a clinic-referred sample (n = 407) were grouped based on a semistructured diagnostic interview: ADHD only (n = 41), ADHD + ANX (n = 31), and ANX Only (n = 62).

Results: Findings supported greater parent-reported anxiety symptoms in anxiety groups, and greater parent- and teacher-reported attention problems in ADHD groups. ADHD groups performed worse on a continuous performance test, whereas ADHD + ANX performed worse on working memory than ADHD Only. ADHD + ANX reported more physical anxiety symptoms than ADHD Only.

Conclusion: Comorbid anxiety should be considered in ADHD assessment and treatment

Journal of Child and Family Studies. 2016 Jul;25:2279-91.

THE ROLE OF ADHD AND NEGATIVE EMOTIONAL LABILITY IN PREDICTING CHANGES IN PARENTING DAILY HASSLES.

Walerius DM, Fogleman ND, Rosen PJ.

The present study examined the extent to which children's negative emotional lability (measured via ecological momentary assessment—EMA) and ADHD diagnostic status predicted changes in the frequency of daily parenting hassles and the stress resulting from daily hassles at one-week follow-up when controlling for baseline parenting hassles. Parents of 84 children 8–12 years-old (47 with ADHD, 37 without ADHD) completed a measure of parenting daily hassles at baseline and follow-up and participated in EMA assessment protocol ratings of their child's mood (3-times daily) for one week. Analyses of covariance indicated that parents of children with ADHD reported significantly greater frequency of daily parenting hassles and intensity of parenting stress resulting from daily hassles than parents of children without ADHD at baseline and follow-up. Hierarchical regression analyses suggested that children's negative emotional lability was a significant predictor of the intensity of parenting stress resulting from daily hassles, but not the frequency of daily parenting hassles. There was also an interaction of ADHD diagnostic status and greater EMA-derived negative emotional lability in the prediction of the frequency of daily parenting hassles due to children's challenging behaviors. Specifically, greater negative emotional lability predicted more frequent daily parenting hassles due to children's challenging behaviors among parents of children without ADHD but not among parents of children with ADHD. Overall, this study suggests that children's negative emotional lability is a significant predictor of aspects of daily parenting hassles across parents of children with and without ADHD

Journal of Clinical Child and Adolescent Psychology. 2016 Jul;45:510-21.

PERSONALIZED TREATMENT OF MOTHERS WITH ADHD AND THEIR YOUNG AT-RISK CHILDREN: A SMART PILOT.

Chronis-Tuscano A, Wang CH, Strickland J, et al.

Young children of mothers with adult attention-deficit/hyperactivity disorder (ADHD) are at risk for ADHD by virtue of genetics and environmental factors. Moreover, parent ADHD is associated with maladaptive parenting and poor child behavioral treatment response. Thus, a combined approach consisting of behavioral parent training (BPT) and maternal stimulant medication (MSM) may be needed to effectively treat ADHD within families. However, providing combined BPT + MSM initially to all families may be unnecessarily burdensome because not all families likely need combined treatment. The purpose of this study is to examine how to combine, sequence, and personalize treatment for these multiplex families in order to yield benefits to both the parent and child, thereby impacting the course of child ADHD and disruptive behavior symptoms. This article presents our rationale for, design of, and preliminary experiences (based on 26 participants) with an ongoing pilot Sequential Multiple Assessment Randomized Trial (SMART) designed to answer questions

regarding the feasibility and acceptability of study protocols and interventions. This article also describes how the subsequent full-scale SMART might change based on what is learned in the SMART pilot and illustrates how the full-scale SMART could be used to inform clinical decision making about how to combine, sequence, and personalize treatment for complex children and families in which a parent has ADHD

Journal of Clinical Child and Adolescent Psychology. 2016 Jul;45:416-27.

COMPARATIVE COST ANALYSIS OF SEQUENTIAL, ADAPTIVE, BEHAVIORAL, PHARMACOLOGICAL, AND COMBINED TREATMENTS FOR CHILDHOOD ADHD.

Page TF, Pelham WEI, Fabiano GA, et al.

We conducted a cost analysis of the behavioral, pharmacological, and combined interventions employed in a sequential, multiple assignment, randomized, and adaptive trial investigating the sequencing and enhancement of treatment for children with attention deficit hyperactivity disorder (ADHD; Pelham et al., 201X; N = 146, 76% male, 80% Caucasian). The quantity of resources expended on each child's treatment was determined from records that listed the type, date, location, persons present, and duration of all services provided. The inputs considered were the amount of physician time, clinician time, paraprofessional time, teacher time, parent time, medication, and gasoline. Quantities of these inputs were converted into costs in 2013 USD using national wage estimates from the Bureau of Labor Statistics, the prices of 30-day supplies of prescription drugs from the national Express Scripts service, and mean fuel prices from the Energy Information Administration. Beginning treatment with a low-dose/intensity regimen of behavior modification (large-group parent training) was less costly for a school year of treatment (\$961) than beginning treatment with a low dose of stimulant medication (\$1,669), regardless of whether the initial treatment was intensified with a higher "dose" or if the other modality was added. Outcome data from the parent study (Pelham et al., 201X) found equivalent or superior outcomes for treatments beginning with low-intensity behavior modification compared to intervention beginning with medication. Combined with the present analyses, these findings suggest that initiating treatment with behavior modification rather than medication is the more cost-effective option for children with ADHD

Journal of Clinical Child and Adolescent Psychology. 2016 Jul;45:396-415.

TREATMENT SEQUENCING FOR CHILDHOOD ADHD: A MULTIPLE-RANDOMIZATION STUDY OF ADAPTIVE MEDICATION AND BEHAVIORAL INTERVENTIONS.

Pelham WEJr, Fabiano GA, Waxmonsky JG, et al.

Behavioral and pharmacological treatments for children with attention deficit/hyperactivity disorder (ADHD) were evaluated to address whether endpoint outcomes are better depending on which treatment is initiated first and, in case of insufficient response to initial treatment, whether increasing dose of initial treatment or adding the other treatment modality is superior. Children with ADHD (ages 5–12, N = 146, 76% male) were treated for 1 school year. Children were randomized to initiate treatment with low doses of either (a) behavioral parent training (8 group sessions) and brief teacher consultation to establish a Daily Report Card or (b) extended-release methylphenidate (equivalent to .15 mg/kg/dose bid). After 8 weeks or at later monthly intervals as necessary, insufficient responders were rerandomized to secondary interventions that either increased the dose/intensity of the initial treatment or added the other treatment modality, with adaptive adjustments monthly as needed to these secondary treatments. The group beginning with behavioral treatment displayed significantly lower rates of observed classroom rule violations (the primary outcome) at study endpoint and tended to have fewer out-of-class disciplinary events. Further, adding medication secondary to initial behavior modification resulted in better outcomes on the primary outcomes and parent/teacher ratings of oppositional behavior than adding behavior modification to initial medication. Normalization rates on teacher and parent ratings were generally high. Parents who began treatment with behavioral parent training had substantially better attendance than those assigned to receive training

following medication. Beginning treatment with behavioral intervention produced better outcomes overall than beginning treatment with medication

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J Dev Behav Pediatr. 2016 Jun;37:395-404.

EFFECTS OF METHYLPHENIDATE ON SLEEP FUNCTIONING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Becker SP, Froehlich TE, Epstein JN.

Objective: To examine the effects of stimulant medication on the sleep functioning of children with attention-deficit/hyperactivity disorder (ADHD) and identify predictors of sleep problems as a side effect of taking stimulant medication.

Method: One hundred sixty-three stimulant-naïve children (72% boys) aged 7 to 11 years diagnosed with ADHD (120 with ADHD predominantly inattentive type, 43 with ADHD combined type) participated in a 4-week, randomized, double-blind, placebo-controlled trial of once-daily (long-acting) methylphenidate (MPH). Parents completed weekly side-effect ratings including an item related to sleep problems.

Results: Ten percent of patients had parent-rated sleep problems before the initiation of medication. Rates of parent-rated sleep problems during MPH titration generally increased with increasing MPH dose (placebo: 8%; low dose: 18%; medium dose: 15%; high dose: 25%). Differences emerged between children with ($n = 16$) or without ($n = 147$) preexisting sleep problems. Although 23% of children without preexisting sleep problems went on to have sleep problems at the highest MPH dose, only 37.5% of children with preexisting sleep problems still had sleep problems at the highest MPH dose. Lower weight and lower body mass index (BMI) were associated with increased sleep problems during MPH titration.

Conclusion: This study demonstrated a general association between increased MPH dose and increased sleep problems in children with ADHD, particularly for children of lower weight/BMI. However, a substantial proportion of children with preexisting sleep difficulties no longer had sleep problems on the highest MPH dose, which may help explain mixed findings reported to date in studies examining the impact of MPH on sleep functioning in children with ADHD and suggests that MPH dose titration should not be avoided solely on the basis of a child's premorbid sleep problems. Future research is needed to replicate and extend these findings to more specific domains of sleep functioning and to identify differences between children with persistent or improved sleep functioning as a result of MPH use

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J Dev Behav Pediatr. 2016 Jun;37:385-94.

SLEEP AND SELF-REGULATION FROM BIRTH TO 7 YEARS: A RETROSPECTIVE STUDY OF CHILDREN WITH AND WITHOUT ATTENTION-DEFICIT HYPERACTIVITY DISORDER AT 8 TO 9 YEARS.

Williams KE, Sciberras E.

Objective: To examine mean level differences and longitudinal and reciprocal relations among behavioral sleep problems, emotional dysregulation, and attentional regulation across early childhood for children with and without attention-deficit hyperactivity disorder (ADHD) at 8 to 9 years.

Method: This study used data from Growing Up in Australia: The Longitudinal Study of Australian Children (LSAC)—Infant Cohort ($n = 4,109$ analyzed). Children with and without ADHD were identified at age 8 to 9 years via parent report of ADHD diagnosis and the 5-item Inattention-Hyperactivity subscale from the Strengths and Difficulties Questionnaire. Maternal report of child sleep problems and self-regulation was collected at 0 to 1, 2 to 3, 4 to 5, and 6 to 7 years of age. Analysis of variance was used to compare mean level differences in sleep problems and emotional and attentional regulation by ADHD group. Longitudinal structural equation modeling examined the relations among sleep and self-regulation across time in children with and without ADHD.

Results: Children with ADHD had persistently elevated levels of sleep problems (from infancy) and emotional and attentional dysregulation compared to controls (from 2 to 3 years of age). Sleep problems, emotional dysregulation, and attentional regulation were stable over time for both groups. Sleep problems were associated with greater emotional dysregulation 2 years later from 2 to 3 years of age for both groups, which

in turn was associated with poorer attentional regulation. There was no direct relationship between sleep problems and later attentional regulation.

Conclusion: Sleep problems in children with and without ADHD are associated with emotional dysregulation, which in turn contributes to poorer attentional functioning. This study highlights the importance of assessing and managing sleep problems in young children

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J Dev Behav Pediatr. 2016 Jun;37:405-14.

SLEEP PROBLEM TRAJECTORIES AND WELL-BEING IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A PROSPECTIVE COHORT STUDY.

Lycett K, Sciberras E, Hiscock H, et al.

Objective: Sleep problems affect up to 70% of children with attention-deficit/hyperactivity disorder (ADHD) and are associated with poorer child and family well-being in cross-sectional studies. However, whether these associations hold longitudinally is unclear. The authors aimed to examine the longitudinal relationship between sleep problem trajectories and well-being in children with ADHD.

Method: Children with ADHD (n = 186), aged 5 to 13 years, were recruited from 21 pediatric practices across the state of Victoria, Australia. Sleep problem severity data were collected at 3 time points (baseline, 6, and 12 mo) and were used to classify sleep problem trajectories. Child and family well-being (e.g., child emotional and behavioral problems, quality of life [QoL]) were measured at baseline and 12 months by teacher and/or caregiver-report. The well-being of children with “transient” and “persistent” sleep problems was compared with those “never” experiencing sleep problems using a series of hierarchical linear regression models.

Results: After accounting for socio-demographic factors, children with transient and persistent sleep trajectories experienced more caregiver-reported behavioral and emotional problems (effect size [ES] both 0.7) and poorer child QoL (ES: -0.7 and -1.2, respectively). These associations remained after also accounting for ADHD medication and symptom severity and comorbidities, but after accounting for baseline measures many associations weakened to the point of nonsignificance. In the fully adjusted model—transient sleep problems were associated with behavioral and emotional problems (ES: 0.2). These associations were not evident by teacher-report.

Conclusion: Children with ADHD experiencing transient or persistent sleep problems have poorer caregiver-reported well-being. Managing sleep problems in children with ADHD may improve child well-being

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Journal of Health Psychology. 2016 Jun;21:1055-65.

ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMATOLOGY AND PEDIATRIC OBESITY: PSYCHOPATHOLOGY OR SLEEP DEPRIVATION?

Lundahl A, Nelson TD.

The relationship between attention deficit hyperactivity disorder (ADHD) and obesity in children has received considerable attention in recent years. However, the literature currently overlooks the potential causal and maintaining role that sleep problems may play in this relationship. Using a biopsychosocial framework, this article highlights how sleep problems impact the biological, psychological, and social aspects of both ADHD symptomatology and obesity. An in-depth examination of this model illustrates the imperative need for future research and clinical practice to recognize and explore the role sleep has in the link between obesity and ADHD symptomatology

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Journal of Learning Disabilities. 2016 Jul;49:410-23.

EXAMINING ASSOCIATIONS AMONG ADHD, HOMEWORK BEHAVIOR, AND READING COMPREHENSION: A TWIN STUDY.

Little CW, Hart SA, Schatschneider C, et al.

Previous literature has indicated an important association between reading comprehension and both attention-deficit/hyperactivity disorder (ADHD) and homework habits. This investigation sought to extend

previous knowledge by providing information about how ADHD and homework behavior (i.e., completing homework regularly) may jointly influence reading comprehension. Using a genetically sensitive design, this study examined the genetic and environmental influences on and between ADHD, homework behavior and reading comprehension. Participants for this study included 691 twin pairs (351 monozygotic, 340 same-sex dizygotic) from the Florida Twin Project on Behavior and Environment (FTP-BE) and 2647 twin pairs (865 monozygotic, 1782 dizygotic) from the larger Florida Twin Project on Reading (FTP-R) in Grades 3 through 7. Three separate models, each representing a different definition of ADHD (full ADHD, inattention only, and hyperactivity/impulsivity only), showed similar patterns of results; therefore, results of the full ADHD model are discussed. Overlapping genetic influences were found between ADHD, homework behavior, and reading comprehension, but no shared environmental influences among all three. However, shared environmental influences overlapped between homework behavior and reading comprehension. Although the sources of this environmental overlap are unknown, these results have implications for improving homework practices and their subsequent influence on literacy skills through homework environments

Journal of Positive Behavior Interventions. 2016 Jul;18:168-79.

AN EVALUATION OF A SELF-MANAGEMENT INTERVENTION TO INCREASE ON-TASK BEHAVIOR WITH INDIVIDUALS DIAGNOSED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Slattery L, Crosland K, Iovannone R.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent disorders in school-age children. Children with ADHD often have difficulty at school and at home. Medication is a common treatment for children with ADHD; however, it has been shown to be more effective when combined with behavioral interventions. Self-management has extensive research support showing its effectiveness for children with ADHD primarily in academic settings. The purpose of this study was to examine the impact a self-management intervention would have on the on-task behavior of children during various routines, both academic and nonacademic, in the home setting. Participants were trained to use a self-management intervention. In addition, parents were trained to conduct accuracy checks on their child's performance as well as deliver feedback and rewards. All three participants showed an increase in on-task behavior following the implementation of the self-management intervention; two of the three participants' on-task behavior maintained high, stable levels as the self-management schedule was faded. One participant's on-task behavior did not maintain high levels and therefore required implementation of a self-management plus reinforcement for on-task behavior condition to reestablish high, stable levels of on-task behavior. For one participant, the duration of the targeted routine increased. Current limitations are discussed, and recommendations for future research in this area are provided

J Sleep Res. 2016 Jun;25:333-40.

DISTURBED SLEEP IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) IS NOT A QUESTION OF PSYCHIATRIC COMORBIDITY OR ADHD PRESENTATION.

Virring A, Lambek R, Thomsen PH, et al.

Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous psychiatric disorder with three different presentations and high levels of psychiatric comorbidity. Serious sleep complaints are also common, but the role of the presentations and comorbidity in sleep is under-investigated in ADHD. Consequently, the goal of the study was to investigate sleep problems in medicine-naive school-aged children (mean age = 9.6 years) with ADHD compared to controls using objective methods and to examine the role of comorbidity and presentations. Ambulatory polysomnography results suggested that children with ADHD (n = 76) had significantly more sleep disturbances than controls (n = 25), including a larger percentage of rapid eye movement (REM) sleep and more sleep cycles, as well as lower mean sleep efficiency, mean non-REM (NREM) sleep stage 1 and mean NREM sleep stage 3. No significant between-group differences were found on the multiple sleep latency test. Stratifying for comorbidity in the ADHD group did not reveal major differences between groups, but mean sleep latency was significantly longer in children with ADHD and no

comorbidity compared to controls (36.1 min; SD = 30.1 versus 22.6 min; SD = 15.2). No differences were found between ADHD presentations. Our results support the presence of night-time sleep disturbances in children with ADHD. Poor sleep does not appear to be attributable to comorbidity alone, nor do sleep disturbances differ within ADHD presentations

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Med Law. 2014 Oct;33:119-30.

THERAPEUTIC COPING WITH ADHD AMONG CHILDREN FROM THE ARAB ISRAELI SECTOR WITH AN EMPHASIS ON THE THERAPIST-PATIENT RELATIONSHIP.

Gith E.

Over the past two decades, the Arab Israeli society's awareness to the need to treat children suffering from Attention Deficit/Hyperactivity Disorder (ADHD) has been rising. The State of Israel provides educational and psychological services in almost every Arab-Israeli town, allowing for identification, diagnosis and treatment. However, misleading prejudice stemming from lack of basic knowledge poses difficulties when offering appropriate therapy. The present paper aims to demonstrate the implications of such unawareness and stigmas, as well as to present the dilemmas and flaws in the professional relationship required between those involved in rendering appropriate care. It concludes that a multi-system therapeutic approach must be adopted by the Arab Israeli society, with emphasis placed on the therapist-patient relationship and the ability to take into consideration the individual needs of each case

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Mol Autism. 2016;7:8.

EFFECT OF CO-TWIN GENDER ON NEURODEVELOPMENTAL SYMPTOMS: A TWIN REGISTER STUDY.

Eriksson JM, Lundstrom S, Lichtenstein P, et al.

BACKGROUND: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are neurodevelopmental disorders thought to have both genetic and environmental causes. It has been hypothesized that exposure to elevated levels of prenatal testosterone is associated with elevated traits of ASD and ADHD. Assuming that testosterone levels from a dizygotic male twin fetus may lead to enhanced testosterone exposure of its co-twins, we aimed to test the prenatal testosterone hypothesis by comparing same-sex with opposite-sex dizygotic twins with respect to neurodevelopmental symptoms.

METHODS: Neuropsychiatric traits were assessed in a population-based twin cohort from the Child and Adolescent Twin Study in Sweden (CATSS). Parental interviews were conducted for 16,312 dizygotic twins, 9 and 12 years old, with the Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC).

RESULTS: Girls with a female co-twin had an increased risk of reaching the cut-off score for ADHD compared with girls with a male co-twin. Both boys and girls with a female co-twin displayed a larger number of traits related to attention deficit and repetitive and stereotyped behaviors than those with a male twin. In girls, this also extended to social interaction and the combined measures for ASD and ADHD, however, with small effect sizes.

CONCLUSIONS: Our results are reverse to what would have been expected from the prenatal testosterone hypothesis but consistent with a previous study of ASD and ADHD traits in dizygotic twins. The seemingly protective effect for girls of having a twin brother may be an effect of parent report bias, but may also be an unexpected effect of sharing the intrauterine environment with a male co-twin

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Paediatr Drugs. 2016 Aug;18:319-29.

HEAD-TO-HEAD COMPARISON OF ARIPIPRAZOLE AND RISPERIDONE IN THE TREATMENT OF ADHD SYMPTOMS IN CHILDREN WITH AUTISTIC SPECTRUM DISORDER AND ADHD: A PILOT, OPEN-LABEL, RANDOMIZED CONTROLLED STUDY.

Lamberti M, Siracusano R, Italiano D, et al.

BACKGROUND: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are frequently overlapping neurodevelopmental disorders. Individuals in whom the disorders are comorbid show more severe impairment because of deficits in the processing of social situations, adaptive functioning, and executive control than individuals with either disorder alone.

OBJECTIVE: This open-label pilot study aimed to evaluate and compare the efficacy and tolerability of risperidone and aripiprazole for treating ADHD symptoms in patients with both ASD and ADHD over the course of 24 weeks of treatment.

METHODS: Patients (n = 44) were randomly assigned to start treatment with risperidone (22 patients) or aripiprazole (22 patients). Children were evaluated before starting treatment (T0), and after 12 weeks (T1) and 24 weeks (T2) of treatment. At each visit, specific psychiatric clinical scales were administered to assess the efficacy of the two drugs.

RESULTS: The mean age was 8.4 +/- 2.9 years in the aripiprazole group and 7.8 +/- 2.3 years in the risperidone group. A total of 37 children (29 boys and 8 girls) completed the study (18 in the aripiprazole group and 19 in the risperidone group). Aripiprazole and risperidone appeared to have similar benefits in terms of efficacy and tolerability, although there were slight differences between the two drugs. Both groups showed a significant improvement in ADHD symptoms after 24 weeks of treatment (ADHD Rating Scale, Conners Parent Rating Scale-Hyperactivity, and Clinical Global Improvement-Severity Scale). No significant difference between the two drugs on any parameters at 24 weeks were found. Prolactin levels were decreased in the aripiprazole group. Both drugs were well tolerated, with no serious adverse events detected.

CONCLUSIONS: Our study confirms the efficacy of both aripiprazole and risperidone in ameliorating ADHD symptoms of children also presenting with ASD

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Pediatr Nephrol. 2016 May;31:689-92.

INCONTINENCE AND PSYCHOLOGICAL PROBLEMS IN CHILDREN: A COMMON CENTRAL NERVOUS PATHWAY?

Van HC, Vande WJ.

Nocturnal enuresis is caused by a mismatch between the nocturnal bladder capacity and the nocturnal diuresis rate, in the presence of a deficient arousability in the majority of patients, according to the pediatric and urologic literature. Psychiatric and psychologic literature are still concentrating on the potential role of psychological factors and central nervous mechanisms in the pathogenesis, as is reflected in the DMS-5 criteria. However, research has clearly shown several important comorbidities between neuropsychological dysfunctions and nocturnal enuresis. Due to the increased comorbidity of (neuro)psychological problems, sleep problems, circadian rhythms, and enuresis, the question arises as to whether there is a possible common central pathway in the pathogenesis. It is likely that the coexistence of these problems can be attributed to a common central nervous system involvement. The specific role of the central nervous system remains unclear, but several pathways are possible. The high comorbidity between enuresis, sleep, and (neuro)psychological functioning is probably attributable to a common pathogenetic pathway, emphasizing the importance of a multidisciplinary focus in screening and treatment in children with nocturnal enuresis

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Pediatrics. 2016 Mar;137:e20154450.

IMPROVING CARE FOR CHILDREN WITH ADHD: THE INFORMATION IS JUST A RATING SCALE AWAY.

Barbaresi WJ.

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Pharmacology, Biochemistry and Behavior. 2016 Jun;145:24-26.

NECESSITY FOR RESEARCH DIRECTED AT STIMULANT TYPE AND TREATMENT-ONSET AGE TO ACCESS THE IMPACT OF MEDICATION ON DRUG ABUSE VULNERABILITY IN TEENAGERS WITH ADHD.

Kantak KM, Dwoskin LP.

This opinion article discusses necessity for research directed at stimulant type and treatment-onset age to access the impact of medication on drug abuse vulnerability in teenagers with ADHD. Controversy continues regarding increased vulnerability for addiction to cocaine and other drugs of abuse in adulthood following the use of stimulant medications for the treatment of Attention Deficit Hyperactivity Disorder. Stimulant medication in childhood is associated with a reduction in the risk for subsequent SUD during adolescence and young adulthood. Initiation of stimulant medication during adolescence may have different consequences for subsequent SUD than initiation in childhood is derived from research specifically analyzing age of treatment onset in ADHD patients. Initiation of stimulant medication, methylphenidate in particular for ADHD during adolescence may have negative consequences with respect to later SUD. ADHD is known to be comorbid with SUD. Meta-analysis of patients with non-medicated ADHD show 2–3 times greater use of cocaine, other stimulants, tobacco, and marijuana during adolescence and adulthood compared to controls without ADHD

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PLoS ONE. 2016;11:e0148841.

THE EFFECTS OF CLASSROOM INTERVENTIONS ON OFF-TASK AND DISRUPTIVE CLASSROOM BEHAVIOR IN CHILDREN WITH SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A META-ANALYTIC REVIEW.

Gaasra GF, Groen Y, Tucha L, et al.

Children with attention-deficit/hyperactivity disorder (ADHD) often exhibit problem behavior in class, which teachers often struggle to manage due to a lack of knowledge and skills to use classroom management strategies. The aim of this meta-analytic review was to determine the effectiveness of several types of classroom interventions (antecedent-based, consequence-based, self-regulation, combined) that can be applied by teachers in order to decrease off-task and disruptive classroom behavior in children with symptoms of ADHD. A second aim was to identify potential moderators (classroom setting, type of measure, students' age, gender, intelligence, and medication use). Finally, it was qualitatively explored whether the identified classroom interventions also directly or indirectly affected behavioral and academic outcomes of classmates. Separate meta-analyses were performed on standardized mean differences (SMDs) for 24 within-subjects design (WSD) and 76 single-subject design (SSD) studies. Results showed that classroom interventions reduce off-task and disruptive classroom behavior in children with symptoms of ADHD (WSDs: MSMD = 0.92; SSDs: MSMD = 3.08), with largest effects for consequence-based (WSDs: MSMD = 1.82) and self-regulation interventions (SSDs: MSMD = 3.61). Larger effects were obtained in general education classrooms than in other classroom settings. No reliable conclusions could be formulated about moderating effects of type of measure and students' age, gender, intelligence, and medication use, mainly because of power problems. Finally, classroom interventions appeared to also benefit classmates' behavioral and academic outcomes

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PLoS ONE. 2016;11:e0149189.

COGNITION AND BEHAVIOUR IN SOTOS SYNDROME: A SYSTEMATIC REVIEW.

Lane C, Milne E, Freeth M.

BACKGROUND: Research investigating cognition and behaviour in Sotos syndrome has been sporadic and to date, there is no published overview of study findings.

METHOD: A systematic review of all published literature (1964-2015) presenting empirical data on cognition and behaviour in Sotos syndrome. Thirty four journal articles met inclusion criteria. Within this literature, data relating to cognition and/or behaviour in 247 individuals with a diagnosis of Sotos syndrome were reported. Ten papers reported group data on cognition and/or behaviour. The remaining papers employed a case study design.

RESULTS: Intelligence quotient (IQ) scores were reported in twenty five studies. Intellectual disability (IQ < 70) or borderline intellectual functioning (IQ 70-84) was present in the vast majority of individuals with Sotos syndrome. Seven studies reported performance on subscales of intelligence tests. Data from these studies indicate that verbal IQ scores are consistently higher than performance IQ scores. Fourteen papers provided data on behavioural features of individuals with Sotos syndrome. Key themes that emerged in the behavioural literature were overlap with ASD, ADHD, anxiety and high prevalence of aggression/tantrums.

CONCLUSION: Although a range of studies have provided insight into cognition and behaviour in Sotos syndrome, specific profiles have not yet been fully specified. Recommendations for future research are provided

Prax Kinderpsychol Kinderpsychiatr. 2016;65:298-314.

ADAPTIVE AND MALADAPTIVE STRATEGIES OF EMOTION REGULATION IN ADOLESCENTS WITH ADHD.

Lange S, Troster H.

The present study investigated differences between adolescents with ADHD and control subjects in their adaptive und maladaptive regulation of negative emotions. We assessed emotion regulation strategies using the German self-report questionnaire FEEL-KJ in a sample of adolescents (between 11 and 18 years) with ADHD (disturbance of activity, impulsivity and attention: n = 32, hyperkinetic conduct disorder: n = 26) and controls (n = 58). We found that adolescents with ADHD reported using less adaptive strategies for dealing with negative emotions than control subjects. No effects were found for maladaptive emotion regulation strategies for anger, fear and sadness. Our findings indicate that adolescents with ADHD should be encouraged in the development of adaptive emotion regulation

Prax Kinderpsychol Kinderpsychiatr. 2016;65:315-27.

EFFECTIVENESS OF AN EDUCATOR TRAINING ABOUT THE ATTENTION-DEFICIT-/HYPERACTIVITY DISORDER (ADHD).

Both F, Schmiedeler S, Abelein P, et al.

The purpose of the current study was to examine the effectiveness of a workshop for teachers focussing on ADHD. A total of 44 educators answered a short version of the Knowledge of Attention Deficit Disorders Scale (KADDS) and self-report questions before, shortly after, and three month subsequent (follow-up) to a 2.5 hour long workshop. Results showed a significant increase in the educators' knowledge at post-test, which remained stable in the follow-up. Whereas uncertainties ("don't-know"-answers) decreased, heterogeneous results were found concerning the number of misconceptions. Educators upgraded their knowledge perception as well as their certainty in dealing with an affected child at post-test. The results show that even a relatively short workshop had a positive and persistent impact on educators' ADHD expertise, which illustrates the potential of such workshops

Przegl Lek. 2016;73:148-51.

CLINICAL AND NEUROPHYSIOLOGICAL DATA OF NEUROFEEDBACK THERAPY IN CHILDREN WITH ADHD.

Kubik A, Kubik P, Stanios M, et al.

INTRODUCTION: ADHD occurs in 3% of school-age children (and in 70% of them in adulthood) and represents an important medical and social problem. It is characterized by attention deficits, hyperactivity and impulsiveness. Neurofeedback therapy (EEG biofeedback, NF) is carried out based on the analysis of EEG.

OBJECTIVE: To investigate the effect of NF therapy on clinical status and parameters of the EEG in ADHD.

MATERIALS AND METHODS: In the years 2007-2014, 287 children (191 boys), aged 6-17 years were included into the study. Some children with ADHD had other coexisting disorders like: tics, dyslexia, emotional or behavior disorders. Visual analysis of EEG was made and 7 selected parameters of bioelectrical activity were assessed. EEG tracing before and after NF therapy were compared. NF therapy lasted from 9

months to 3 years (mean 1.5 years). 60-240 NF training sessions were performed with the use of NF device, video-games and 16-channel Elmiko devices. Statistical analysis of the results was made. RESULTS: Children with ADHD additionally presented low self-esteem, anxiety and sleep disorders. The baseline theta/beta ratio in children with ADHD and ADHD with cooccurring dyslexia was >4.0 and in children with ADHD and coexisting tics 3.0-3.8, with coexisting behavioral disorders 3.7-4.0 and emotional disorders 3.3-3.7. After therapy, this ratio decreased significantly in all groups, but most significantly in ADHD and ADHD with dyslexia group. In the group with dyslexia theta and alpha activity in the left fronto-temporo-parietal region (the speech centers) has been increased. In children with ADHD and behavior disorders right-sided paroxysmal changes in the form of slow and sharp waves in the temporo-centro-parietal regions were found. In emotionally disturbed children increased fast beta activity in the right hemisphere (anxiety, fear) was observed. Initially NF therapy reduced hyperactivity and impulsivity of children, subsequently improvement of attention was observed and eventually reduction of emotional and behavior disturbances was noticed. Noticeable improvement in the self-esteem was observed as well. The therapy had a positive impact on the spatial organization of EEG in each group. It proved to be particularly useful in children with ADHD and dyslexia.

CONCLUSIONS: Neurofeedback therapy is a valuable tool with beneficial impact on children with ADHD and accompanying disorders. Characteristics of brain bioelectric activity provides a reliable basis to establish individual EEG bio-feedback protocols of therapy in children and monitor the effectiveness of treatment. In the last 4 years the number of children with ADHD and cooccurring tics who applied for neurofeedback therapy has increased significantly

Psychiatry Res. 2016 Jun;240:1-3.

THE PREVALENCE OF SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN PARENTS OF CHILDREN WITH AUTISM SPECTRUM DISORDER.

Bonatto SJ, Kerner M, Merelles S, et al.

This study aims to estimate the prevalence of symptoms of attention-deficit/hyperactivity disorder (ADHD) in parents of children with autism spectrum disorder (ASD). This is a cross-sectional study conducted with the parents of 89 children previously diagnosed with ASD. The research instrument used was the 18-item Adult ADHD Self-Report Scale (ASRS). Symptoms of ADHD were present in 10.4% of the mothers of children with a diagnosis of ASD and in 11.3% of the fathers. These results suggest that the prevalence of symptoms of ADHD in the parents of children with autism is higher than that found in the general adult population

Psychoanal Study Child. 2015;69:394-415.

CHILD PSYCHOTHERAPY, CHILD ANALYSIS, AND MEDICATION: A FLEXIBLE, INTEGRATIVE APPROACH.

Whitman L.

For children with moderate to severe emotional or behavioral problems, the current approach in child psychiatry is to make an assessment for the use of both psychotherapy and medication. This paper describes integration of antidepressants and stimulants with psychoanalytically oriented techniques

Sheng Wu Yi Xue Gong Cheng Xue Za Zhi. 2016 Feb;33:161-66.

STUDY OF EVENT-RELATED BRAIN POTENTIAL IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Zhu L, Zeng Q, Jiang Y, et al.

This study aims to explore the differences of event-related potential (ERP) between attention deficit hyperactivity disorder (ADHD) and normal children, so that these differences provide scientific basis for the diagnosis of ADHD. Eight children were identified to be ADHD group by the diagnostic criteria of DSM-IV (diagnostic and statistical manual of mental disorders-IV), and the control group also consisted of 8 normal children. Modified visual-continuous performance test (CPT) was used as the experiment paradigm. The

experiment included two major conditions, i. e. Go and NoGo. All the 16 subjects participated in the study. A high density EEG acquisition instrument was used to record the EEG signal and processed these EEG data by means of ERP and spectrum analysis. P2-N2 peak-peak value and spectral peak around 11 Hz were analyzed between ADHD subjects and those in the control group, and then statistical tests were applied to these two groups. Results showed that: (1) Under the condition of Go, ADHD group had a significant lower P2-N2 peak-peak value than the values in the control group ($P < 0.05$); but under the condition of NoGo there was no significant difference in between. (2) Compared with the control group, the ADHD group had significant lower spectral amplitude around 11 Hz under the condition of NoGo ($P < 0.05$). However, under the condition of Go the difference was insignificant. In conclusion, there is certain cognitive dysfunction in ADHD children. P2-N2 peak-peak value and spectral peak around 11 Hz could be considered as clinical evaluation indexes of ADHD children's cognitive function. These two objective indexes provide an early diagnosis and effective treatment of ADHD

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Z Kinder Jugendpsychiatr Psychother. 2016;44:231-39.

EFFECTIVENESS OF THE PREVENTION PROGRAM FOR EXTERNALIZING PROBLEM BEHAVIOR (PEP) IN PRESCHOOLERS WITH SEVERE AND NO OR MILD ADHD SYMPTOMS.

Eichelberger I, Plucka J, Hautmann C, et al.

OBJECTIVE: The prevention program for externalizing problem behavior (PEP), developed for parents and teachers of preschool children, showed the effectiveness of both modules (PEP-PA and PEP-TE) under routine care conditions in two separate studies. This secondary analysis examined the effects of both modules on preschool children with severe attention deficit/hyperactivity disorder (ADHD) symptoms compared with children with no or mild ADHD symptoms.

METHODS: In the within-subject control group, design changes in child symptoms and problem behavior in specific situations at home and school during the waiting period were compared with changes during the intervention period (3 months each).

RESULTS: For children with severe ADHD, parent training reduced specific problem situations at home (HSQ-D[please provide full name here]), and teacher training showed significant effects on oppositional-aggressive behavior as well as the total problem score of the Caregiver Teacher Report Form (C-TRF). Children with no or mild ADHD benefited from parent training on the HSQ-D score, oppositional-aggressive behavior and the total problem score of the Child Behavior Checklist (CBCL), while teacher training had significant effects on all outcomes assessed.

CONCLUSION: Our results suggest that parent training reduces mainly specific behavior problems at home in children with severe ADHD symptoms and with no/mild ADHD symptoms, while teacher training reduces ADHD symptoms and ODD[please provide full name here] symptoms including specific behavior problems in the kindergarten in children with no/mild ADHD symptoms. However, in children with severe ADHD only overall problems and ODD symptoms were significantly reduced by teacher training

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Head-to-Head Comparison of Aripiprazole and Risperidone in the Treatment of ADHD Symptoms in Children with Autistic Spectrum Disorder and ADHD: A Pilot, Open-Label, Randomized Controlled Study

Marco Lamberti^{1,2} · Rosamaria Siracusano³ · Domenico Italiano² · Norma Alosi¹ · Francesca Cucinotta¹ · Gabriella Di Rosa¹ · Eva Germanò¹ · Edoardo Spina² · Antonella Gagliano¹

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Abstract

Background Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are frequently overlapping neurodevelopmental disorders. Individuals in whom the disorders are comorbid show more severe impairment because of deficits in the processing of social situations, adaptive functioning, and executive control than individuals with either disorder alone.

Objective This open-label pilot study aimed to evaluate and compare the efficacy and tolerability of risperidone and aripiprazole for treating ADHD symptoms in patients with both ASD and ADHD over the course of 24 weeks of treatment.

Methods Patients ($n = 44$) were randomly assigned to start treatment with risperidone (22 patients) or aripiprazole (22 patients). Children were evaluated before starting treatment (T0), and after 12 weeks (T1) and 24 weeks (T2) of treatment. At each visit, specific psychiatric clinical scales were administered to assess the efficacy of the two drugs.

Results The mean age was 8.4 ± 2.9 years in the aripiprazole group and 7.8 ± 2.3 years in the risperidone group. A total of 37 children (29 boys and 8 girls)

completed the study (18 in the aripiprazole group and 19 in the risperidone group). Aripiprazole and risperidone appeared to have similar benefits in terms of efficacy and tolerability, although there were slight differences between the two drugs. Both groups showed a significant improvement in ADHD symptoms after 24 weeks of treatment (ADHD Rating Scale, Conners Parent Rating Scale–Hyperactivity, and Clinical Global Improvement–Severity Scale). No significant difference between the two drugs on any parameters at 24 weeks were found. Prolactin levels were decreased in the aripiprazole group. Both drugs were well tolerated, with no serious adverse events detected.

Conclusions Our study confirms the efficacy of both aripiprazole and risperidone in ameliorating ADHD symptoms of children also presenting with ASD.

Key Points

Attention-deficit/hyperactivity disorder (ADHD) is a common comorbidity in autism spectrum disorder (ASD), with more severe behavioral disturbances seen in individuals with this morbidity than in individuals with either disorder alone.

Risperidone and aripiprazole seem to be effective in improving the behavioral pattern by the reduction of inattention and hyperactivity in patients with ASD and ADHD.

Both drugs were well tolerated, and no serious adverse events were detected in our sample.

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1 Introduction

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are lifelong neurodevelopmental disorders with high rates of comorbidity with other psychiatric disorders. The potential for ASD and ADHD to coexist has been a contentious issue for many years. More recently, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [1] has allowed for the comorbid diagnoses of ADHD and ASD. The prevalence of ADHD symptoms in individuals with a primary clinical diagnosis of ASD ranges between 13 and 50 % in population- and community-based studies [2–9]. In addition, in individuals with co-occurring ASD and ADHD, compared with patients with only a single diagnosis, symptoms are more severely impairing on several levels and lead to deficits of social processing, adaptive functioning, and executive control [10, 11]. Currently, management of individuals with ASD requires a multimodal approach of behavioural, educational, and pharmacological treatments [12, 13]. Previous epidemiological studies report a high rate of pharmacotherapy (up to 83 %) in children with ASD [14–20]. Evidence for efficacy seems weakest for newer antidepressants, anxiolytics, and mood stabilizers [21]; on the other hand, it is strongest for psychostimulants, noradrenergic reuptake inhibitors, antipsychotics, and alpha adrenergic agonists [22–24].

Among atypical antipsychotic (AAP) medications, risperidone and aripiprazole are the only US FDA-approved agents for the treatment of irritability and associated aggressive behaviours in individuals with ASD [13, 25–27]. These agents also seem to be effective in reducing stereotypy and hyperactivity in patients with ASD [28]. Epidemiological studies have shown that antipsychotics, particularly risperidone, are also widely used in

patients with comorbid ASD and ADHD [17]. Probably, these patients are mostly non-responders to more standard forms of treatment. Indeed, despite not being approved for the treatment of ADHD, current evidence suggests that children with ADHD (and no other psychiatric comorbidity) account for one in seven prescriptions of atypical antipsychotic medications [13, 29]. In particular, empirical evidence supports the efficacy of aripiprazole in the treatment of ADHD core symptoms [30, 31] and of risperidone in improving aggressive and disruptive behaviour, when added to parent training and optimized stimulant treatment in children with ADHD [32].

The aim of this study was therefore to evaluate and compare the efficacy of risperidone and aripiprazole for treating ADHD symptoms in a group of patients with comorbid ASD and ADHD over the course of 24 weeks of treatment. The secondary outcome was to evaluate tolerability.

2 Materials and Method

2.1 Study Population

Children and adolescents (aged 6–13 years) diagnosed with ASD and ADHD comorbidity according to DSM-5 criteria, attending our programs in the Unit of Child Neurology and Psychiatry of the University Hospital of Messina, Messina, Italy, were considered for this randomized, controlled, open-label, prospective study (see Table 1 for demographic characteristics). Patient recruitment started in September 2013.

These children were assessed using the Autism Diagnostic Interview-R [33] and the Autism Diagnostic Observation Schedule (ADOS) [34]. We used the Schedule for Affective Disorders and Schizophrenia for School-Age

Table 1 Demographic characteristics and baseline rating scale scores of the two groups

Characteristic	Aripiprazole ($n = 22$)	Risperidone ($n = 22$)
Age (years)	8.4 ± 2.9	7.9 ± 2.3
Male	17	18
Female	5	4
ADHD hyperactive/impulsive subtype	6	5
ADHD inattentive subtype	5	5
ADHD combined subtype	11	12
CGI-S	5.4 ± 0.5	5.5 ± 0.6
C-GAS	38 ± 8.3	31.4 ± 12
ADHD-RS	39.4 ± 2.8	37.4 ± 3.9
CPRS-I	5.7 ± 0.7	5.4 ± 0.7
CPRS-H	5.4 ± 0.8	4.9 ± 0.9

Data are presented as mean ± standard deviation or n

ADHD attention deficit/hyperactivity disorder, ADHD-RS ADHD Rating Scale, C-GAS Children's Global Assessment Scale, CGI-S Clinical Global Impression–Severity Scale, CPRS-I Conners Rating Scales–Hyperactivity, CPRS-I Conners Rating Scales–Inattention

Children–Present and Lifetime Version (K-SADS-PL) [35] to identify other psychiatric conditions, including ADHD symptoms. The inclusion criteria were (1) diagnosis of ASD and a Children’s Global Assessment Scale (C-GAS) score <60 and a Clinical Global Improvement–Severity scale (CGI-S) score ≥ 4 ; (2) diagnosis of ADHD according to the DSM-5 criteria for ADHD, including duration and impairment (CGI-S score ≥ 4 ; C-GAS score ≤ 60). We excluded subjects with low IQ (total IQ <55 according to the Wechsler Intelligence Scale for Children–Third Edition [WISC-III]) [36], schizophrenia, or neurological diseases (neurogenetic diseases, epilepsy, brain injuries, or cerebral lesions documented by magnetic resonance imaging) and patients previously treated with antipsychotics.

2.2 Study Design

All subjects underwent a full baseline psychiatric and medical examination. Subjects and parents received detailed information about the characteristics and potential adverse effects of the treatment. Included patients were antipsychotic-naïve children randomly assigned by coin tossing to receive treatment with aripiprazole or risperidone. The participants randomized to aripiprazole received the medication in the morning (once daily) at an initial dose of 1.25–2.5 mg/day. The dosage was then titrated upwards to a maximum of 15 mg/day based on clinical response. In the risperidone group, the medication was started at 0.25–0.5 mg/day and gradually titrated up to a maximum of 3 mg/day, also in a single morning dose. Patients were evaluated at baseline (T0), after 12 weeks (T1) and after 24 weeks (T2) of treatment. All patients were clinically evaluated in person at 12 and 24 weeks, but their status was monitored monthly via a telephone interview with a pediatric nurse. During dose titration, telephone interviews were considered appropriate rather than in-person examinations because the dose titration was pre-planned and implemented as per the therapeutic plan. Any issues related to side effects could be identified during these phone calls; if the patient reported an adverse event (AE), a physical examination and clinical evaluation was conducted and a decision to continue treatment or otherwise was made. At each visit, a trained physician administered the Conners Parent Rating Scales–Revised (CPRS-R), the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS), the CGI-S and the Clinical Global Impression–Improvement Scale (CGI-I), and the C-GAS. The primary endpoint of this study was drug efficacy, assessed by comparing score modifications of all the scales within each treatment group and between the two groups. The primary efficacy measurement was the change of ADHD-RS and CGI-I from baseline to endpoint. The secondary efficacy measurement included change of CPRS

and CGI-S score from baseline to endpoint. The tolerability of the two drugs was our secondary endpoint. To achieve this aim, we took routine medical measurements such as cardiac adverse reactions (e.g., QT-interval prolongation on electrocardiography [ECG]), somatic parameters (blood pressure, pulse, body weight, height, body mass index, abdominal circumference), and abnormal laboratory test results (fasting blood glucose, insulin and lipid levels, prolactin, other general blood tests). We also used the Abnormal Involuntary Movement Scale (AIMS) to monitor for AEs, according to a side effect review of Research Unit on Pediatric Psychopharmacology (RUPP) in using atypical antipsychotics [37].

All parents signed a written informed consent, and all patients, when able, also gave their consent. The study was approved by the local Ethics Committee.

2.3 Study Instruments

The C-GAS is a numeric scale (1–100) used by clinicians in psychiatry to rate the general functioning of children aged <18 years. Scores >90 indicate superior functioning, whereas scores <70 indicate impaired global functioning [38].

The CGI has two components: the CGI–Severity, which rates illness severity, and the CGI–Improvement, which rates change from the initiation (baseline) of treatment [39].

The CGI-S asks the clinician one question: “Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?” The answer is rated on the following seven-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients. This rating is based upon observed and reported symptoms, behavior, and function in the previous 7 days. Clearly, symptoms and behavior can fluctuate over a week; the score should reflect the average severity level across the 7 days.

The CGI-I is similarly simple in its format. Each time the patient is seen after medication has been initiated, the clinician compares the patient’s overall clinical condition to that in the 1-week period just prior to the initiation of medication use (the so-called baseline visit). The CGI-S score obtained at the baseline (initiation) visit serves as a good basis for making this assessment. Again, only the following one query is rated on a seven-point scale: “Compared to the patient’s condition at admission to the project [prior to medication initiation], this patient’s condition is 1 = very much improved since the initiation of treatment; 2 = much improved; 3 = minimally improved; 4 = no change from baseline (the initiation of treatment);

5 = minimally worse; 6 = much worse; 7 = very much worse since the initiation of treatment.”

The *ADHD Rating Scale* is a self-report inventory comprising 18 questions for parents regarding a child's behavior over the past 6 months [40]. Items 1–9 in the questionnaire measure inattention symptoms, and items 10–18 measure impulsivity and hyperactivity symptoms.

The *Conners Parent Rating Scales—Revised* (PRS, Conners, 1997) is commonly used to quantify ADHD symptoms [41]. We asked the parents to complete the Conners Parents Rating Scales Revised, Short Form (CPRS-R:S, Conners, 1989). The CPRS-R:S contains 27 items and covers a subset of the subscales and items on the long parent form. It provides the following sub-scores:

- Oppositional: probes whether children are “predisposed” to break rules,
- Cognitive problems/inattention: probes whether subjects may experience learning difficulties, or difficulty in organizing schoolwork,
- Hyperactivity: probes whether the subject finds it difficult to sit in the classroom or pay attention for a long time,
- ADHD Index: probes to identify children/adolescents “at risk” of ADHD.

2.4 Statistical Analysis

The data are presented as mean \pm standard deviation (SD). Ranges are also presented for the respective measurements. Mann–Whitney *U* tests were used for comparison, and two-sided tests were used and statistical significance was accepted at a *p* value of <0.05 . For each group, a multiple comparison was also performed of results at T0, T1, and T2 with general linear model (GLM) multivariate, and a post hoc analysis with Bonferroni correction. All data were analyzed using GraphPad Prism version 5 (GraphPad Software). According to the intention-to-treat principle, data imputation of patients who withdrew were managed by assignment of an average value of outcome variable among those in that treatment group with complete data.

3 Results

A total of 44 children were recruited, two of who withdrew before the first follow-up measurement (risperidone/aripiprazole: 1/1). Two patients treated with risperidone and three patients treated with aripiprazole discontinued the study before the second week. Among the latter, two subjects discontinued because of subjective restlessness combined with akathisia ($N = 1$) or sleeplessness ($N = 1$). Two other patients stopped because of medication non-

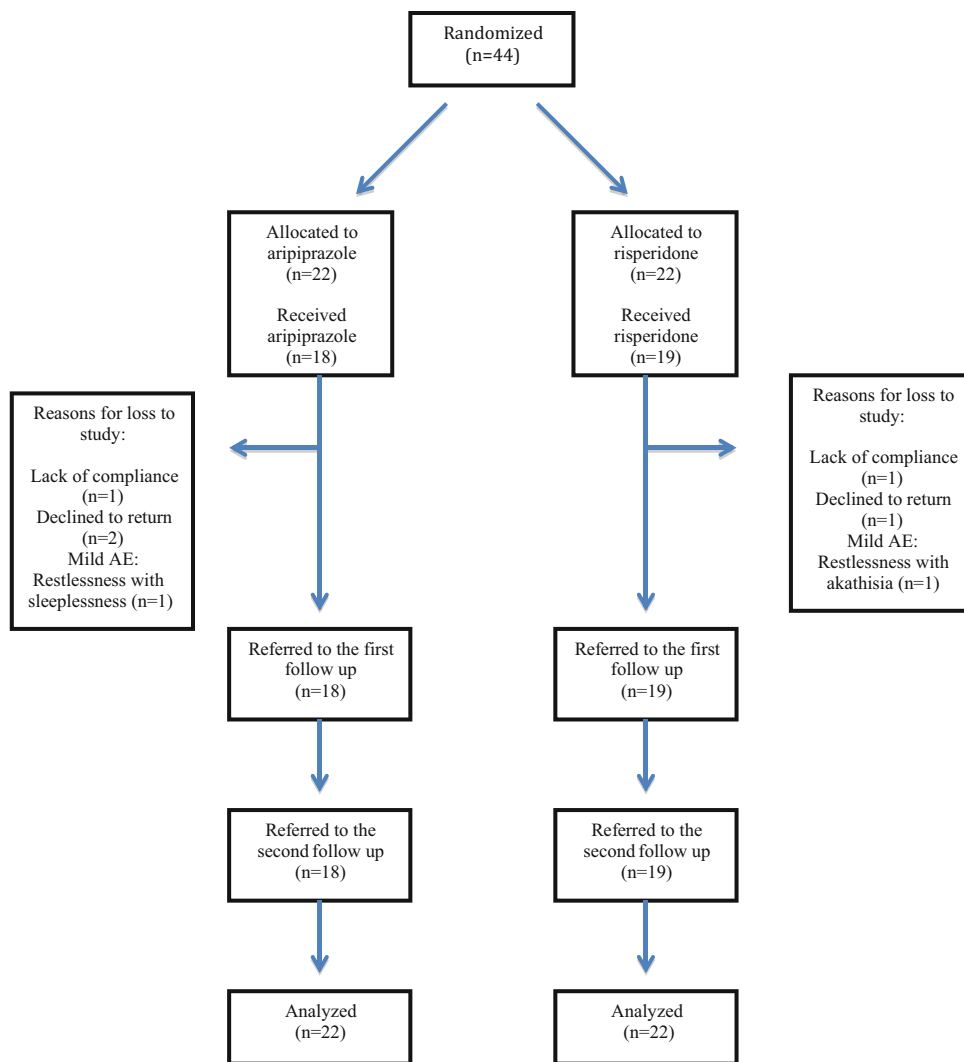
compliance, and one for unknown reasons (see Fig. 1). Thus, 37 patients (29 males, 8 females) completed the study. The mean age was 8.4 ± 2.9 years in the aripiprazole group (22 patients) and 7.9 ± 2.3 years in the risperidone group (22 patients). The groups were comparable for sex, age of patients, baseline CPRS and ADHD-RS scores, level of education, number of siblings, and socio-economic background (Table 1). At baseline, there were no statistically significant differences between the two groups in any of the scales investigated (Table 2). Both groups were characterized by a severe impairment (CGI-S group aripiprazole = 5.4 ± 0.5 ; CGI-S group risperidone = 5.5 ± 0.6 ; $p = 0.740$) and high global failure/dysfunction (C-GAS group aripiprazole = 38 ± 8.3 , C-GAS group risperidone = 31.4 ± 12.4 ; $p = 0.211$). A total of 25 patients were drug-naïve; the other 19 had received previous treatment with methylphenidate (12 patients) or atomoxetine (seven patients). At baseline, all patients had been drug free for at least 1 week. None of the included patients had a history, signs, or symptoms of cardiovascular, pulmonary, or endocrine disorders. In the group of children treated with aripiprazole, the mean final dose was 6.6 ± 4.4 mg/day. The mean final dose of risperidone was 1.7 ± 0.5 mg/day.

3.1 Treatment Responses from Risperidone and Aripiprazole

The group treated with aripiprazole exhibited a statistically significant reduction in CGI-S ($p < 0.001$), ADHD-RS ($p < 0.001$), CPRS-Hyperactivity (CPRS-H; $p = 0.004$), and CPRS-I (inattention, $p = 0.038$) scores at T1 versus T0 (see Table 2). Conversely, C-GAS scores were significantly increased ($p = 0.014$). At T2, the average scores on the CGI-S ($p < 0.001$), ADHD-RS ($p < 0.001$), CPRS-H ($p = 0.001$), and CPRS-I ($p = 0.003$) showed a statistically significant lowering compared with T0. No statistically significant differences were found by comparing the mean scores between T1 and T2. The mean scores of C-GAS were significantly ($p = 0.006$) increased in T2 when compared with T0. At T2, 11 subjects were considered responders (with a CGI-S of 1 or 2).

The group treated with risperidone exhibited a significant difference between T1 and T0 in CGI-S ($p = 0.019$) and ADHD-RS ($p = 0.019$) scores (see Table 2). After 24 weeks of treatment, the mean scores on the CGI-S ($p < 0.001$), ADHD-RS ($p < 0.001$), and CPRS-H ($p = 0.003$) scales were significantly lower than at T0. The mean scores of the C-GAS scale increased, and the mean scores of the CPRS-I scales reduced in T1 and T2 compared with T0, albeit they did not reach statistical significance. At T2, 12 subjects were considered responders (with a CGI-S of 1 or 2).

Fig. 1 Flow chart for the clinical trial of aripiprazole versus risperidone



3.2 Comparison Between the Two Treatment Groups

The comparison between the two groups exhibited significant differences only at T1 (see Table 2). After 12 weeks of treatment, the aripiprazole group showed significantly lower scores in the CGI-I ($p = 0.001$) and in the ADHD-RS ($p = 0.017$) compared with the risperidone group. Furthermore, the group treated with aripiprazole showed higher values at the C-GAS ($p = 0.014$). After 12 weeks of treatment, no statistically significant differences were found in the CGI-S and CPRS-I scores between the two groups. No difference was found between the two groups at T2 in any of the investigated efficacy parameters.

3.3 Adverse Events

In the group of children treated with aripiprazole, the three main AEs observed during the study period were increased

appetite (five patients), weight gain (four patients), and drowsiness (four patients). Most were evident only in the first phase of treatment and subsequently disappeared (see Table 3). The mean weight gain during the 24 weeks of treatment was 1.9 kg (from 34.5 ± 17.5 to 36.4 ± 18.4 kg).

In the group of children treated with risperidone, the three AEs most frequently reported were increased appetite (11 patients), weight gain (eight patients), and drowsiness (four patients). As in the aripiprazole group, most of these AEs, such as somnolence, were evident in the first 2 weeks of the treatment (see Table 3). The mean weight gain during the 24 weeks of treatment was 4 kg (from 30.7 ± 10.6 to 34.7 ± 11.5 kg).

No extrapyramidal AEs were detected in either group using the AIMS scale. One patient in the aripiprazole group reported stiff muscles. After 24 weeks of treatment, there were no changes in electroencephalogram (EEG), nor were ECG abnormalities observed in any patient.

Table 2 Efficacy parameters in the aripiprazole and risperidone groups at baseline (T0), 12 weeks (T1) and 24 weeks (T2)

Parameter	T0	T1	T2	T0–T1 <i>p</i> value ^a	T0–T2 <i>p</i> value ^a	T1–T2 <i>p</i> value ^a
CGI-S						
Aripiprazole	5.4 ± 0.5	3.9 ± 0.7	4.0 ± 0.8	<0.001	<0.001	1.0
Risperidone	5.5 ± 0.6	4.6 ± 0.7	4.1 ± 0.6	0.019	<0.001	0.242
<i>p</i> value ^b	0.740	0.069	0.969			
CGI-I						
Aripiprazole	NA	2.2 ± 0.6	3 ± 1.2			0.087
Risperidone	NA	3.5 ± 0.9	2.4 ± 0.7			0.006
<i>p</i> value ^b		0.001	0.356			
C-GAS						
Aripiprazole	38 ± 8.3	50.4 ± 9.4	51.8 ± 9.8	0.014	0.006	1.0
Risperidone	31.42 ± 12.4	36.5 ± 12.5	42.7 ± 11.5	0.952	0.132	0.763
<i>p</i> value ^b	0.211	0.014	0.113			
ADHD-RS						
Aripiprazole	39.4 ± 2.8	27.1 ± 6.5	26.7 ± 7.8	<0.001	<0.001	1.0
Risperidone	37.4 ± 3.9	32.7 ± 4.3	29.1 ± 3	0.019	<0.001	0.128
<i>p</i> value ^b	0.169	0.017	0.842			
CPRS-H						
Aripiprazole	5.7 ± 0.7	3.8 ± 0.7	3.4 ± 1.8	0.004	0.001	1.0
Risperidone	5.4 ± 0.7	4.8 ± 1.2	3.6 ± 1.2	0.617	0.003	0.128
<i>p</i> value ^b	0.235	0.059	0.720			
CPRS-I						
Aripiprazole	5.4 ± 0.8	4.1 ± 0.9	3.6 ± 1.5	0.038	0.003	1.0
Risperidone	4.9 ± 0.9	4.5 ± 1.3	3.8 ± 1	1.0	0.147	0.528
<i>p</i> value ^b	0.235	0.346	0.604			

Data are shown as mean ± standard deviation

ADHD-RS Attention-Deficit/Hyperactivity Disorder Rating Scale, *C-GAS* Children's Global Assessment Scale, *CGI-I* Clinical Global Impression–Improvement Scale, *CGI-S* Clinical Global Impression–Severity Scale, *CPRS-I* Conners Rating Scales–Hyperactivity, *CPRS-I* Conners Rating Scales–Inattention, *NA* Not Applicable

^a Intragroup analysis between baseline (T0), week 12 (T1), and week 24 (T2)

^b Between-group analysis at baseline (T0), week 12 (T1), and week 24 (T2)

Other parameters such as resting heart rate and blood pressure showed no abnormalities. The comparison between the two groups in the life parameters (height, weight, body mass index [BMI], and blood glucose assay) showed no significant differences (see Table 4). Plasma prolactin levels higher than baseline developed in only three patients treated with risperidone. The mean prolactin level in the risperidone group during the 24 weeks of treatment increased from 167.5 ± 80 to 464.6 ± 190. In the aripiprazole group, the mean prolactin level during the 24 weeks of treatment decreased from 158.2 ± 70.2 to 127.5 ± 75.1 UI/ml. After 24 weeks of treatment, statistically significant differences were found in prolactin levels between the two groups (*p* < 0.001) in favor of aripiprazole (see Table 4).

4 Discussion

Our results showed the efficacy of both aripiprazole and risperidone for ADHD symptoms in a sample of children diagnosed with ASD. To our knowledge, this is the first head-to-head study comparing aripiprazole and risperidone in the treatment of children with ASD and ADHD symptoms. Both drugs appeared to have similar benefits in terms of efficacy and tolerability. Risperidone seemed to be effective after 12 weeks of treatment, although greater clinical improvement was evident after 24 weeks. Conversely, the benefit of aripiprazole treatment was already evident at 12 weeks, and no further improvement was observed at 24 weeks. At the first clinical evaluation, patients in the aripiprazole group also showed significantly

Table 3 Adverse events reported in the two treatment groups during the study period

Event	Aripiprazole (n = 22)	Risperidone (n = 22)
Increased appetite	5 (22)	11 (50)
Weight gain ≥7 %	4 (18)	8 (42)
Drowsiness	4 (18)	6 (27)
Enuresis	2 (9)	4 (18)
Dry mouth	2 (9)	3 (13)
Drooling	1 (4)	2 (9)
Anxiety	1 (4)	1 (4)
Dizziness	1 (4)	0
Diarrhea	0	1 (4)
Nausea/vomiting	2 (9)	0
Restlessness	1 (4)	1 (4)
Akathisia	0	1 (4)
Sleeplessness	1 (4)	0

Data are presented as n (%)

lower CGI-I and higher C-GAS scores than those in the risperidone group. We suggest that the occurrence of hyperactivity and impulsivity may strongly influence the level of functioning in patients with ASD-ADHD comorbidity and that the reduction of these symptoms leads to an overall clinical improvement.

Our results confirm what has already been underlined in the literature on the effectiveness of both risperidone [42–47] and aripiprazole [27, 48–51] in the treatment of behavioral disorders associated with ASD (such as irritability, aggression, repetitive behaviors). In 2007, the Cochrane collaboration published a systematic review and meta-analysis on the use of risperidone in ASD [52]. They identified three randomized controlled trials investigating risperidone in different age groups: one trial recruited adults [53], and two trials included children/adolescents [44, 54]. A meta-analysis of combined data from children/adolescents showed benefits not only on the Aberrant Behavior Checklist (ABC) subscales pertaining to irritability (mean improvement of 8.07 points on ABC) and social withdrawal (mean improvement of 3.0 points) but also in hyperactivity (mean improvement of 8.98 points). In 2012, the Cochrane collaboration published an updated systematic review and meta-analysis on aripiprazole in ASD [51]. The authors identified two randomized controlled trials [27, 49], with a total of 308 patients (210 receiving active treatment, 98 controls), aged 6–17 years, with dosages ranging from 2.5–15 mg/day. This review confirmed there is a moderate quality of evidence to support the efficacy of aripiprazole in reducing irritability (mean improvement of 6.17 points) associated with an improvement of global functioning (1.33 points up on CGI-I). The ABC hyperactivity subscale also showed

Table 4 Clinical measurements: comparison at baseline (T0), 12 weeks (T1), and 24 weeks (T2) between the two groups

Measurement	Aripiprazole		Risperidone		T0-T0		T1-T1		T2-T2			
	T0	T1	T0	T1	Z	P	Z	P	Z	P		
Weight (kg)	34.5 ± 17.5	34.4 ± 19.0	36.4 ± 18.4	30.7 ± 10.6	33.2 ± 11.2	34.7 ± 11.5	-0.216	0.833	-0.399	0.722	-0.368	0.720
BMI	18.7 ± 5.2		19.3 ± 5.3	18.1 ± 3.0		20.2 ± 3.9	-0.185	0.880			-0.776	0.447
SBP (mmHg)	96.3 ± 14.1	95.5 ± 6.8	98.5 ± 10.8	97.5 ± 7.2	95.0 ± 10.2	95.5 ± 10.1	-0.825	0.445	-0.313	0.771	-0.514	0.661
DBP (mmHg)	60.9 ± 7.0	62.5 ± 5.4	63.0 ± 6.7	68.3 ± 10.9	61.2 ± 8.5	61.1 ± 9.6	-1.698	0.118	-0.617	0.582	-1.143	0.315
HR (bpm)	83.0 ± 11.1	81.1 ± 8.4	86.4 ± 9.9	79.8 ± 8.5	79.9 ± 11.2	82.8 ± 12.8	-0.944	0.525	-0.729	0.497	-0.698	0.497
Blood glucose (mg/dL)	84.2 ± 5.6	84.4 ± 7.7	88.2 ± 6.7	85.3 ± 5.2	88.2 ± 7.3	88.6 ± 12.8	-0.648	0.525	-0.960	0.346	-0.082	0.968
Prolactin (UI/mL)	158.2 ± 70.2	154.9 ± 81.9	127.5 ± 75.1	167.5 ± 80	441.1 ± 215.6	464.6 ± 190	-0.249	0.803	-4.003	0.000**	-4.441	0.000**

All scores are shown as mean ± standard deviation

Prolactin normal range: men 53–360 UI/ml; women 64–424 UI/ml. UI/ml = ng/ml × 21.2

BMI body mass index, DBP diastolic blood pressure, HR heart rate, SBP systolic blood pressure

*** p < 0.01

significant benefits (mean improvement of 7.93 points), whereas modest benefits were found overall for stereotypy and inappropriate speech. Side effects were more common, with relative risks of 4.28 for sedation, 9.48 for drooling, and 10.26 for tremors. Other studies highlight the improvement of hyperactivity symptoms [27, 43, 54, 55] or both inattentive and hyperactive symptoms, supported by an overall improvement of functioning for patients with either the inattentive or the combined subtype of ADHD [30]. In our study, both children treated with aripiprazole and those treated with risperidone exhibited not only an improvement of ADHD symptoms after 6 months of treatment but also a global clinical improvement. This result appears to be in accordance with most of the studies performed on long-term treatment with risperidone in patients with ASD (36.8 % of responders in Masi et al. [47] and 47 % of responders in RUPP [37]), albeit these studies are not homogeneous and the clinical outcome may be influenced by the age of subjects and the severity of autistic symptoms [47]. Ching and Pringsheim [51] evaluated the effectiveness of aripiprazole in individuals with ASD and concluded it was moderately effective. Conversely, other studies showed a clinical improvement in 37 % of patients with ASD and hyperactivity disorder [56]. In line with previous studies, our findings highlight the importance of the hyperactivity–impulsivity component on the overall functioning of children with ASD. In fact, most of our patients experienced an overall clinical improvement mainly due to the reduction of hyperactivity and inattention symptoms. Our study also shows that both drugs are effective in improving the behavioral pattern via the reduction of inattention and hyperactivity. Risperidone appeared slightly less effective on the inattention symptoms but significantly active on the hyperkinetic symptoms of ADHD.

Both drugs were well tolerated and no serious AEs were detected. Nevertheless, about half of the patients treated with aripiprazole experienced one or more side effects during the study period. These results are in line with literature reports [48, 50]. In particular, many studies show the importance of weight monitoring during treatment with aripiprazole [49, 57–59]. In our research, we found a mean weight gain of 1.6 kg, consistent with that shown in most studies (1.6 kg) [27]. On the other hand, in the group of patients treated with risperidone, all subjects showed at least one AE over the study period. The weight gain was the main AE in our sample. This result was expected, since increased appetite and weight gain are the most discussed AEs in studies on the tolerability of risperidone [43, 44, 58] because of the association with the onset of metabolic syndrome. In our sample, we found an average increase in weight of 4 kg, which is consistent with findings in most studies on long-term treatment with risperidone. For

example, patients in the RUPP study [37] showed a mean weight increase of 5.1 kg after 6 months of treatment, and those in Masi et al. [47] showed an average weight gain of 3.6 kg after 12 months. Again in line with currently available literature, no cardiovascular AEs were associated with risperidone and aripiprazole in our patients [60, 61]. As expected, our patients treated with risperidone had high prolactin levels, but none of them showed clinical symptoms. This finding is in agreement with what has already been widely documented in the literature [47]. Conversely subjects in the aripiprazole group showed a slight reduction in prolactin serum levels, as described by previous studies in children and adolescents [62]. Altogether, aripiprazole seems to have a better tolerability profile, as already highlighted by previous studies [63–65].

4.1 Study Limitations

Our study has some limitations. The first concerns the relatively small sample size, even if the ASD–ADHD comorbidity represents an unique phenotype with behavioral and cognitive peculiarities. The small sample size meant we were unable to identify characteristics that might predict response.

Another limitation is the sensitivity of the rating scales we used to assess our series of patients with ASD. Some of these tools are independent from the diagnosis of patients (CGI-S, CGI-I, C-GAS) and allow the assessment of the overall functioning of children with complex comorbidities. Others, such as the ADHD-RS, are more specific and evaluate only a small number of symptoms. In fact, the ADHD-RS and CPRS are validated only in patients with ADHD and not in individuals with ASD. Nevertheless, there is a lack of valuable instruments intended to evaluate patients with complex comorbidities such as ASD, so we found it difficult to stratify the sample by ADHD subtypes. Further, this study does not include specific tools aimed at evaluating the ASD core symptoms (such as the ABC) because it is focused on the ADHD symptoms and their impact on overall functioning. Moreover, the open-label study design represents a limitation because the prescribers also scored all the scales. Additional limitations include the absence of a placebo control group and the lack of baseline ADHD inclusion criteria and baseline irritability determination.

5 Conclusions

Our study confirms the efficacy and safety of aripiprazole and risperidone in the treatment of patients with complex comorbidities such as ASD and ADHD. Based on the study of a small sample, our data highlight the interference of

comorbid ADHD symptoms on overall functioning in ASD children and adolescents. It seems important to consider that ADHD symptoms are often masked by the severity of autistic symptoms (“diagnostic overshadowing”). On the other hand, the presence of comorbid conditions changes the expression, clinical severity, prognosis, and response to treatment [8, 11, 13, 66–68]. Our results suggest these drugs could be useful as alternative treatments in children with comorbid phenotype who are non-responders to standard therapies. A quick and accurate assessment and treatment of ADHD symptoms is needed in ASD subjects. A better knowledge of the overlapping phenotype of the two disorders is required to plan appropriate treatment that is effective on both specific symptoms and overall functioning.

Compliance with Ethical Standards

The material is original, has not been published except in abstract form, and is not being considered for publication elsewhere, including publicly accessible websites or e-print servers. All authors have read the manuscript and approve its submission. All research has been conducted adhering to the recommendations contained in the Declaration of Helsinki, and it complies with the International Guiding Principles that regulate research on human participants and/or animals.

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EXPERT
REVIEWS

Guanfacine for the treatment of attention deficit hyperactivity disorder in children and adolescents

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Guanfacine is an α_{2A} -adrenoreceptor agonist currently indicated for the treatment of attention deficit hyperactivity disorder (ADHD). This article reviews the chemistry, pharmacodynamics and pharmacokinetics of guanfacine, as well as the clinical trial literature on guanfacine for the treatment of ADHD in children and adolescents, mainly focusing on the use of guanfacine extended-release (GXR). Six already published prospective randomized controlled trials (RCTs) and one unpublished RCT study were identified for GXR in the treatment of ADHD. All RCTs trials showed superiority over placebo on the primary outcome measure. Guanfacine, especially XR, seems to be an effective and safe treatment option for ADHD in children and adolescents.

KEYWORDS: α_{2A} -adrenoreceptor agonist • attention deficit hyperactivity disorder • guanfacine extended-release • guanfacine immediate-release • treatment

Attention deficit hyperactivity disorder (ADHD) is an early onset, clinically heterogeneous, complex neurobiological disorder, defined by symptoms of inattention and hyperactivity/impulsivity and has been associated with a broad range of impairments for patients affected [1]. ADHD is the most common psychiatric disorder of childhood with prevalence in school-age children estimated to be between 8 and 10% [2]. Three subtypes of ADHD are now recognized: predominantly hyperactive/impulsive, predominantly inattentive and a combined type characterized by a combination of the first two subtypes [1].

Children and adolescents suffering from ADHD experience a broad range of impairments, including cognitive, academic, behavioral, emotional and social functioning [3]. In addition, ADHD often presents with one or more comorbidities such as oppositional defiant disorder (ODD), chronic tic disorders, anxiety disorder, mood disorders, conduct disorders and learning disabilities [4].

Although the exact etiology of ADHD is still unknown, frontostriatal networks (including dorsolateral prefrontal cortex [dlPFC],

dorsal anterior cingulate cortex and striatum) and cerebellum have emerged as the primary areas showing deficits in ADHD [5,6].

The network activity between these areas is strongly modulated by dopaminergic and noradrenergic systems. Several studies have reported that dopamine receptor density is lower than normal in different brain regions of ADHD patients [7]. Whereas abnormal noradrenaline receptor density has not been reported as yet, there is abundant evidence showing that disrupting α_{2A} -adrenoreceptor-modulated neurotransmission may lead to impaired attention and impulse control and hyperactivity. The most common medications used to treat ADHD in routine clinical practice act primarily by enhancing dopaminergic and noradrenergic transmission in the prefrontal cortex (stimulants like methylphenidate or other amphetamine derivatives; atomoxetine) or directly modulating postsynaptic noradrenergic α_{2A} -receptors [8].

In the last 11 years, 13 guideline documents on diagnosis and/or management of ADHD from 10 medical associations have been published [9]. Multimodal management approaches

are advocated. Treatment options for ADHD include medication management, behavioral treatment or a combination of the two with medication management being the most cost-effective [10,11].

Overview of the market

Psychostimulant medications exhibited large effect sizes and shorter effect latency when used for the treatment of ADHD symptoms [12], and therefore remain the most commonly prescribed class of medications for ADHD. However, around 25–30% of patients do not respond adequately to stimulants [13,14]. Additionally, some children and adolescents may not tolerate psychostimulants, and their use may be restricted because of the presence of comorbidities or risk of abuse [15]. In some cases, parents or caregivers may simply prefer the use of a non-stimulant medication. For these patients, the availability of two α_{2A} -adrenoreceptor agonists (clonidine and guanfacine) offers another option for the management of ADHD.

Introduction to the drug

Focus was placed primarily on the extended-release formulation of guanfacine (GXR). The medical literature has been reviewed selecting articles based on the following inclusion criteria: double-blind, randomized controlled trials (RCTs) comparing guanfacine in XR formulation with placebo in ADHD children and adolescents. Article search updated to September 2014 was conducted using MEDLINE and EMBASE.

Chemistry & pharmacodynamics

Guanfacine is a highly selective agonist of α_{2A} -adrenoceptors ($K_i = 71.8$ nM), with very little affinity for other noradrenergic receptors, including α_{2B} - and α_{2C} -adrenoreceptors. Guanfacine preferentially binds to postsynaptic α_{2A} adrenoreceptors in the prefrontal cortex, while other mediators of noradrenergic transmission used in ADHD such as stimulants or 2A-adrenoceptors rather than atomoxetine act on preynaptic postsynaptic. The development and clinical application of guanfacine has been strongly driven by its modulation of postsynaptic α_{2A} -adrenoceptors of the dlPFC, with subsequent control over working memory and other executive functions (organization, planning, response inhibition, etc.) primarily affected in neurodevelopmental disorders like ADHD [16]. The catecholaminergic arousal system is involved in the coordination between arousal and cognitive functions, modulating, among other aspects, the relationship between exposure to stressors and executive functioning performance. Guanfacine modulates dlPFC connectivity via feedforward calcium-cAMP signaling opening potassium (K^+) channels [16]. Activating α_{2A} -adrenoceptors in the dlPFC, guanfacine closes these receptor-coupled ion channels, lowering their intracellular signaling [17,18]. This specific effect strengthens the connectivity of the recurrent dlPFC excitatory circuits involved in the shaping of the contents of working memory, and is thought to form the basis of the therapeutic effect of guanfacine over executive functions. Rodent models have also shown that, via this mechanism of action, guanfacine may

promote the maturation of dendritic spines in the medial prefrontal cortex, suggesting an active role in the development of connectivity also within this sub-region of the prefrontal cortex [19].

Earlier animal studies showed that low doses of guanfacine improve working memory without reducing blood pressure or causing significant sedation, whereas higher doses exerting relevant hypotensive and sedative effects also caused memory impairment [20,21].

Pharmacokinetics & metabolism

Guanfacine is available in an immediate-release (IR) and in an XR formulation. The oral bioavailability of the IR formulation is approximately 80%, and there is no clear evidence of first-pass metabolism. Its main clearance route is renal, with an elimination half-life of about 17 h [22]. There is moderate transformation of the compound through metabolism, with an epoxide intermediate and a main metabolite represented by 3-hydroxy-guanfacine [23].

Unlike the IR formulation that requires two administrations through the day, GXR allows a once-daily administration. GXR hydrochloride is manufactured in matrix tablets containing organic acids and ionic and enteric polymers that guarantee the extended mode of gastrointestinal release [24]. The pharmacokinetic properties of oral GXR has been evaluated in 14 children (aged 6–12) and 14 adolescents (aged 13–17) in a Phase I–II study by Boellner *et al.* [25]. Patients received a single 2-mg dose on day 1, then 2 mg on days 9–15, 3 mg on days 16–22 and 4 mg on days 23–29. The pharmacokinetics of the formulation appeared to be linear. After the single 2-mg dose, half-life was 14.4 ± 2.4 h in children and 17.9 ± 5.8 h in adolescents. The mean area under the concentration–time curves ranged from 65.2 ng \times h/ml in children and 47.3 ng \times h/ml in adolescents after a single 2-mg dose (area under the curve $[AUC]_{0-\infty}$), to 162 and 117 ng \times h/ml, respectively, for multiple 4-mg doses (AUC_{0-24} h). The mean C_{max} ranged from 2.55 ng/ml in children and 1.69 ng/ml in adolescents after a single 2-mg dose, to 10.1 and 7 ng/ml, respectively, for multiple 4-mg doses. The differences in pharmacokinetic properties between children and adolescents are likely to be due to the larger body weight of adolescents. The same design was applied by the same group to 49 adults (mean age 32.9 years) who received single doses of 1, 2 and 4 mg of GXR [26]. This study confirmed similarly linear pharmacokinetic properties, with increases in mean C_{max} and AUC tendentially proportional to the dose of guanfacine.

The kinetic properties of the IR- and XR formulations differ, and therefore switching on a 1:1 dose ratio is not accurate. Two open-label, single-dose studies compared the kinetic properties of the two formulations [21,24]. In these reports, T_{max} for GXR is twice as long (6 h) that of the IR formulation (3 h). The C_{max} of GXR was reduced by 60% compared with that of IR guanfacine, and $AUC_{0-\infty}$ by 43%, leading to an overall bioavailability of the XR formulation of 58%.

Pharmacokinetic studies have also highlighted potential interaction effects related to the XR formulation. High fat-content meals were shown to increase by approximately 75% the C_{max} and by about 40% the AUC of this formulation at a 4-mg dose [24]. Cytochrome P450 inhibitors like ketoconazole may lead to accumulation [24].

IR guanfacine is available in 1- and 2-mg tablets, whereas XR is available in 1-, 2-, 3- and 4-mg tablets. The daily dose ranges between 1 and 4 mg; importantly, doses above 4 mg/day have not been adequately studied in terms of safety and efficacy. It has been advised that the daily dose should not be increased by more than 1 mg/week, when required and well tolerated [21]. More experience in patients with ADHD is necessary to evaluate the safety of other titration regimes. There is evidence showing that abrupt tapering of GXR may not lead to a higher risk of rebound hypertension compared with gradual tapering [27].

Efficacy, safety & tolerability of guanfacine

The efficacy of IR guanfacine has been evaluated in children and adolescents with ADHD and tic disorder in one study funded by the Children's Clinical Research Center, Yale Mental Health Research Center and Tourette Syndrome Association [28]. The GXR as monotherapy has been evaluated in children and adolescents with ADHD in five prospective industry-sponsored RCTs [28–33] and in one unpublished RCT (TABLE 1) [34].

Scahill *et al.* completed a single-center RCT with an 8-week duration in 34 children of 7–15 years of age with DSM-IV diagnoses of ADHD and tic disorder. Patients were treated with guanfacine (1.5–3 mg/day) or placebo for 8 weeks. The primary outcome measure was the ADHD rating scale IV (ADHD-RS-IV) total score; secondary outcome measures were the Clinical Global Impression of Improvement (CGI-I) scale, the hyperactivity index of the Parent Conners questionnaire (CGI-I), the Yale Global Tic Severity Scale, the Children's Yale Brown Obsessive Compulsive Scale and the Continuous Performance test. After 8 weeks of treatment, guanfacine was associated with a mean improvement of 37% in the total score on ADHD-RS-IV, compared with 8% improvement with placebo. Nine of 17 subjects who received guanfacine were blinded-rated on the CGI-I as either 'much improved' or 'very much improved', compared with none of the 17 subjects who received placebo. Tic severity decreased by 31% in the guanfacine group compared with 0% in the placebo group [28].

Biederman *et al.* [29] completed a multicenter RCT with an 8-week duration in 240 children of 6–17 years of age with a DSM-IV-TR diagnosis of ADHD. The study used a fixed-dosage escalation design in which patients were randomly assigned to placebo or GXR at doses of 2, 3 or 4 mg. The primary outcome measure was the ADHD-RS-IV total score, whereas secondary outcome measures included the CGI-I, Clinical Global Impression of severity (CGI-S) scales, the Conners' Parent Rating Scale-Revised-Short form (CPRS-R) and Conner's Teacher Rating Scale Revised-Short form. All children

groups taking GXR showed significant improvement on the hyperactivity/impulsivity and inattentiveness subscales of the primary and secondary measures. Significant differences among age subgroups were also detected: ADHD-RS-IV total scores showed greater efficacy of GXR for 6- to 12-year-old patients compared with 13- to 17-year-old patients.

The lack of significant change from baseline to end point in any GXR groups for patients aged 13–17 compared with placebo may have been attributable to the small size of the subgroup. In addition, it is also possible that a higher dosage may be required to achieve optimal efficacy in this age range.

Sallee *et al.* [30] conducted a double-blind, 9-week, multicenter (51 sites in the USA) RCT in 322 subjects with a DSM-IV-TR diagnosis of ADHD were randomized to placebo or GXR 1, 2, 3 or 4 mg/day. Randomization was stratified by baseline weight. The primary outcome measure was ADHD-RS-IV score from baseline to end point. Secondary outcomes measures were: scores of hyperactive/impulsive and inattentive ADHD-RS-IV subscales; clinicians and parent ratings: CPRS-R and the Parent Global Assessment; duration of clinical effects: CGI-I. All GXR dose groups showed statistically and clinically significant decreases in ADHD-RS-IV total score from baseline to end point: –19.6 (standard deviation [SD]: 13.9), compared with –12.2 (SD: 13.0) for placebo. When examined by age group, changes in ADHD-RS-IV mean total score were significant for all GXR doses in the younger subjects (aged 6–12 years), but not for older age group (aged 13–17 years). However, it is possible that the lack of efficacy is due to a lower weight correct dosing distribution, and to the low number of subjects (i.e., 76 of 306) in the older age group. Subgroup analysis showed no efficacy of GXR at any dose in adolescents.

Connor *et al.* [31] conducted a 9-week multicenter (33 USA sites), flexible dose-optimization RCT in 217 children aged 6–12 years: 138 were randomized to receive GXR (1–4 mg/day) and 79 to receive placebo. The primary efficacy measure was the change from baseline to end point on the oppositional subscale of the CPRS-R:Long Form score. The ADHD-RS-IV was the secondary efficacy measure. In the overall study population, 180/214 (84.1%) had been diagnosed with the combined ADHD subtype, 27/214 (12.6%) with the inattentive subtype and 7/214 (3.3%) with the hyperactive/impulsive subtype. Screening and washout periods were followed by a 5-week dose-optimization period, a 3-week dose maintenance period and a 1-week tapering period. The least-square mean change from baseline in the oppositional subscale of the CPRS-R:Long Form to end point was –10.9 for the GXR-treated children, and –6.8 for placebo-treated subjects ($p < 0.001$; effect size = 0.59). The least square mean decrease from baseline to end point in ADHD-RS-IV total score was 23.8 points for subjects receiving GXR compared with 11.5 for placebo ($p < 0.001$; effect size = 0.92).

Kollins *et al.* [32] conducted a 6-week multicenter (9 US sites) RCT in 182 subjects aged 6–17 years with a diagnosis of ADHD. Psychomotor functioning, alertness and daytime

Table 1. Characteristics of included randomized controlled trials.

Study (year)	Patient (n)	Mean age/range (years)	Diagnosis	Drug dose	Study design	Study duration (weeks)	Ref.
Scahill <i>et al.</i> (2001)	34	10.4	ADHD and tic DSM-IV CT: 100% TS: 58.8% CMTD: 35.3% SITD: 5.9%	3 mg	Prospective RCT	8	[28]
Biederman <i>et al.</i> (2008)	345	10.5/6–17	ADHD DSM-IV-TR IA: 26.1% CT: 72% HI: 2%	2 mg 87 3 mg 86 4 mg 86 PLA 86	Prospective RCT monotherapy fixed-dose escalation	8	[29]
NCT01081132 (2008)	314	14.5	ADHD DSM-IV-TR CT and HI: % not specified	1–7 mg PLA	Prospective RCT	13	[34]
Sallee <i>et al.</i> (2009)	324	11.0/6–17	ADHD DSM-IV-TR IA: 26% CT: 73% HI: 2%	1 mg 62 2 mg 65 3 mg 65 4 mg 65 PLA 65	Prospective RCT monotherapy fixed-dose escalation	9	[30]
Connor <i>et al.</i> (2010)	217	9.4/6–12	ADHD DSM-IV-TR IA: 13% CT: 84% HI: 3%	1–4 mg/day (mean 2.87 mg/day) vs PLA	Prospective RCT flexible dose monotherapy	9	[31]
Kollins <i>et al.</i> (2011)	182	12.6/6–17	ADHD DSM-IV-TR IA: 24% CT: 75% HI: 2%	1–3 mg/day (mean 2.46 mg/day) vs PLA	Prospective RCT flexible dose monotherapy	6	[32]
Newcorn <i>et al.</i> (2013)	333	9.1/6–17	ADHD DSM-IV-TR subtype distribution not specified	am 1–4 mg/day pm 1–4 mg/day	Prospective RCT monotherapy dose optimization	8	[33]

ADHD: Attention deficit hyperactivity disorder; CMTD: Chronic motor tic disorder; CT: Combined type; HI: Hyperactive type; IA: Inattentive type; RCT: Randomized controlled trial; SITD: Stimulant-induced tic disorder; TS: Tourette's syndrome.

sleepiness were assessed through several measures including the choice reaction time and the Cambridge Neuropsychological Test Automated Battery in a laboratory classroom. There were no significant differences between the GXR and placebo groups on measures of psychomotor functioning or alertness on the choice reaction time at end point. Most sedative adverse events were mild to moderate and occurred during dose titration, decreased with dose maintenance and resolved during the study period. GXR treatment was associated with a significant improvement in ADHD symptoms, quantified as average change of 6.3 ($p = 0.001$) on the ADHD-RS-IV total score at end point.

Newcorn *et al.* [33] conducted an 8-week, dose-optimization, multicenter (47 sites in the USA and Canada) RCT in

333 children aged 6–12 years with a primary diagnosis of ADHD with combined subtypes defined by DSM-IV-TR. Patients were randomized to receive GXR (1–4 mg/day) in the morning, upon awakening and matching placebo in the evening (GXR am; 107 subjects), or placebo in the morning and GXR in the evening (GXR pm, 114 subjects), or twice-daily placebo (112 subjects). The primary efficacy measure was the investigator-administered ADHD-RS-IV from baseline to end point. GXR monotherapy administered either in the morning or in the evening was associated with significantly greater ADHD symptom improvement compared with placebo. Significant reductions were observed in ADHD-RS-IV total scores as well as in hyperactivity/impulsivity and inattention subscale scores. The decrease in ADHD-RS-IV total scores was

significant for both GXR treatment groups combined (mean -20.0 [SD:12.97]), and separately GXR am (mean -19.8 [SD 12.95]), GXR pm (mean -20.1 [SD 13.04]), compared with placebo (mean -11.0 [SD 12.93]), respectively ($p < 0.001$ for all three GXR groups vs placebo). Effects sizes across GXR treatments groups were 0.77, 0.75 and 0.78 for the all-active, GXR am, and GXR pm groups, respectively.

A Phase III, parallel-group, double-blind, placebo-controlled trial [34] conducted in the USA tested the efficacy of optimized extended-release guanfacine hydrochloride (dose range 0.05–0.12 mg/kg/day) in youth aged 13–17 scoring ≥ 32 on the ADHD-RS-IV and ≥ 4 on CGI-S in the absence of ODD, major depressive disorders or any severe axis I or axis II disorder. Data on the primary outcome measure (change from baseline of the ADHD-RS-IV total score at week 13) were completed by 215 patients and showed statistically and clinically significant improvement with a mean difference of 6 points. Regarding secondary outcome measures, a significantly higher percentage of patients in the guanfacine arm showed normal or borderline scores on the CGI-S and ‘very much’ or ‘much’ improvement on the CGI-I. The frequency of serious adverse effects did not differ significantly between the two arms.

In their recent meta-analysis of α_{2A} -agonists for ADHD in youth, Hirota *et al.* stated that clonidine extended-release (CLON-XR) and GXR were significantly superior to placebo for total ADHD symptoms [35]. Alpha_{2A}-agonist monotherapy significantly reduced overall ADHD symptoms, hyperactivity/impulsivity, inattention and ODD symptoms. Similarly, α_{2A} -agonists add-on treatment significantly reduced overall ADHD symptoms, hyperactivity/impulsivity and inattention, but effect sizes were lower than in monotherapy trials. In their meta-analysis, Ruggiero *et al.* [36] included other two trials [34], which had not been included in the previous meta-analysis by Hirota *et al.* [35], and confirmed the same findings on the efficacy of GXR. However, these authors also stressed the need for future studies comparing guanfacine with other ADHD pharmacological interventions.

The choice of starting treatment with α_{2A} -agonists in patients with ADHD using their extended-release formulation rather than the IR formulation, as well as the decision to switch from the IR- to the XR formulation, appears to be supported by available evidence coming from meta-analysis research. Analyzing the individual formulations separately, Hirota *et al.* [35] concluded that CLON-XR and GXR were significantly superior to placebo for total ADHD symptoms, whereas clonidine-IR and guanfacine-IR did not separate from placebo. Likewise, CLON-XR and GXR were significantly superior to placebo for hyperactive/impulsive symptoms and inattentive symptoms analyzed separately, but there were no significant differences between the two IR formulation groups and placebo. However, it is important to consider that active comparator trials of XR versus IR formulations of α_{2A} -agonists are needed to confirm the potential advantages of XR formulations suggested by this meta-analysis.

Safety & tolerability

Sedation, somnolence, fatigue, drowsiness, headache and upper abdominal pain were the adverse effects that occurred at the highest frequency in GXR RCTs [30–33]. In most cases reporting sedation, this occurred generally within 2–3 weeks from starting treatment, was dose-related, mild to moderate in severity and decreased over time. However, GXR efficacy does not correlate with the frequency of sedation [32]. Cardiovascular safety systolic and diastolic blood pressure, and heart rate reductions were observed in GXR-treated patients mostly in a dose-dependent fashion. Bradycardia and QTc prolongation were observed in the majority of the RCTs [30–32]; however, none of these observed prolongations was considered clinically significant. No significant increase of QTc was reported in the studies by Kollins *et al.* [32] and Wilens *et al.* [37]. Such prolongations should be considered in children with known prolonged QTc interval.

Importantly, all the available data summarized above were retrieved from short-term studies. To date, only two open-label extension studies of published trials [38,39] provide information on the tolerability of guanfacine on the 24-month period. Serious adverse events that occurred in more than one patient were: syncope (2%) and convulsions (0.4%) in combined data from the two trials [38,39]. Overall, it is interesting to note that the results from these two open-label extension studies were similar to those of the short-term studies [36].

Regulatory affairs

GXR has been approved by the US FDA in March 2011 for use in combination with a stimulant to treat children and adolescents aged 6–17 years. In March 2014, this medication has been filed and is currently under investigation by the European Medicinal Agency for treatment of ADHD in patients aged 6–17 years.

Expert commentary & five-year view

Guanfacine was shown to be an effective and safe non-stimulant treatment option for ADHD in children 6–12 years of age as monotherapy.

Although the GXR is more expensive than the IR formulation, it offers the advantage of increased patient compliance and allows confidentiality of treatment within the school environment. The switch from IR to XR formulations is associated with an improvement in both adherence and effectiveness. Importantly, there were no differences between IR and XR formulations in terms of tolerability, and the advantages of using either type of formulation need to be balanced against fatigue, somnolence/sedation, hypotension, bradycardia and possibly QTc prolongation [35].

Overall, there is good quality evidence supporting the efficacy of GXR in the treatment of the combined subtype of ADHD. Analyzing the response to this treatment in subjects with the combined subtype of ADHD, the least square mean ADHD-RS-IV total score reduction from the baseline to end point was significantly greater than the one observed in the

Table 2. Outcome measures ADHD-RS-IV: hyperactive-impulsive and inattentiveness subscale scores.

Study (year)	Study design and efficacy						Ref.
Biederman <i>et al.</i> (2008)	2 mg	3 mg	4 mg	PLA			[29]
	HI	-7.33	-7.32	-9.31	-3.51		
	p-value	0.0002	0.0002	<0.001	-		
	IA	-8.7	-9.11	-9.44	-4.92		
	p-value	0.0011	0.0006	0.0002	-		
Kollins <i>et al.</i> (2011)	Starting dose week 1	Dose optimization weeks 2-4		Dose maintenance weeks 4-6			[32]
	Visits 1-2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	
	HI	NS	1.5	1.5	1.5	1.5	0.6
	p-value		<0.001	<0.001	<0.001	<0.001	0.008
	IA	NS	0.2	0.5	0.8	1.0	1.3
p-value		0.027	0.015	0.006	0.003	0.001	
Newcorn <i>et al.</i> (2013)	GXR am vs PLA end of treatment		GXR pm vs PLA end of treatment				[33]
	am	pm	am	pm			
	HI	-10.0	-9.9	-10.2	-5.3		
	p-value	<0.001	<0.001	<0.001	<0.001		
	IA	-9-9	-9-9	-10.0	-5.7		
p-value	<0.001	<0.001	<0.001	<0.001			

ADHD-RS-IV: Attention deficit hyperactivity disorder rating scale IV; CT: Combined type; GXR: Guanfacine extended-release; HI: Hyperactive type; IA: Inattentive type; NS: Not significant; PLA: Placebo.

placebo arm. ADHD-RS-IV hyperactivity-impulsivity and inattentiveness subscale scores were also significantly reduced from baseline to end points in the three studies in which these have been evaluated ([29-31]; TABLE 2). However, the dearth of subjects enrolled in the reviewed trials who had a diagnosis of ADHD-hyperactive/impulsive subtype (between 2 and 3% of the whole study population in four of the five trials) precluded analysis of this subgroup ([27-31]; TABLE 1).

In recent years, at least 12 new products have received the FDA approval as pharmacotherapies for ADHD. However, these products mostly represented different pharmaceutical dosage formulations delivering either methylphenidate or amphetamine. These agents have a demonstrated efficacy in the treatment of ADHD. Nevertheless, up to 30% of patients may not have an optimal response to these agents, may display limiting side effects or other relative contraindications to stimulant use [13,14]. Guanfacine has, therefore, an important place in ADHD pharmacotherapy. In the future, it would be helpful to have long-term efficacy and safety data in a larger number of subjects, comparing effects in children versus adolescents, and assessing effects on quality of life. Effectiveness of guanfacine on all ADHD subtypes should be explored further, together with aggressive behavior and other psychiatric comorbidities.

We acknowledge some general limitations of our review. The main limitation consists in having limited review and

discussion exclusively to data on children and adolescents. There is a substantially smaller body of evidence with respect to the use of α_{2A} -agonists in the treatment of adult ADHD, and more studies are necessary to draw firmer conclusions in systematic reviews or meta-analyses. Another limitation of the conclusions of our review pertains to the characteristics of the reviewed studies, which have a relatively short duration of observation; long-term follow-up would be necessary to comment with greater accuracy on the efficacy, safety and tolerability of this drug over a longer period of time in the course of the illness. Finally, we believe that head-to-head active comparator trials of guanfacine versus psychostimulants are also much awaited to confirm the relative efficacy of guanfacine, and fine tune the role that this drug should have within therapeutic algorithms for ADHD.

Information resources

The neural mechanisms underlying the beneficial effect of guanfacine in young patients with ADHD are a fascinating area which is currently being eagerly explored. Further suggested readings on the most recent evidence from clinical research and animal models include:

- Bédard AC *et al.*, *Psychiatry Res.* 2015 Jan 19. pii: S0925-4927(15)00013-X. doi: 10.1016/j.psychres.2015.01.012. [Epub ahead of print] PMID: 25659477

- Kawaura K et al., Behav Brain Res. 2014 Aug 15;270:349-56. doi: 10.1016/j.bbr.2014.05.044. Epub 2014 May 29. PMID: 24882610
- Pillidge K et al., Br J Pharmacol. 2014 Oct;171(20):4785-96. doi: 10.1111/bph.12860. PMID: 25074741

The effect of α_{2A} -agonists in other neurodevelopmental disorders frequently co-existing with ADHD, such as Tourette syndrome, may differ depending on whether ADHD is present or not. Readers might be interested in the following meta-analysis, which addresses this issue:

- Weisman H et al., Neurosci Biobehav Rev. 2013 Jul;37(6):1162-71. doi: 10.1016/j.neubiorev.2012.09.008. PMID: 23099282

Finally, readers may consult these recent useful reviews for a broader overview to treatment options in youth with ADHD:

- Sibley MH et al. Clin Psychol Rev. 2014 Apr;34(3):218-32. doi: 10.1016/j.cpr.2014.02.001. Epub 2014 Feb 27. PMID: 24632046
- Childress AC, Sallee FR. CNS Drugs. 2014 Feb;28(2):121-9. doi: 10.1007/s40263-013-0130-6. PMID: 24402970
- Obioha O, Adesman A. Curr Opin Pediatr. 2014 Feb;26(1):119-29. doi: 10.1097/MOP.000000000000053. PMID: 24370490

Financial & competing interests disclosure

R Rizzo worked on guanfacine trial SPD503-318. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Key issues

- Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder diagnosed in children and adolescents.
- Although effective stimulant treatment is available for ADHD, a substantial number of children do not respond adequately to the stimulants.
- Guanfacine extended-release formulation was shown to be an effective and safe treatment option for ADHD in children.

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