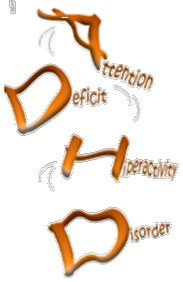
NEWSLETTER



INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD GIUGNO 2015

Acta Medica Martiniana. 2015;15:20-26.

ATOMOXETINE AND METHYLPHENIDATE TREATMENT IN ADHD.

Snircova E, Hrtanek I, Kulhan T, et al.

Objective: ADHD (Attention deficit/hyperactivity disorder) is the most common diagnosed neurobehavioral disorder in childhood and adolescence. Core symptoms of ADHD are persistent inattention, hyperactivity and impulsivity. In Slovakia, there are two specific medication choices to treat ADHD - atomoxetine and methylphenidate. Even though methylphenidate is option number one according to guidelines, the highest amount of patients are taking atomoxetine.

Aim: Our aim was to observe atomoxetine and methylphenidate effect in 40 child and adolescent patients with ADHD to compare their efficacy in child and adolescent patients using ADHD-RS-IV scale and CGI scale.

Methods: We included 40- hospitalised patients, 20 patients were taking atomoxetine and 20 patients methylphenidate. Therapeutic effect on symptoms of inattention, hyperactivity/impulsivity and global score was measured by ADHD-rating scale IV. Global clinical condition of patients was evaluated by CGI (Clinical Global Impression Scale). Symptomatology was measured before treatment, and every 2 weeks during 8 weeks of treatment. CGI was administrated before and after treatment.

Results: We found significant therapeutic effect of atomoxetine and methylphenidate on core symptoms of ADHD after 8 weeks of treatment both with atomoxetine and methylphenidate. We found non-significant difference CGI scale scores.

Conclusion: Our study evaluated atomoxetine and methylphenidate treatment effect on ADHD. Atomoxetine and methylphenidate showed significant effect on core symptoms of ADHD, there were no significant between group differences in ADHD-RS-IV. Our study revealed non-significant difference CGI scale scores between medication groups.

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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.

ADHD Atten Deficit Hyperact Disord. 2015;7:129-39.

TURKISH VALIDITY AND RELIABILITY STUDY OF THE WEISS FUNCTIONAL IMPAIRMENT RATING SCALE-PARENT REPORT.

Tarakcioglu MC, Cakin MN, Olgun NN, et al.

Attention deficit hyperactivity disorder (ADHD) is seen frequently in childhood and leads to marked impairment in functioning. There is no scale in Turkey with documented validity and reliability that assesses ADHD-specific functional impairment (FI). This study aimed at adapting the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P), which assesses ADHD-related FI, for use in Turkey, and examining psychometric aspects of the scale. The study included 250 children diagnosed with ADHD and 250 healthy children and their parents. Internal consistency and testnullretest methods were used to test the reliability of the scale. Validity was tested with exploratory and confirmatory factor analyses and convergent and discriminant validity analyses. Since all six questions of the WFIRS-P were scored 0, analyses were conducted for the original scale questionnaire consisting of 50 items and the questionnaire consisting of 44 items where the six questions scored 0 were not included. The Cronbachnulls alpha coefficient was 0.93 for the whole scale. The Spearmannulls correlation coefficient was 0.93 for testnullretest reliability. The exploratory factor analysis run on the 44-item questionnaire showed that the scale items were best represented in a 7-factor structure, but some items were placed in different subdomains than those of the original scale. In the confirmatory factor analysis, the root mean square error of approximation was 0.061, and the comparative fit index was 0.95 for the whole model. Therefore, the Turkish WFIRS-P is valid and reliable in testing functional impairment in children with ADHD.

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ADHD Atten Deficit Hyperact Disord. 2015.

LIFETIME STABILITY OF ADHD SYMPTOMS IN OLDER ADULTS.

Semeijn EJ, Comijs HC, de Vet HCW, et al.

Attention-deficit/hyperactivity disorder (ADHD) has been shown to continue into old age. Studies in children and younger adults show a reduction in hyperactive-impulsive symptoms, whereas the number of inattentive symptoms stays stable. The current study examined the lifetime stability of ADHD symptoms up to old age. Data on ADHD diagnosis and symptoms were collected in a two-phase side-study (N = 231) of the Longitudinal Aging Study Amsterdam. Paired t tests and ANCOVAs were used to analyze the data. Paired t test suggests continuity of the number of reported ADHD symptoms currently present and present in childhood. The change in the balance of inattentive/hyperactive-impulsive symptoms at present and in childhood is also the same in persons with ADHD.Finally, the difference in the change in the balance of inattentive/hyperactive-impulsive symptoms in those with and without ADHD suggests continuity throughout the life span. Our results suggest that diagnostic criteria developed for younger adults may be used among older adults. However, we collected our data retrospectively, which may have biased our results. Future research should follow larger cohorts of patients with ADHD prospectively over the life span.

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Alcohol Clin Exp Res. 2015;39:74A.

PARENT-VERSUS SELF-REPORTED ALCOHOL PROBLEMS FOR YOUNG ADULTS WITH CHILDHOOD ADHD.

Molina BSG, Walther CAP, Pedersen SL, et al.

Children diagnosed with ADHD have an increased risk of alcohol use disorder by adulthood (Lee et al., 2011). Research on factors contributing to this outcome for children with ADHD has been accumulating (Barkley et al., 2008; Knop et al., 2009; Molina et al., 2007, 2014;Wymbs et al., in press). These studies have generally relied on self-reported alcohol use and problems. Although self-report is the standard practice for assessment of alcohol use in longitudinal studies, research on individuals with ADHD has revealed a common tendency toward under-reporting of ADHD symptoms and impairment (Barkley et al., 2002; Hoza et al., 2002; Sibley et al., 2012). In the current study we examined, at the follow-up age of 25, comparison between self-reported symptoms of alcohol use disorder and parent-reported rating of problem drinking. Data were from the Pittsburgh ADHD Longitudinal Study (PALS) of 313 children diagnosed with

ADHD and followed to age 25 compared to 216 same-aged demographically similar adults without childhood ADHD (88% male; 83% white). Symptoms of DSM-IV alcohol use disorder were summed from a self-report structured clinical interview (see Molina et al., 2007) and compared to parent ratings of their son?s/daughter?s alcohol use on a scale of 1 (never drank) to 4 (definite problem drinker) using the Mann Family Tree (Mann et al., 1985). More individuals in the ADHD than non ADHD group were rated by their parents as ? definite problem drinkers? when the young adult reported zero symptoms (7.5%vs. 2.3%, (chi)2 = 4.06. p = 0.04). Directionality of the ADHD group differences in presence of alcohol problems depended on rater source. For example, more individuals in the non ADHD group reported 2+ AUD symptoms compared to the ADHD group, 16.2%vs. 10.5%, (chi)2 = 3.65, p = 0.056, but more parents in the ADHD group rated their adult children as nulldefinite problem drinkersnull 7.8%vs. 2.2%, (chi)2 = 6.33, p = 0.012. These findings, plus other analyses that will consider persistence of ADHD symptoms, reveal the importance of considering the use of additional informants when studying populations known to be characterized by under-reporting of mental health symptoms and impairment.

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Alcohol Clin Exp Res. 2015;39:134A.

ADHD SUBTYPES AND CO-OCCURRING PSYCHIATRIC SYMPTOMS IN AN AOD TREATMENT SAMPLE OF ADOLESCENTS.

Regan T, Tubman J.

Attention Deficit Hyperactivity Disorder (ADHD) is a commonly diagnosed psychiatric disorder that is overrepresented among adolescents in treatment for alcohol and other drug (AOD) problems. ADHD symptoms such as hyperactivity, impulsive behavior, distractedness, and difficulty following directions may negatively impact treatment adherence and outcomes. Adolescents diagnosed with ADHD often report co-occurring symptoms of other psychiatric disorders. The purpose of this study was to determine the prevalence of ADHD subtypes in a diverse sample of adolescents in outpatient AOD treatment and to assess relations between ADHD diagnosis and scores for co-occurring psychiatric symptoms. In addition, gender differences in symptom presentation were examined. Structured interviews were administered to 396 adolescents (271 males, 110 females, M = 16.22 years, SD = 1.13 years) receiving outpatient AOD treatment services as part of a larger randomized clinical trial targeting HIV-risk reduction. ADHD diagnostic subtypes and other past year psychiatric disorders were assessed using the Brief Michigan Version of the Composite International Diagnostic Interview (CIDI). Multivariate analyses of variance (MANOVAs) were used to describe differences in mean levels of five psychiatric symptom scores by gender and ADHD subtype status. Inattentive and Hyperactive-Impulsive ADHD subtypes were significantly associated with higher scores for all past year psychiatric symptoms assessed (i.e., alcohol abuse and dependence, drug abuse and dependence, conduct disorder, anxiety disorders and affective disorders). The combined ADHD subtype was associated with higher scores for all psychiatric symptoms except affective disorders. Gender was significantly associated with alcohol abuse and dependence, anxiety and affective disorder symptoms, with girls exhibiting significantly more symptoms than boys. Results documented the high prevalence of ADHD among adolescents in this sample, and patterns of associations of co-occurring psychiatric symptoms by ADHD subtype. Brief screening for ADHD among adolescents entering AOD treatment may identify adolescents less likely to engage in, and adhere to, their treatment protocols. The findings of this study may inform clinicians regarding key factors (i.e., ADHD status, gender) by which AOD treatments may be tailored to improve treatment engagement, adherence and outcomes.

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Alcohol Clin Exp Res. 2015;39:203A.

SMOKING CESSATION DURING TREATMENT AMONG YOUTH WITH AND WITHOUT ADHD.

Delos Reyes CM, Kurtz SP, Pagano ME.

Purpose: Three out of four alcoholics enter treatment as smokers. Research with adults suggests that smoking cessation does not interfere with treatment outcomes and is associated with improved outcomes

for quitters with co-morbid mood/anxiety disorders. The purpose of this study is to determine if smoking cessation interferes with treatment response among youth with and without co-morbid ADHD.
Method: One-hundred ninety-five substance-dependent adolescents (50% female, aged 14-18) who were referred to a residential treatment program were assessed at intake, prospectively during the 8-week treatment period, and at discharge. Multi-informant data was prospectively collected from youth self-reports, clinician-rated assessments, biomarkers, and medical chart records.
Results: Three out of four (76%) youths entered treatment as smokers and approximately half (46%) quit during treatment. Smokers entered treatment with greater HIV/STD risk behaviors, trauma, attempted suicide, and rates of ADHD ($p < 0.05$). Youths with ADHD (inattentive only or combination type) were less likely to quit smoking than youths without ADHD ($p < 0.0001$). For youths without ADHD or inattentive ADHD only, smoking cessation was associated with greater treatment response in terms of treatment completion ($p < 0.05$), service participation ($p < 0.001$), step-work ($p < 0.01$), global functioning ($p < 0.01$), and lower cravings ($p < 0.05$). Quitting smoking with combination ADHD was associated with greater likelihood of testing positive during treatment ($p < 0.05$).
Conclusion: Smoking cessation appears unlikely to hinder and may even help recovery from substance use disorders among youths without ADHD and with inattentive ADHD. In a climate of finite treatment resources, nicotine-replacement therapies should be targeted at adolescent smokers with combination ADHD.

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Alcohol Clin Exp Res. 2015;39:163A.

DIFFERENCES IN YOUNG ADULT ALCOHOL PROBLEMS DUE TO ADHD HISTORY AND COMPLETION OF POSTSECONDARY EDUCATION.

Walther CAP, Pedersen SL, Pelham J, et al.

Children diagnosed with ADHD are at increased risk of problem alcohol use as adolescents and young adults compared to those without ADHD histories (Lee et al., 2011; Molina et al., 2007; Molina & Pelham, 2003). Exposure to environments in which heavy alcohol use is normative, such as postsecondary education (e.g., college),may place young adults with ADHD histories at even greater risk for alcohol problems in adulthood (Baker et al., 2012; Rooney et al., 2012). However, this prediction is complicated by the fact that college attendance may be a marker of improved functioning for those with childhood ADHD. This study examined completion of higher education as a moderator of the association between childhood ADHD diagnosis and alcohol problems at age 25. The sample consisted of 508 young adults, 295 with and 213 without childhood ADHD, who have been followed longitudinally as part of the Pittsburgh ADHD Longitudinal Study (PALS). Participants reported the completion of any education or training after high school. Alcohol problems at age 25 were selfreported, and participant-reported binge drinking at age 25 was included as a covariate. Participants without a history of ADHD had a higher level of alcohol problems at age 25 than those with ADHD histories ($F(1, 504) = 4.47$, $p < 0.05$). This difference in alcohol problems was at least partially explained by higher education ($F(1, 504) = 6.42$, $p < 0.05$), as the group difference was only present among those who had completed higher education. When binge drinking was included as a covariate, the main effect of ADHD was no longer significant, and the interaction between ADHD and higher education was marginally significant. These findings suggest that young adults with ADHD histories who complete postsecondary education may be at lower, rather than greater, risk for alcohol problems than peers without childhood ADHD. Persistence of ADHD symptoms and associated features may need to be considered in order to further understand heterogeneity of vulnerability within these subgroups. Additional analyses will consider this as well as parent report of alcohol problems to adjust for potential under-reporting by the young adults in the sample.

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Anadolu Psikiyatr Derg. 2015;16:357-63.

ODOR AND TASTE SENSITIVITY IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Akin SB, Taskintuna N.

Objective: Attention Deficit/Hyperactivity Disorder (ADHD) is diagnosed using Diagnostic and Statistical Manual of Mental Disorders criteria, neuropsychological testing, examinations, and parent, teacher, and self-evaluation forms. Diagnosing of ADHD depends on clinical evaluation, others are auxilary methods. No biological, electrophysio-logical, or neuroimaging markers currently exist to diagnose ADHD. Many studies about the biological markers for diagnosing ADHD have been conducted. Olfactory and gustatory dysfunctions have not been well studied in ADHD for this purpose. For this reason this study aimed to evaluate both the olfactory and gustatory functions of children with ADHD.

Methods: A total of 34 children with ADHD and a control group containing 31 children aged 6-15 years participated in the study. We used the Sniffinnull Sticks odor tests and propylthiouracil (PROP) bitterness sensitivity test to examine odor and taste sensitivity, respectively.

Results: We found no statistically significant differences between the ADHD and control groups in terms of odor sensitivity, odor discrimination, and odor identification. A statistically significant difference between groups was observed in PROP scores. Children in the ADHD group were less sensitive to bitterness than the control group.

Conclusion: PROP bitterness test is in an advantageous state for being a marker in advanced years due to ease of use, independence of age and very short test period. As a result, in our study, it is concluded that PROP bitterness test may be a biological marker for ADHD diagnosis, however, further studies are needed.

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Autism Res. 2015;8:328-37.

OVERLAP BETWEEN AUTISM SPECTRUM DISORDERS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: SEARCHING FOR DISTINCTIVE/COMMON CLINICAL FEATURES.

Craig F, Lamanna AL, Margari F, et al.

Recent studies support several overlapping traits between autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD), assuming the existence of a combined phenotype. The aim of our study was to evaluate the common or distinctive clinical features between ASD and ADHD in order to identify possible different phenotypes that could have a clinical value. We enrolled 181 subjects divided into four diagnostic groups: ADHD group, ASD group, ASD+ADHD group (that met diagnostic criteria for both ASD and ADHD), and control group. Intelligent quotient (IQ), emotional and behavior problems, ADHD symptoms, ASD symptoms, and adaptive behaviors were investigated through the following test: Wechsler Intelligence Scale for Children, Wechsler Preschool and Primary Scale of Intelligence or Leiter International Performances Scale Revised, Child Behavior Checklist, Conners' Rating Scales-Revised, SNAP-IV Rating Scale, the Social Communication Questionnaire, Vineland Adaptive Behavior Scales. The ASD+ADHD group differs from ADHD or ASD in some domains such as lower IQ mean level and a higher autistic symptoms severity. However, the ASD+ADHD group shares inattention and hyperactivity deficit and some emotional and behavior problems with the ADHD group, while it shares adaptive behavior impairment with ASD group. These findings provide a new understanding of clinical manifestation of ASD+ADHD phenotype, they may also inform a novel treatment target.

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Behav Brain Funct. 2015;11.

A 40-BP VNTR POLYMORPHISM IN THE 3'-UNTRANSLATED REGION OF DAT1/SLC6A3 IS ASSOCIATED WITH ADHD BUT NOT WITH ALCOHOLISM.

Sery O, Paclt I, Drtilkova I, et al.

Background: ADHD and alcoholism are psychiatric diseases with pathophysiology related to dopamine system. DAT1 belongs to the SLC6 family of transporters and is involved in the regulation of extracellular dopamine levels. A 40 bp variable number tandem repeat (VNTR) polymorphism in the 3'-untranslated

region of DAT1/SLC6A3 gene was previously reported to be associated with various phenotypes involving disturbed regulation of dopaminergic neurotransmission.
Methods: A total of 1312 subjects were included and genotyped for 40 bp VNTR polymorphism of DAT1/SLC6A3 gene in this study (441 alcoholics, 400 non-alcoholic controls, 218 ADHD children and 253 non ADHD children). Using miRBase software, we have performed a computer analysis of VNTR part of DAT1 gene for presence of miRNA binding sites.
Results: We have found significant relationships between ADHD and the 40 bp VNTR polymorphisms of DAT1/SLC6A3 gene ($P < 0.01$). The 9/9 genotype appeared to reduce the risk of ADHD about 0.4-fold ($p < 0.04$). We also noted an occurrence of rare genotypes in ADHD (frequency different from controls at $p < 0.01$). No association between alcoholism and genotype frequencies of 40 bp VNTR polymorphism of DAT1/SLC6A3 gene has been detected.
Conclusions: We have found an association between 40 bp VNTR polymorphism of DAT1/SLC6A3 gene and ADHD in the Czech population; in a broad agreement with studies in other population samples. Furthermore, we detected rare genotypes 8/10, 7/10 and 10/11 present in ADHD boys only and identified miRNAs that should be looked at as potential novel targets in the research on ADHD.

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Biological Trace Element Research. 2015.
CHANGED PLASMA LEVELS OF ZINC AND COPPER TO ZINC RATIO AND THEIR POSSIBLE ASSOCIATIONS WITH PARENT- AND TEACHER-RATED SYMPTOMS IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Viktorinova A, Ursinyova M, Trebaticka J, et al.
Attention-deficit hyperactivity disorder (ADHD) is associated with alterations in the metabolism of some trace elements which may participate in the pathogenesis of this disorder. The aims of the present study were to investigate the trace element status (copper (Cu), zinc (Zn), copper to zinc ratio (Cu/Zn ratio), selenium (Se), and lead (Pb)) of ADHD children and compare them with the control group. Associations between examined elements and ratings of ADHD symptoms were also assessed. Fifty-eight ADHD children and 50 healthy children (aged 6null14 years) were included in the study. The concentrations of Cu, Zn, and Se in the plasma and Pb in the whole blood were measured by atomic absorption spectrometry. We found lower Zn level ($p = 0.0005$) and higher Cu/Zn ratio ($p = 0.015$) in ADHD children when compared with the control group. Copper levels in ADHD children were higher than those in the control group, but not significantly ($p > 0.05$). No significant differences in levels of Se and Pb between both groups were found. Zinc levels correlated with parent-rated score for inattention ($r = null0.231$, $p = 0.029$) as well as with teacher-rated score for inattention ($r = null0.328$, $p = 0.014$). Cu/Zn ratio correlated with teacher-rated score for inattention ($r = 0.298$, $p = 0.015$). Significant associations of Se and Pb with parent- and teacher-rated symptoms were not observed. The results of this study indicate that there are alterations in plasma levels of Cu and Zn as well as significant relationships to symptoms of ADHD.

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BioMed Research International. 2014;2014.
ABNORMAL FUNCTIONAL RESTING-STATE NETWORKS IN ADHD: GRAPH THEORY AND PATTERN RECOGNITION Analysis of fMRI Data.
Dos Santos SA, Biazoli Junior CE, Comfort WE, et al.
The framework of graph theory provides useful tools for investigating the neural substrates of neuropsychiatric disorders. Graph description measures may be useful as predictor variables in classification procedures. Here, we consider several centrality measures as predictor features in a classification algorithm to identify nodes of resting-state networks containing predictive information that can discriminate between typical developing children and patients with attention-deficit/hyperactivity disorder (ADHD). The prediction was based on a support vector machines classifier. The analyses were performed in a multisite and publicly available resting-state fMRI dataset of healthy children and ADHD patients: the ADHD-200 database. Network centrality measures contained little predictive information for the discrimination between ADHD patients and healthy subjects. However, the classification between

inattentive and combined ADHD subtypes was more promising, achieving accuracies higher than 65% (balance between sensitivity and specificity) in some sites. Finally, brain regions were ranked according to the amount of discriminant information and the most relevant were mapped. As hypothesized, we found that brain regions in motor, frontoparietal, and default mode networks contained the most predictive information. We concluded that the functional connectivity estimations are strongly dependent on the sample characteristics. Thus different acquisition protocols and clinical heterogeneity decrease the predictive values of the graph descriptors.

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BMC Psychiatry. 2015.

EXPERIENCES OF ADOLESCENTS AND YOUNG ADULTS WITH ADHD IN HONG KONG: TREATMENT SERVICES AND CLINICAL MANAGEMENT.

Cheung KKW, Wong ICK, Ip P, et al.

Background: Specialist services for the treatment of attention deficit hyperactivity disorder (ADHD) in adulthood in Hong Kong are yet to be developed. This study aims to explore the experiences of adolescents and young adults with ADHD in accessing treatment and services, coping with ADHD-related impairment, and their expectations of future treatment in Hong Kong.

Method: Qualitative interviews were conducted with a semi-structured guide. Forty young adult patients aged between 16 and 23 were included in the study. The interview recordings were transcribed verbatim and anonymised. Data were analysed with a thematic approach based on key principles of Grounded Theory.

Results: Four meta-themes were developed: Accessing ADHD diagnosis and treatment services; ADHD-related impairment; Experience of ADHD treatments; and Attitudes and expectations of future ADHD treatment. The role of parents and schools were highly significant in accessing services for patients diagnosed with ADHD in childhood. In general, ADHD affected every aspect of patients' lives including academic outcome, employment, family and social relationships. Medications were the principal treatment for ADHD amongst the interviewees and were reported to be generally effective. Half of the patients received non-pharmacological treatments in childhood but these effects were reported to be temporary. There was general consensus that the needs of patients with ADHD could not be met by the current service. In particular, there is a lack of specialist service for adults with ADHD, follow-up by different clinicians, and insufficient provision of non-pharmacological treatments.

Conclusion: The findings suggest that further development of specialist ADHD services and non-pharmacological options for young adults are essential to meet their diverse needs with a holistic approach.

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Brain Stimul. 2014;7:793-99.

TRANSCRANIAL OSCILLATORY DIRECT CURRENT STIMULATION DURING SLEEP IMPROVES DECLARATIVE MEMORY CONSOLIDATION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TO A LEVEL COMPARABLE TO HEALTHY CONTROLS.

Prehn-Kristensen A, Munz M, Goder R, et al.

Background Slow oscillations (<1 Hz) during slow wave sleep (SWS) promote the consolidation of declarative memory. Children with attention-deficit/hyperactivity disorder (ADHD) have been shown to display deficits in sleep-dependent consolidation of declarative memory supposedly due to dysfunctional slow brain rhythms during SWS

Objective Using transcranial oscillating direct current stimulation (toDCS) at 0.75 Hz, we investigated whether an externally triggered increase in slow oscillations during early SWS elevates memory performance in children with ADHD

Methods: 12 children with ADHD underwent a toDCS and a sham condition in a double-blind crossover study design conducted in a sleep laboratory. Memory was tested using a 2D object-location task. In addition, 12 healthy children performed the same memory task in their home environment

Results Stimulation enhanced slow oscillation power in children with ADHD and boosted memory performance to the same level as in healthy children
Conclusions These data indicate that increasing slow oscillation power during sleep by toDCS can alleviate declarative memory deficits in children with ADHD.

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Breastfeeding Med. 2015;10:283-84.
BREASTFEEDING HISTORY IN CHILDREN WITH AUTISM AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Say GN, Babadanulli Z, Karabekiroaylu K.

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British Journal of Ophthalmology. 2015.
ASSOCIATION BETWEEN PENETRATING EYE INJURIES AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.
Bayar H, Coskun E, oner V, et al.
Purpose To investigate whether there is an association between penetrating eye injuries and attention deficit hyperactivity disorder (ADHD) symptoms in children.
Methods 45 children aged 3-18 years who were treated due to penetrating ocular injuries (patient group) and 75 control subjects (control group) were enrolled in the study. The symptoms of ADHD were evaluated by the Turkish adapted and validated form of the Conner Parent Rating Scale (CPRS).
Results The mean age was 8.9(plus or minus)4.1 years in the patient group and 9.7(plus or minus)3.7 years in the control group. All subscale scores of CPRS were higher in the patient group compared with the control group (all $p<0.05$). Gender-specific analyses showed that the boys of the patient group had significantly higher mean scores of all subscales, including inattentiveness, hyperactivity, oppositional defiant disorder and conduct disorder, compared with the boys of the control group (all $p<0.05$). However, the girls of the patient group had higher mean scores of only the conduct disorder subscale ($p<0.05$) compared with the girls of the control group. Three of 45 patients (6.6%) and 0 of 75 control subjects (0%) had a history of previous ocular trauma ($p<0.05$).
Conclusions There was an association between penetrating eye injuries and inattentiveness, hyperactivity, oppositional defiant disorder and conduct disorder in boys, and conduct disorder in girls. An appropriate evaluation of ADHD symptoms may prevent vision loss due to penetrating eye injuries in children. In addition, evaluation by a child psychiatrist of children presenting with penetrating eye injuries may prevent repetition of injuries.

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Child Neuropsychol. 2015.
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.

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Current Pain and Headache Reports. 2015;19.

HEADACHE AND ADHD IN PEDIATRIC AGE: POSSIBLE PHYSIOPATHOLOGICAL LINKS .

Paolino MC, Ferretti A, Villa MP, et al.

Primary headache and attention-deficit/hyperactivity disorder (ADHD) are common disorders in children and adolescences, frequently associated to severe cognitive, emotional, and behavioral impairments. They both are a disabling condition with consequences on family and childnulls quality of life. Literature data on their association are contrasting. Dopaminergic system dysfunction, brain iron deficiency, and sleep disturbance should be considered to better understand headache and ADHD overlap. In this review, we analyze the complex association between these two diseases and the potential impact on child neurodevelopment.

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Drug Design, Development and Therapy. 2015;9:2767-75.

POPULATION PHARMACOKINETICS OF METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE MULTIPLE-LAYER BEADS IN PEDIATRIC SUBJECTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Teuscher NS, Adjei A, Findling RL, et al.

A new multilayer-bead formulation of extended-release methylphenidate hydrochloride (MPH-MLR) has been evaluated in pharmacokinetic studies in healthy adults and in Phase III efficacy/safety studies in children and adolescents with attention deficit hyperactivnullity disorder (ADHD). Using available data in healthy adults, a two-input, one-compartment, first-order elimination population pharmacokinetic model was developed using nonlinear mixed-effect modeling. The model was then extended to pediatric subjects, and was found to adequately describe plasma concentrationnulltime data for this population. A pharmacokinetic/pharmacodynamic model was also developed using change from baseline in the ADHD Ratnulling Scale (ADHD-RS)-IV total scores from a pediatric Phase III trial and simulated plasma concentrationnulltime data. During simulations for each MPH-MLR dose level (10null80 mg), increased body weight resulted in decreased maximum concentration. Additionally, as maximum concentration increased, ADHD-RS-IV total score improved (decreased). Knowledge of the relationship between dose, body weight, and clinical response following the administration of MPH-MLR in children and adolescents may be useful for clinicians selecting initial dosing of MPH-MLR. Additional study is needed to confirm these results.

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Eur Child Adolesc Psychiatry. 2015.

A COMPREHENSIVE SCOPING REVIEW OF ABILITY AND DISABILITY IN ADHD USING THE INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH-CHILDREN AND YOUTH VERSION (ICF-CY).

de SE, Lundequist A, Wilteus AL, et al.

This is the first in a series of four empirical investigations to develop International Classification of Functioning, Disability and Health (ICF) Core Sets for Attention Deficit Hyperactivity Disorder (ADHD). The objective here was to use a comprehensive scoping review approach to identify the concepts of functional ability and disability used in the scientific ADHD literature and link these to the nomenclature of the ICF-CY. Systematic searches were conducted using Medline/PubMed, PsycINFO, ERIC and Cinahl, to extract the relevant concepts of functional ability and disability from the identified outcome studies of ADHD. These concepts were then linked to ICF-CY by two independent researchers using a standardized linking

procedure. Data from identified studies were analysed until saturation of ICF-CY categories was reached. Eighty studies were included in the final analysis. Concepts contained in these studies were linked to 128 ICF-CY categories. Of these categories, 68 were considered to be particularly relevant to ADHD (i.e., identified in at least 5 % of the studies). Of these, 32 were related to Activities and participation, 31 were related to Body functions, and five were related to environmental factors. The five most frequently identified categories were school education (53 %), energy and drive functions (50 %), psychomotor functions (50 %), attention functions (49 %), and emotional functions (45 %). The broad variety of ICF-CY categories identified in this study underlines the necessity to consider ability and disability in ADHD across all dimensions of life, for which the ICF-CY provides a valuable and universally applicable framework. These results, in combination with three additional preparatory studies (expert survey, focus groups, clinical study), will provide a scientific basis to define the ICF Core Sets for ADHD for multi-purpose use in basic and applied research, and every day clinical practice.

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Eur Child Adolesc Psychiatry. 2015.

HEALTH-RELATED QUALITY OF LIFE OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER VERSUS CHILDREN WITH DIABETES AND HEALTHY CONTROLS.

Coghill D, Hodgkins P.

The impact of attention-deficit/hyperactivity disorder (ADHD) on health-related quality of life (HRQoL) is reported to be similar to that of other mental health and physical disorders. In this cross-sectional study, we hypothesized that children with ADHD and children with type 1 diabetes mellitus (T1DM) would have significantly worse HRQoL compared with healthy children, and that better clinical status in ADHD and T1DM would be associated with better HRQoL. Children were recruited from three outpatient services in Scotland. Responses to two frequently used validated HRQoL instruments, the Paediatric Quality of Life Inventory (PedsQL) and Child Health and Illness Profile-child edition (CHIP-CE), were obtained from parents/carers and children (6null16 years) with/without ADHD or T1DM. Child and parent/carer-completed HRQoL measurements were evaluated for 213 children with ADHD, 58 children with T1DM and 117 healthy children (control group). Significantly lower self and parent/carer ratings were observed across most PedsQL ($P < 0.001$) and CHIP-CE ($P < 0.05$) domains (indicating reduced HRQoL) for the ADHD group compared with the T1DM and control groups. Parent/carer and child ratings were significantly correlated for both measures of HRQoL (PedsQL total score: $P < 0.001$; CHIP-CE all domains: $P < 0.001$), but only with low-to-moderate strength. Correlation between ADHD severity and HRQoL was significant with both PedsQL and CHIP-CE for all parent/carer ($P < 0.01$) and most child ($P < 0.05$) ratings; more ADHD symptoms were associated with poorer HRQoL. These data demonstrate that ADHD has a significant impact on HRQoL (as observed in both parent/carer and child ratings), which seems to be greater than that for children with T1DM.

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Exp Dermatol. 2015;24:E1.

ATOPIC DERMATITIS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: ALTERED GRANULE TRANSPORT MECHANISMS PAVE THE ROAD TO ATOPY.

Glemnitz M, Wolfer W, Krauel K, et al.

Epidemiology suggests atopic dermatitis (AD) to be an independent risk factor for attention deficit hyperactivity disorder (ADHD) and vice versa. We recently demonstrated a significant increase of parameters typical for AD pathophysiology in ADHD children treated with methylphenidate (MP, Ritalin) as compared to healthy controls (HC). These preliminary data were now expanded. In addition, we investigated the putative influence of MP-treatment on these parameters. Serum levels of IgE, eosinophilic cationic protein (ECP) and tryptase (Pharmacia- CAP-system), eosinophils (%) and the portion of CD8hi+ cytotoxic T cells (CTL) positive for lytic perforincontaining granules before and after stimulation with iomomycin/PMA (flow cytometry) as well as the dermographism were determined in 21 ADHD children treated with MP after diagnosis was confirmed in a day-care clinical setting over several weeks, 12

matched AD children diagnosed according to the criteria of Rajka and Hanifin and 9 healthy control individuals w/o any atopic/psychiatric background. In addition, a subgroup of MP-treated ADHD children (n = 14) were investigated before and after a therapeutic break of 42 (plus or minus) 5 days. 3/33 children suffered from AD and ADHS and were excluded from further analysis. All other ADHD children did not show any history for nor any clinical evidence of atopy. ADHD and AD children showed significantly higher (i) IgE serum level (185 (plus or minus) 305 and 375 (plus or minus) 745; HC: 33 (plus or minus) 51 kU/l), (ii) eosinophils (6.4 (plus or minus) 8% and 8.7 (plus or minus) 6%; HC: 1.9 (plus or minus) 1%) and (iii) ECP level (27 (plus or minus) 26 and 44 (plus or minus) 26; HC: 12 (plus or minus) 7 (mu)g/l). In >90% of ADHD children a white dermographism (mediated by noradrenalin-granule release) was demonstrable. CTL of AD- and ADHD children released their perforin-containing granules significantly faster as CTL of HC. During the MP treatment break, the following significant changes were observed: percentage of perforinpos lymphocytes and serum tryptase levels rose; ionomycin/PMA stimulated perforin release from CTL was slower. The latter two parameters correlated positively. Changes in IgE and ECP levels after the break correlated positively as well. Our data demonstrate an unexpected tight connection between AD and ADHD on the pathophysiological level and, thus, support epidemiological findings. Both entities showed a facilitated and accelerated release of storage granules (noradrenalin, perforin). Since the perforin-granule system is involved in control of IgE production and noradrenaline supports T-type2 reactions, abnormalities described may contribute in these patients to their increased disposition for atopy. The finding of altered granule transport mechanisms in ADHD opens new views on ADHD pathophysiology. Surprisingly, MP treatment altered granule based mechanisms (tryptase, perforin). One may speculate that part of MP's beneficial effect is mediated by influencing granule transport mechanisms in the central nervous system as well.

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Front Psychiatry. 2015;6.

A PARIETAL BIOMARKER FOR ADHD LIABILITY: AS PREDICTED BY THE DISTRIBUTED EFFECTS PERSPECTIVE MODEL OF ADHD.

Sigi HT, Wiley JF, Smalley SL, et al.

Background: We previously hypothesized that poor task-directed sensory information processing should be indexed by increased weighting of right hemisphere (RH) biased attention and visuo-perceptual brain functions during task operations and have demonstrated this phenotype in ADHD across multiple studies, using multiple methodologies. However, in our recent distributed effects model of ADHD, we surmised that this phenotype is not ADHD specific, but rather more broadly reflective of any circumstance that disrupts the induction and maintenance of an emergent task-directed neural architecture. Under this view, increased weighting of RH-biased attention and visuo-perceptual brain functions is expected to generally index neurocognitive sets that are not optimized for task-directed thought and action, and when durable expressed, liability for ADHD.

Method: The current study tested this view by examining whether previously identified rightward parietal EEG asymmetry in ADHD was associated with common ADHD characteristics and comorbidities [i.e., ADHD risk factors (RFs)].

Results: Barring one exception (non-right handedness), we found that it was. Rightward parietal asymmetry (RPA) was associated with carrying the DRD4-7R risk allele, being male, having mood disorder, and having anxiety disorder. However, differences in the specific expression of RPA were observed, which are discussed in relation to possible unique mechanisms underlying ADHD liability in different ADHD RFs.

Conclusion: Rightward parietal asymmetry appears to be a durable feature of ADHD liability, as predicted by the Distributed Effects Perspective Model of ADHD. Moreover, variability in the expression of this phenotype may shed light on different sources of ADHD liability.

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Indian J Psychiatry. 2015;57:208-09.

X-LINKED ADRENOLEUKODYSTROPHY PRESENTING AS ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Siva IT, Nambi S.

X-linked adrenoleukodystrophy (X-ALD) is one the leukodystrophies causing a progressive decline in neurological function mainly affecting the children. The most common symptoms are changes in behavior, including social withdrawal or aggression, poor memory or poor scholastic performance. Here, we present a 7-year-old boy who presented with symptoms of inattention and hyperactivity and later turned out to be a case of X-ALD.

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Indian Journal of Public Health Research and Development. 2014;5:90-94.

ROLE OF MICRONUTRIENTS ON CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A CONTENTIOUS ISSUE.

Bisht AT, Kukreti VT.

Attention deficit hyperactivity disorder (ADHD) is a heterogeneous disorder with a complex etiology and manifestation, which is, originally expressed in the brain. Neurotransmitters play a pivotal role in the efficient working of brain cells. They can be synthesized and maintained by balanced nutrition. The aim of the present paper is to review the literature related to the contentious role of nutrients in ADHD. Evidences were reviewed to outline the role of two nutrients-vitamins, and minerals in ADHD. It was concluded that there is a more need of standardized long term clinical trials for drawing a concrete association of these nutrients with ADHD. Also, probably an integrated nutrient approach would be better protocol for combating ADHD than supplementation of single nutrient.

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Int J Environ Res Public Health. 2015;12:6261-80.

AN IPAD-BASED TOOL FOR IMPROVING THE SKILLS OF CHILDREN WITH ATTENTION DEFICIT DISORDER.

Wronska N, Garcia-Zapirain B, Mendez-Zorrilla A.

Attention Deficit Hyperactivity Disorder (ADHD), with a worldwide prevalence of 5.29%null7.1%, is one of the most common neurodevelopmental disorders among children and adolescents. Apart from typical symptoms like inattention, hyperactivity and impulsiveness, patients also evidence attention deficit problems with reading comprehension. This in turn causes poor school performance and widens the gap with peers without ADHD. This paper presents a novel and interactive tool based on Serious Games for Health, whose aim is not only to improve comprehension, but also hold the usernulls attention. This tool is geared towards assessing reading quality and is intended for iPad devices. Preliminary results obtained from the experiment performed to evaluate the game are included in this report. A group of six typically developing children from Colegio Vizcaya aged between 8 and 12 took part in the evaluation of motivation, satisfaction and usability of the same therapy in the new media. Results obtained by participants playing the game were analysed together with questionnaires concerning the usability of the system. Game evaluation resulted in relatively good statistics-average score was 3 points out of 4 and average time for completing the exercise was 59 seconds. A SUS questionnaire with an average score of 92.75 out of 100 indicates that the game presented is user-friendly and an effective tool. Moreover, based on the feedback obtained from participants, the game had been improved and additional functionality introduced. Older participants completed the first game faster than the younger ones, but age was not influential in subsequent games.

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Int J Neuropsychopharmacol. 2014;17:39.

TREATMENT OF ADHD ACROSS THE LIFESPAN: THE PSYCHOTHERAPEUTIC PERSPECTIVE.

Gross-Lesch S.

Objective: Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with profound cognitive, behavioural and psychosocial impairments in multiple domains of personal and professional life frequently persisting across the lifespan. Given a prevalence of 4.4% (NCS-R; Kessler et al., 2005), the persistence of ADHD is associated with a psychiatric comorbidity rate of more than 60% in adults (Jacob et al., 2013). Due to the high prevalence and societal impact ofADHDand the limited effectiveness of existing pharmacologic treatment strategies there is a considerable need for psychotherapeutic treatment options.

Methods: Taking into account the disorder's variable and changing phenotype and also different expectations regarding age-related behaviour the main focus here will be on non-medical options which are propagated in various national and international guidelines. Since for pre-schoolers and school children stimulant medication may - dependent on the severity of symptoms and impairments - not be the first-line treatment, the initial step is to provide information about diagnosis and treatment options to parents or caregivers. Emphasis will be on parental training programs, most often offered as group training. Providing information to teachers should support behavioral interventions at school. With moderate to severe levels of impairment, and for older children individual psychological interventions rather than group training, focus should be put on acquiring social skills with peers, problem solving, self control, listening skills and dealing with and expressing feelings.

Results: For adolescents and adults there are CBT programmes with different therapeutic aims, e.g. comorbidity, disorganisation, or problems with keeping a daily routine. A recent German study used a different therapeutic approach, taking into account some shared symptoms between ADHD and borderline personality disorder. Mindfulness offers a opportunity to improve self-awarness, a typical problem related to the core symptom of inattention, and therefore is the critical step into emotion regulation and improving impulsivity.

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Int J Neuropsychopharmacol. 2014;17:122.

METHYLPHENIDATE IMPROVES HANDWRITING OF CHILDREN WITH ADHD; A SYSTEMATIC REVIEW OF CONTROLLED CLINICAL TRIALS.

Ghanbari M, Ghanizadeh A.

Objective: While many studies compared handwriting ability of children with ADHD and those children without ADHD, contribution of medications on handwriting in children with attention deficit hyperactivity disorder (ADHD) has been sparse. No systematic review examined the role of stimulants in this regard.

Methods: Literature was searched according to a planned search strategy using the electronic databases PubMed and Google scholar. Inclusion criteria were interventional studies investigating the effects of stimulants on handwriting quality in children and adolescents diagnosed with ADHD. Those articles without the intervention were excluded.

Results: Only nine out of 64 retrieved articles met inclusion criteria. The assessments used for handwriting was very heterogeneous to perform a pooled data analysis. Five articles reported double blind control clinical trials. All the controlled and non-controlled clinical trials administered methylphenidate. These trials reported that methylphenidate improved handwriting quality.

Conclusion: Current evidence supports that the use of methylphenidate is an effective option for the treatment of handwriting in children and adolescents with ADHD. Recommendations for future studies considering current literature limitations are provided.

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Int J Pediatr Otorhinolaryngol. 2015.

EFFECT OF ADENOTONSILLECTOMY ON ADHD SYMPTOMS OF CHILDREN WITH ADENOTONSILLAR HYPERTROPHY AND SLEEP DISORDERED BREATHING.

Amiri S, AbdollahiFakhim S, Lotfi A, et al.

Background: Adenotonsillar hypertrophy is the most common etiologic agent for the obstruction of the upper airways in children, which might be associated with attention-deficit hyperactivity disorder (ADHD), one of the most common psychiatric disorders of childhood. Despite the concurrence of these two conditions, i.e., obstruction of the airways and ADHD, no exact etiologic relationship has been established between adenotonsillectomy (AT) and ADHD symptoms. This study was undertaken to evaluate the effect of AT on the ADHD symptoms in children with adenotonsillar hypertrophy and sleep disordered breathing (SDB).

Methods: The design of the present study consisted of pre-test and post-test, followed by post hoc tests. Fifty-three children aged 3-12 were included in this study, selected from those referring to the Pediatric Hospital of Tabriz University of Medical Sciences, with SDB, adenotonsillar hypertrophy and ADHD based on DSM-IV criteria, by availability of the subjects undergoing adenotonsillectomy after evaluation of the severity of ADHD symptoms. The scores of ADHD symptoms were evaluated before AT and at 3- and 6-month postoperative intervals based on Conner's Parent Rating Scale-Revised (CPRS-R) Questionnaire. Repeated-measures ANOVA and Fisher's exact test were used for data analysis.

Results: AT resulted in a significant decrease in the severity of ADHD symptoms (oppositional behavior, cognitive disorders, inattention, hyperactivity and ADHD index) at 3- and 6-month postoperative intervals (P <. 0.001), with more significant decreases at 6-month postoperative interval compared to 3-month interval (P <. 0.001).

Conclusions: Based on the results of this pilot study, AT in children with SDB associated with ADHD resulted in a significant decrease in the severity of ADHD symptoms.

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JAMA Psychiatry. 2015;72:490-99.

DEVELOPMENTALLY STABLE WHOLE-BRAIN VOLUME REDUCTIONS AND DEVELOPMENTALLY SENSITIVE CAUDATE AND PUTAMEN VOLUME ALTERATIONS IN THOSE WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THEIR UNAFFECTED SIBLINGS.

Greven CU, Bralten J, Mennes M, et al.

IMPORTANCE: Attention-deficit/hyperactivity disorder (ADHD) is a heritable neurodevelopmental disorder. It has been linked to reductions in total brain volume and subcortical abnormalities. However, owing to heterogeneity within and between studies and limited sample sizes, findings on the neuroanatomical substrates of ADHD have shown considerable variability. Moreover, it remains unclear whether neuroanatomical alterations linked to ADHD are also present in the unaffected siblings of those with ADHD.

OBJECTIVE: To examine whether ADHD is linked to alterations in whole-brain and subcortical volumes and to study familial underpinnings of brain volumetric alterations in ADHD.

DESIGN, SETTING, AND PARTICIPANTS: In this cross-sectional study, we included participants from the large and carefully phenotyped Dutch NeuroIMAGE sample (collected from September 2009-December 2012) consisting of 307 participants with ADHD, 169 of their unaffected siblings, and 196 typically developing control individuals (mean age, 17.21 years; age range, 8-30 years).

MAIN OUTCOMES AND MEASURES: Whole-brain volumes (total brain and gray and white matter volumes) and volumes of subcortical regions (nucleus accumbens, amygdala, caudate nucleus, globus pallidus, hippocampus, putamen, thalamus, and brainstem) were derived from structural magnetic resonance imaging scans using automated tissue segmentation.

RESULTS: Regression analyses revealed that relative to control individuals, participants with ADHD had a 2.5% smaller total brain ((beta) = -31.92; 95% CI, -52.69 to -11.16; P = .0027) and a 3% smaller total gray matter volume ((beta) = -22.51; 95% CI, -35.07 to -9.96; P = .0005), while total white matter volume was unaltered ((beta) = -10.10; 95% CI, -20.73 to 0.53; P = .06). Unaffected siblings had total brain and total gray matter volumes intermediate to participants with ADHD and control individuals. Significant age-by-diagnosis interactions showed that older age was linked to smaller caudate (P < .001) and putamen (P = .01) volumes (both corrected for total brain volume) in control individuals, whereas age was unrelated to

these volumes in participants with ADHD and their unaffected siblings. Attention-deficit/hyperactivity disorder was not significantly related to the other subcortical volumes.
CONCLUSIONS AND RELEVANCE: Global differences in gray matter volume may be due to alterations in the general mechanisms underlying normal brain development in ADHD. The age-by-diagnosis interaction in the caudate and putamen supports the relevance of different brain developmental trajectories in participants with ADHD vs control individuals and supports the role of subcortical basal ganglia alterations in the pathophysiology of ADHD. Alterations in total gray matter and caudate and putamen volumes in unaffected siblings suggest that these volumes are linked to familial risk for ADHD.

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J Child Adolesc Psychopharmacol. 2015;25:378-79.
THE RELATIONSHIP BETWEEN ACUTE DYSKINESIA WITH A SINGLE DOSE OF METHYLPHENIDATE AND RECENT RISPERIDONE DISCONTINUATION IN A CHILD WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Ince E, Algedik P, Demirdogen ES, et al.

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J Child Adolesc Psychopharmacol. 2015 Mar;25:176-79.
PHARMACOTHERAPEUTIC CHALLENGES IN TREATMENT OF A CHILD WITH 'THE TRIAD' OF OBSESSIVE COMPULSIVE DISORDER, ATTENTION- DEFICIT/HYPERACTIVITY DISORDER AND TOURETTE'S DISORDER.
Rice T, Coffey B.
This article discusses pharmacotherapeutic challenges in treatment of a child with "the triad" of obsessive compulsive disorder, attention- deficit/hyperactivity disorder and Tourette's disorder. J is a 9-year old boy boy with attention-deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), and Tourette's disorder (TD) who was referred for medication management following group cognitive behavioral therapy (CBT) for OCD, which had resulted in dramatically changed symptomatology. The development and evolution of J.'s symptoms and clinical course overtime represents a common but challenging dilemma for child and adolescent psychiatrists. J. had a suboptimal response to social skills group treatment, parent management training, and eventually to a trial of selective serotonin reuptake inhibitor (SSRI) monotherapy. J.'s comorbid anxiety appeared to be the priority for his treatment team at that time; indeed clinicians are frequently in a quest for parsimony: to find one disorder to explain the full presentation of symptoms. As is the case for J., ADHD and OCD symptoms usually cause greater distress and/or impairment in children with TD. The ADHD-OCD-TD triad, described in categorical nosology, may in fact represent one specific neurodevelopmental phenotype. This case demonstrates the unique factors that must be considered when treating a child with the triad of ADHD, OCD, and TD.

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J Child Adolesc Psychopharmacol. 2015 Apr;25:246-53.
NEUROCOGNITIVE PERFORMANCE AND BEHAVIORAL SYMPTOMS IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DURING TWENTY-FOUR MONTHS OF TREATMENT WITH METHYLPHENIDATE.
Wang LJ, Chen CK, Huang YS.
Objective: This study investigated the trends in neurocognitive function and behavioral symptoms among patients with attention-deficit/hyperactivity disorder (ADHD) during 24 months of treatment with methylphenidate in a clinical setting.
Methods: Study participants consisted of 181 ADHD patients with a mean age of 13.4 ± 2.5 years (ages ranged from 8 to 18 years; 151 boys and 30 girls) who were prescribed oral short-acting methylphenidate two or three times daily, with each dose ranging between 0.3 and 1.0 mg/kg. At baseline and 6, 12, 18, and 24 months from baseline, neurocognitive function was assessed using the Test of Variables of Attention (TOVA) on the day the patient was off medication, and behavioral symptoms were evaluated using the Swanson, Nolan, and Pelham Version IV Scale for ADHD (SNAP-IV) parent form, the SNAP-IV teacher form, and the ADHD-Rating Scale (completed by a child psychiatrist).

Results: Of the 181 ADHD patients at the initial visit, 103 (56.9%) completed the study. During the 24-month methylphenidate treatment, only the commission errors in TOVA significantly improved; however, the omission errors, response time, response time variability, response sensitivity, and ADHD score did not. The behavioral symptoms of ADHD, observed by various informants, all declined substantially, and were significantly correlated with each other during the long-term followup. The severity of teacher ratings was lower than that of parent and psychiatrist ratings. However, the teacher-rated inattention symptoms showed the strongest correlations with TOVA performance.
Conclusions: Findings suggest that neurocognitive deficits in ADHD patients, except inhibition ability, might be long lasting in realistic settings. In addition, obtaining behavior profile assessments from multiple informants, especially from teachers, is vital for establishing a complete understanding of ADHD patients.

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J Child Neurol. 2015;30:1000-09.

COGNITIVE IMPROVEMENT OF ATTENTION AND INHIBITION IN THE LATE AFTERNOON IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) TREATED WITH OSMOTIC-RELEASE ORAL SYSTEM METHYLPHENIDATE.

Slama H, Fery P, Verheulpen D, et al.

Long-acting medications have been developed and approved for use in the treatment of attention-deficit hyperactivity disorder (ADHD). These compounds are intended to optimize and maintain symptoms control throughout the day. We tested prolonged effects of osmotic-release oral system methylphenidate on both attention and inhibition, in the late afternoon. A double-blind, randomized, placebo-controlled study was conducted in 36 boys (7-12 years) with ADHD and 40 typically developing children. The ADHD children received an individualized dose of placebo or osmotic-release oral system methylphenidate. They were tested about 8 hours after taking with 2 continuous performance tests (continuous performance test-X [CPT-X] and continuous performance test-AX [CPT-AX]) and a counting Stroop. A positive effect of osmotic-release oral system methylphenidate was present in CPT-AX with faster and less variable reaction times under osmotic-release oral system methylphenidate than under placebo, and no difference with typically developing children. In the counting Stroop, we found a decreased interference with osmotic-release oral system methylphenidate but no difference between children with ADHD under placebo and typically developing children.

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J Clin Psychiatry. 2015;76:599-606.

LONGITUDINAL TRAJECTORIES OF ADHD SYMPTOMATOLOGY IN OFFSPRING OF PARENTS WITH BIPOLAR DISORDER AND COMMUNITY CONTROLS.

Kim J-W, Yu H, Ryan ND, et al.

Objective: To compare the psychopathology and longitudinal course of attention-deficit/hyperactivity disorder (ADHD) symptomatology and global functioning between the offspring with ADHD of parents with bipolar disorder and the offspring with ADHD of community control parents.
Method: One hundred twenty-two offspring with ADHD of parents with bipolar disorder and 48 offspring with ADHD of control parents from the Pittsburgh Bipolar Offspring Study (BIOS) were included. DSM-IV lifetime psychiatric disorders were ascertained through the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL). The outcome measures of ADHD symptoms were ascertained at intake and every other year for a period of 6 years using the ADHD section of the K-SADS-PL and the Disruptive Behavior Disorder rating scale (DBD). Global functioning was assessed using the Children's Global Assessment Scale (CGAS).
Results: The offspring with ADHD of parents with bipolar disorder showed higher lifetime prevalence of mood and anxiety disorders relative to the offspring with ADHD of control parents (P values (less-than or equal to) .03). For both groups of offspring with ADHD, the hyperactivity, impulsivity, and total K-SADS-PL ADHD scores decreased over time (P values < .001) without differences between the 2 groups. There were no between- or within-group differences in the inattention scores over time. The DBD ADHD scores

decreased with age in both groups (P values < .002) without differences between the 2 groups. For both groups of offspring with ADHD, the global functioning did not improve over time.
Conclusions: Offspring with ADHD of parents with bipolar disorder have more psychopathology relative to offspring with ADHD of control parents. However, there were no differences in the developmental courses of ADHD symptomatology between these 2 groups of ADHD youth.

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J Consult Clin Psychol. 2015.
A NATIONAL EVALUATION OF PARENTING PROGRAMS IN SWEDEN: THE SHORT-TERM EFFECTS USING AN RCT EFFECTIVENESS DESIGN.
Stattin H, Enebrink P, onullzdemir M, et al.
Objective: We evaluated the effectiveness of 4 parent-training programs for children with externalizing problems. We tested the effectiveness of 3 behavioral programs (Comet, Cope, and Incredible Years) and 1 nonbehavioral program (Connect) in reducing child behavior problems and attention-deficit/hyperactivity disorder (ADHD) symptoms, in improving positive parenting and parenting competence, and in decreasing negative parenting and parents' stress and depressive symptoms.
Method: This national study was designed as a randomized-controlled effectiveness trial (RCT). The treatments were carried out in 30 clinical and community-based practices. Parents of 908 children (ages 3-12 years) were randomly assigned to 1 of 2 parent training programs available at each practice, or to a wait-list condition, where parents had sought help from regular services. Before and after treatment, parents rated child behavior problems and parenting strategies.
Results: At posttreatment, children whose parents had received interventions showed a strong decrease in child conduct problems and a moderate to strong decrease in ADHD symptoms. About half of parents whose children scored over the 95th percentile on the behavior measures (Eyberg Child Behavior Inventory, Swanson, Nolan, and Pelham Rating Scale), a clinically meaningful cutoff, reported that their children were no longer above the cutoff after the intervention. Parents showed considerably less negative behaviors toward their children at posttest compared with pretest; they increased in parental competence, and decreased in both stress and depressive symptoms. Overall, the behavioral programs were more effective than the nonbehavioral program.
Conclusions: The results support the general efficacy of parent training in a short-term perspective.

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J Managed Care Pharm. 2015;21:486-98.
PREDICTORS OF CONCOMITANT USE OF ANTIPSYCHOTICS AND STIMULANTS AND ITS IMPACT ON STIMULANT PERSISTENCE IN PEDIATRIC ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Bali V, Kamble PS, Aparasu RR.
BACKGROUND: Concomitant use of stimulants and atypical antipsychotics is common in pediatric attention deficit hyperactivity disorder (ADHD). However, little is known about the determinants of concomitant use and its utility in the management of pediatric ADHD.
OBJECTIVES: To (a) examine predictors of concomitant stimulant and atypical antipsychotic use and (b) evaluate the impact of concomitant atypical antipsychotic use on the persistence of stimulants in children and adolescents diagnosed with ADHD.
METHODS: The retrospective cohort study was conducted using 4 years (January 2004-December 2007) of IMS LifeLink claims data. The study population included children and adolescents aged 6-16 years with a diagnosis of ADHD and those who initiated long-acting stimulants (LAS) from July 2004 to December 2006. Patients were followed for 1 year after index stimulant use. Concomitant use was defined as the concurrent prescription for LAS and atypical antipsychotic agents with at least 14 days overlap after the index LAS claim. Persistence was measured by summing the total number of days a patient remained on the index LAS from the index prescription date with an allowable gap of no more than 30 days. Multiple logistic regression within the conceptual framework of the Andersen Behavioral Model was performed to determine the predictors of concomitant stimulant and atypical antipsychotic use. Multivariate Cox

proportional hazards regression within the conceptual framework of the Andersen Behavioral Model was used to examine the impact of concomitant atypical antipsychotic use on persistence of stimulants.
RESULTS: The study cohort consisted of 39,981 children who initiated LAS treatment. Most (96.10%) received LAS monotherapy, and 3.90% received LAS and atypical antipsychotic concomitantly. The multiple logistic regression analysis found that gender, health insurance, region, year of cohort entry, season, physician specialty, coexisting mental health conditions, and general mental health status influenced the concomitant use of LAS and atypical antipsychotic agents. Bivariate analyses revealed that concomitant users had longer persistence (by 71 days) than the stimulant-alone users. Cox proportional hazards regression revealed that concomitant atypical antipsychotic was associated with improvement in LAS persistence by 15% (HR = 0.85, 95% CI = 0.76-0.94) in comparison with the LAS recipients who did not use atypical antipsychotic concomitantly. Other factors such as age, region, season, coexisting mental health conditions, use of comedications, and general mental health status influenced the LAS treatment persistence among children and adolescents.
CONCLUSIONS: Various predisposing, enabling, and need factors were associated with the concomitant stimulant and atypical antipsychotic use. Concomitant use of atypical antipsychotics was associated with improved LAS treatment persistence in children and adolescents with ADHD.

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J Pharmacokinet Pharmacodyn. 2014;42:45-65.
MODELING AND SIMULATION OF THE EXPOSURENULLRESPONSE AND DROPOUT PATTERN OF GUANFACINE EXTENDED-RELEASE IN PEDIATRIC PATIENTS WITH ADHD.
Knebel W, Rogers J, Polhamus D, et al.
Guanfacine extended-release (GXR) is a selective (alpha)<inf>2A</inf>-adrenergic receptor agonist approved in the United States for once-daily administration for the treatment of attention-deficit hyperactivity disorder (ADHD) in children and adolescents ages 6null17 years old either as monotherapy or adjunctive to stimulant medications. This analysis integrates exposurenullresponse, placebo, and dropout data from 10 clinical trials that used GXR in adolescents and children with ADHD. In these trials, the ADHD Rating Scale-IV (ADHD RS-IV) score was collected longitudinally within patients over the course of 6null13 weeks. Non-linear mixed effects models were developed and used to describe the exposurenullresponse of the GXR and placebo time course. The OpenBUGS program was utilized to describe the dropout time course across the trials. Placebo time course was best described by an inverse Bateman function with a 3-group mixture model that allowed for the onset and offset of the placebo response. Dropout time modeling indicated a missing at random mechanism for dropouts which was best described by a Weibull distribution with an estimated percentage of non-dropout patients. A linear exposurenullresponse model with an adolescent effect on maximum slope (SLP<inf>max</inf>), and a time delay for reaching SLP<inf>max</inf>, provided the best description of the GXR exposurenullresponse time course. The GXR exposurenullresponse model indicated that the typical (95 % confidence interval) decrease in ADHD RS-IV score from the placebonullresponse trajectory would be 37.1 % (32.2, 42.0 %) per 0.1 mg/kg of GXR exposure. There was little noticeable difference between the exposurenullresponse in adolescents and children or across ADHD subtypes.

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J Psychopathol Behav Assess. 2015;37:196-206.
EXAMINING THE ROLE OF CALLOUS-UNEMOTIONAL TRAITS IN THE ATTRIBUTIONAL STYLES AND SELF COMPETENCE EVALUATIONS OF CHILDREN WITH CONDUCT PROBLEMS AND ADHD.
Haas SM, Waschbusch DA, King S, et al.
It is now well established that there are important behavioral differences between conduct problem (CP) children with and without callous-unemotional traits (CU). Although various externalizing symptoms are differentially related to how youth perceive or explain their own behaviors (e.g., self-perceptions), no research has yet examined whether children with CP-only differ from children with CP/CU in how they perceive or explain their own behaviors. The current study addressed this topic by examining the self-

perceptions and attributions for positive and negative social situations of CP children with and without CU traits. Participants were 72 (76 % boys) elementary school-aged children (M = 9.72, SD = 1.65) who were divided into three groups: typically developing controls (n = 17), CP/ADHD-only (n = 40), or CP/ADHD-CU (n = 15). Results showed that, compared to other groups, children in the CP/ADHD-CU group had lower global self worth yet equal (or higher) pereceived self-competence about their behavior conduct. In addition, the CP/ADHD-CU group made stronger attributions to their own behavior problems as a reason for negative social outcomes, and they made strong external attributions for both negative and positive outcomes. These differences were significant after controlling for depression, narcissism, and CP. These findings may suggest that children with CP/ADHD-CU do not feel as badly as typically developing children about their misbehavior and are thus unmotivated to change it.

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J Psychopathol Behav Assess. 2015.

PLAY BEHAVIOR DIFFERENCES AMONG PRESCHOOLERS WITH ADHD: IMPACT OF COMORBID ODD AND ANXIETY.

Pollack B, Hojnoski R, Dupaul GJ, et al.

The acquisition of positive peer play behavior is an important aspect of child development and an indicator of social competence. Engaging in peer play may pose challenges for children with internalizing and externalizing disorders, particularly those with comorbid disorders. Existing literature contains little information on the peer play behaviors of children with attention-deficit/hyperactivity disorder (ADHD), and even less research is available examining the play behaviors of children with comorbid disorders. The present study assessed the peer play behaviors and social competence of 107 preschoolers with varying combinations of ADHD, oppositional defiant disorder (ODD), and anxiety symptoms. Assessment methods included direct observations and teacher ratings of child behavior. Results indicated there were no differences in observed peer play behaviors or negative behaviors toward peers, but there were differences in teacher-rated social competence between the groups. Results are discussed in terms of assessment method variations as well as directions for additional research in this critical area and implications for practice.

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J Am Acad Child Adolesc Psychiatry. 2015;54:550-56.

PHARMACOTHERAPY OF THE PRESCHOOL ADHD TREATMENT STUDY (PATS) CHILDREN GROWING UP.

Vitiello B, Lazzaretto D, Yershova K, et al.

Objective To describe the long-term psychopharmacological treatment of children first diagnosed with attention-deficit/hyperactivity disorder (ADHD) as preschoolers.

Method In a systematic, prospective, naturalistic follow-up, 206 (68.0%) of the 303 children who participated in the Preschool ADHD Treatment Study (PATS) were reassessed 3 years (mean age 7.4 years) and 179 (59.1%) were reassessed 6 years (mean age 10.4 years) after completion of the controlled study. Pharmacotherapy and clinical data were obtained from the parents. Pharmacotherapy was defined as use of a specific class of medication for at least 50% of the days in the previous 6 months.

Results At year 3, a total of 34.0% of the participants were on no pharmacotherapy, 41.3% were on stimulant monotherapy, 9.2% were on atomoxetine alone or with a stimulant, 8.3% were on an antipsychotic usually together with a stimulant, and the remaining 7.2% were on other pharmacotherapy; overall, 65.0% were on an indicated ADHD medication. At year 6, a total of 26.8% of the participants were on no pharmacotherapy, 40.2% were on stimulant monotherapy, 4.5% were on atomoxetine alone or with a stimulant, 13.4% were on an antipsychotic, and 15.1% were on other pharmacotherapy; overall, 70.9% were on an indicated ADHD medication. Antipsychotic treatment was associated with more comorbidity, in particular disruptive behavior disorders and pervasive development disorders, and a lower level of functioning.

Conclusion In this study, the long-term pharmacotherapy of preschoolers with ADHD was heterogeneous. Although stimulant medication continued to be used by most children, about 1 child in 4 was off medication, and about 1 in 10 was on an antipsychotic.

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J Am Acad Child Adolesc Psychiatry. 2015;54:571-79.

PRESCHOOL ATTENTION-DEFICIT/HYPERACTIVITY AND OPPOSITIONAL DEFIANT PROBLEMS AS ANTECEDENTS OF SCHOOL BULLYING.

Verlinden M, Jansen PW, Veenstra R, et al.

Objective To examine whether early manifestations of attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) increase children's later risk of bullying or victimization.

Method Using a population-based, prospective cohort, our multi-informant approach comprised reports of parents, teachers, and peers. ADHD and ODD behavioral problems at ages 1.5, 3, and 5 years were determined from parental reports on the Child Behavior Checklist. Later bullying behavior at school was reported by teachers using a questionnaire (n = 3,192, mean age 6.6 years), and by peer/self-reports using peer nominations (n = 1,098, mean age 7.6 years). We examined the following: whether problem behavior scores at age 1.5, 3, or 5 years predicted a risk of bullying involvement; and whether high or increasing behavioral problems throughout ages 1.5 to 5 years were associated with bullying involvement at school. Analyses were adjusted for a range of child and maternal covariates.

Results Behavioral problems at a young age each predicted later bullying involvement at school. For example, higher ADHD problem scores at age 3 years were associated with the risks of becoming a bully or a bully-victim (OR<inf>BULLY</inf> = 1.20, 95% CI = 1.07-1.35 [teacher report], OR<inf>BULLY-VICTIM</inf> = 1.28, 95% CI = 1.14-1.43 [teacher report], and OR<inf>BULLY-VICTIM</inf> = 1.35, 95% CI = 1.03-1.78 [peer/self-report]). Children whose behavioral problem scores were high or increased over time consistently had elevated risks of becoming a bully or a bully-victim.

Conclusion Behavioral problems at a young age may predispose children to bullying involvement in early elementary school.

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J Am Acad Child Adolesc Psychiatry. 2015;54:565-70.

IS PHYSICAL ACTIVITY CAUSALLY ASSOCIATED WITH SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER?

Rommel A-S, Lichtenstein P, Rydell M, et al.

Objective Emerging evidence suggests that physical activity (PA) enhances cognition and may be a protective factor for attention-deficit/hyperactivity disorder (ADHD). Yet the impact of PA on ADHD symptoms has been investigated only in a few undersized, nonrandomized, and retrospective studies. We examined the effect of PA during late adolescence on ADHD symptoms in early adulthood while controlling for unmeasured genetic and shared environmental confounding.

Method The effect of PA at age 16 to 17 years (baseline) on ADHD symptoms at age 19 to 20 years (follow-up) was examined using a within-monozygotic (MZ) twins fixed-effects model in 232 MZ twin pairs born in Sweden between May 1985 and December 1986. Parents rated their children's DSM ADHD symptoms at baseline and follow-up. Participants' weekly energy expenditure (in metabolic equivalent task minutes per week) was based on self-reports at baseline of PA frequency, intensity, and duration.

Results Greater weekly energy expenditure in adolescence was significantly associated with reduced ADHD symptom levels in early adulthood, even when controlling for unmeasured confounding (all genetic and environmental factors shared within MZ twin pairs) as well as ADHD symptoms and body mass index (BMI) at baseline, (beta) = -0.21, p =.013 (95% CI = -0.38 to -0.05). Similar results were observed for the 2 ADHD subcomponents: hyperactivity/impulsivity, (beta) = -0.21, p =.022 (95% CI = -0.39 to -0.03), and inattention, (beta) = -0.19, p =.049 (95% CI = -0.36 to -0.0005).

Conclusion In line with a causal hypothesis, PA was inversely associated with ADHD symptoms, even after adjusting for unmeasured confounding. These findings suggest that PA in adolescence might

decrease ADHD symptoms in early adulthood. However, given the size of the effect, the clinical value of this intervention needs to be explored further.

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NeuroImage Clin. 2015;8:390-97.

DIFFERENTIATING SCT AND INATTENTIVE SYMPTOMS IN ADHD USING FMRI MEASURES OF COGNITIVE CONTROL.

Fassbender C, Krafft CE, Schweitzer JB.

Attention Deficit/Hyperactivity Disorder (ADHD) is associated with different impairment profiles in the symptom domains of hyperactivity/impulsivity and/or inattention. An additional symptom domain of sluggish cognitive tempo (SCT) has also been proposed. Although there is a degree of correlation between the SCT symptom domain and inattention, it has been proposed as a distinct disorder independent of ADHD. The objective of this study was to examine the neural substrates of cue-related preparatory processes associated with SCT symptoms versus inattentive symptoms in a group of adolescents with ADHD. We also compared cue-related effects in the entire ADHD group compared with a group of typically developing (TD) peers. A modified cued flanker paradigm and fMRI examined brain activity associated with attention preparation and motor response preparation. Between group contrasts between the ADHD and TD group revealed significant hypoactivity in the ADHD group during general attention preparation in the supplementary motor area (SMA) and in the right superior parietal lobe (SPL) during response preparation. In the ADHD group, greater numbers of SCT symptoms were associated with hypoactivity in the left SPL to cues in general whereas greater numbers of inattentive symptoms were associated with greater activity in the SMA to cues that provided no information and less activity in the thalamus during response preparation. Hypoactivity in the SPL with increasing SCT symptoms may be associated with impaired reorienting or shifting of attention. Altered activity in the SMA and thalamus with increasing inattention may be associated with a general problem with response preparation, which may also reflect inefficient processing of the response preparation cue. Our results support a degree of differentiation between SCT and inattentive symptom profiles within adolescents with ADHD.

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Neurology. 2015;84.

MULTIPLE PAST CONCUSSIONS IN HIGH SCHOOL ATHLETES WITH ADHD.

Wojtowicz M, Iverson G, Mannix R, et al.

OBJECTIVE: To examine cognitive functioning and symptom reporting associated with multiple concussions in male high school athletes with Attention Deficit Hyperactivity Disorder (ADHD).

BACKGROUND: ADHD and history of multiple concussions are important risk factors or modifiers to consider in concussion assessment and management. Current evidence suggests that individuals with ADHD have a higher lifetime prevalence of concussions. To date, however, there are no published studies examining the association between multiple prior concussions, cognition, and symptom reporting in student athletes with ADHD.

DESIGN/METHODS: High school boys with ADHD (N=1,261) completed ImPACT(registered trademark) baseline testing prior to participating in sports. Cognitive test performance and symptom reporting was compared between athletes with ADHD who reported a history of 0, 1, 2, or 3 or more concussions. No athlete reported experiencing a concussion in the past 6 months.

RESULTS: The majority (76.0[percnt]; n=958) of the ADHD sample reported a history of no previous concussions, 15.2[percnt] (n=192) reported a history of 1 concussion, 4.8[percnt] (n=61) reported a history of 2 concussions, and 4.0[percnt] (n=50) reported a history of 3 or more concussions. ImPACT(registered trademark) cognitive composite scores (i.e., verbal memory, visual memory, visual motor, and reaction time) were relatively consistent across these subgroups; those with prior injuries did not perform more poorly than those with no prior injuries. However, athletes with a history of 3 or more prior concussions reported significantly more symptoms at baseline.

CONCLUSIONS: To our knowledge, this is the first large-scale study examining cognitive performance and symptom reporting associated with concussion history in high school athletes with ADHD. Consistent with

previous findings in young athletes with multiple concussions, athletes with ADHD and a history of multiple concussions reported greater symptoms than those with no concussion history.

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Neurology. 2015;84.

VISUAL PERFORMANCE TESTING IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Mueller B, Baner N, Leong D, et al.

OBJECTIVE: Using the King-Devick (K-D) test, a vision-based test of rapid number naming that requires saccades and visual processing, we investigated whether children with Attention Deficit Disorder (ADHD) had worse scores compared to similar aged matched controls.

BACKGROUND: In sideline studies of youth and collegiate athletes with concussion, the K-D test consistently demonstrates higher (worse) time scores post-injury compared to pre-season baseline scores. There is growing evidence that, like concussion and mild traumatic brain injury, ADHD may be associated with visual pathway dysfunction.

DESIGN/METHODS: Time required to complete the K-D test, a 1-2minute test that measures speed of rapid number naming, were collected from patients diagnosed with ADHD (5-21 years of age) seeking care from the NYU Neurology Faculty Group Practice and Child Study Center. Analyses compared K-D scores of patients with ADHD to those of pre-season baseline K-D scores for student-athlete controls matched for age and gender. Participants with known history of previous concussion or visual impairment were excluded.

RESULTS: Among 134 participants in this study, ADHD vs. control status was significantly associated with higher K-D test time scores ($p<0.001$, logistic regression models, accounting for age). Patients with ADHD took an average of 17 seconds longer to complete the K-D test (81.2 seconds for ADHD vs. 63.9 seconds for controls, $p<0.001$, two-sample t-test). Current or previous use of stimulant medications was not associated with differences in K-D time scores within the cohort of patients with ADHD.

CONCLUSIONS: These findings provide evidence that that the visual pathways may perform differently in children with ADHD compared to similar aged student athletes. Correlation of K-D performance test scores with measures from electronic eye movement recordings will help to further characterize the nature of visual pathway involvement in children with ADHD.

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Neurophotonics. 2014;1.

NEUROPHARMACOLOGICAL EFFECT OF METHYLPHENIDATE ON ATTENTION NETWORK IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER DURING ODDBALL PARADIGMS AS ASSESSED USING FUNCTIONAL NEAR-INFRARED SPECTROSCOPY.

Nagashima M, Monden Y, Dan I, et al.

The current study aimed to explore the neural substrate for methylphenidate effects on attentional control in school-aged children with attention deficit hyperactivity disorder (ADHD) using functional near-infrared spectroscopy (fNIRS), which can be applied to young children with ADHD more easily than conventional neuroimaging modalities. Using fNIRS, we monitored the oxy-hemoglobin signal changes of 22 ADHD children (6 to 14 years old) performing an oddball task before and 1.5 h after methylphenidate or placebo administration, in a randomized, double-blind, placebo-controlled, crossover design. Twenty-two age-and gender-matched normal controls without methylphenidate administration were also monitored. In the control subjects, the oddball task recruited the right prefrontal and inferior parietal cortices, and this activation was absent in premedicated ADHD children. The reduced right prefrontal activation was normalized after methylphenidate but not placebo administration in ADHD children. These results are consistent with the neuropharmacological effects of methylphenidate to upregulate the dopamine system in the prefrontal cortex innervating from the ventral tegmentum (mesocortical pathway), but not the noradrenergic system from the parietal cortex to the locus coeruleus. Thus, right prefrontal activation would serve as an objective neurofunctional biomarker to indicate the effectiveness of methylphenidate on ADHD

children in attentional control. fNIRS monitoring enhances early clinical diagnosis and the treatment of ADHD children, especially those with an inattention phenotype.

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Neurophotonics. 2014;1.

NEUROPHARMACOLOGICAL EFFECT OF ATOMOXETINE ON ATTENTION NETWORK IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER DURING ODDBALL PARADIGMS AS ASSESSED USING FUNCTIONAL NEAR-INFRARED SPECTROSCOPY.

Nagashima M, Monden Y, Dan I, et al.

The current study aimed to explore the neural substrate for atomoxetine effects on attentional control in school-aged children with attention deficit hyperactivity disorder (ADHD) using functional near-infrared spectroscopy (fNIRS), which can be applied to young children with ADHD more easily than conventional neuroimaging modalities. Using fNIRS, we monitored the oxy-hemoglobin signal changes of 15 ADHD children (6 to 14 years old) performing an oddball task before and 1.5 h after atomoxetine or placebo administration, in a randomized, double-blind, placebo-controlled, crossover design. Fifteen age-, gender-, and intelligence quotientmatched normal controls without atomoxetine administration were also monitored. In the control subjects, the oddball task recruited the right prefrontal and inferior parietal cortices. The right prefrontal and parietal activation was normalized after atomoxetine administration in ADHD children. This was in contrast to our previous study using a similar protocol showing methylphenidate-induced normalization of only the right prefrontal function. fNIRS allows the detection of differential neuropharmacological profiles of both substances in the attentional network: the neuropharmacological effects of atomoxetine to upregulate the noradrenergic system reflected in the right prefrontal and inferior parietal activations and those of methylphenidate to upregulate the dopamine system reflected in the prefrontal cortex activation.

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Neurosci Lett. 2015;600:45-49.

NEUROANATOMICAL DEFICITS CORRELATE WITH EXECUTIVE DYSFUNCTION IN BOYS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

He N, Li F, Li Y, et al.

Previous structural imaging studies have revealed gray matter volume abnormalities to reflect the etiology of attention deficit hyperactivity disorder (ADHD), however, which are confounded by age, medication and comorbidity and also ignore the core feature of brain structure in the executive impairments of ADHD. In the present study, we explored gray matter volume abnormalities in male children and adolescents with ADHD who were drug-naive and without comorbidities, and tried to connect structural data and behavioral executive dysfunction to provide more information regarding the brain-behavior relationships in ADHD. Seventy-two male subjects (37 patients and 35 controls) underwent three-dimensional high-resolution structural magnetic resonance imaging and executive function assessments, including the Stroop Color-Word Test and Wisconsin Card Sorting Test (WCST). Voxel-based morphometry with diffeomorphic anatomical registration through exponentiated Lie algebra was used to identify gray matter volume differences between the ADHD and controls. Correlation analyses were performed to identify neuroanatomical deficits that were associated with executive dysfunctions. Significantly reduced gray matter volumes were identified in the right orbitofrontal cortex, right primary motor/premotor cortex, left anterior cingulate cortex and left posterior midcingulate cortex of ADHD patients compared with controls (P<. 0.05, corrected for family-wise errors). In patients group, the gray matter volumes of the right orbitofrontal cortex and left posterior midcingulate cortex were positively correlated with the completed categories on the WCST, and the gray matter volume of the left posterior midcingulate cortex was negatively correlated with the total and non-perseverative errors on the WCST (P<. 0.05). The present findings show gray matter volume reductions in motor regions as well as the orbitofrontal and cingulate cortex; this evidence supports theories that suggest frontal abnormalities in children and adolescents with

ADHD at early illness stage. The correlations between structural abnormalities and executive dysfunction suggest that neuroanatomical substrate deficits are implicated in the pathophysiology of ADHD.

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Noropsikiyatr Ars. 2015;52:185-93.

ANXIETY DISORDERS COMORBIDITY IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Gumus YY, Cakin MN, Agaoglu B.

Introduction: Our aim is to investigate the prevalence of comorbidity of anxiety disorders (AD) among patients newly diagnosed with attention deficit hyperactivity disorder (ADHD) and to compare symptom severity of ADHD and sociodemographic parameters between patients with and without AD.

Methods: Among 1683 children and adolescents admitted to Kocaeli University Medical Faculty, Child and Adolescent Mental Health Outpatient Clinic, 447 children and adolescents, who were preliminarily diagnosed as ADHD by clinical interview based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), were invited to participate in the second phase of the study. Kiddie Schedule for Affective Disorder and Schizophrenia, Present and Lifetime-Turkish Version were applied to children and adolescents with ADHD and one of their parents to support the diagnoses of both ADHD and AD. Mothers, fathers, and teachers of the children were asked to complete DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale.

Results: Our study group comprised 170 children and adolescents diagnosed with ADHD of whom 19.4% were girls and 80.6% were boys; 27.6% of patients diagnosed with ADHD showed AD comorbidity. Age of the parents at birth of the patients with AD was significantly lower than that of patients without AD.

Conclusion: In line with the previous studies, the comorbidity rate of AD was found to be higher among patients with ADHD than general population and clinical sample without ADHD. The possibility of comorbidity of AD in patients with ADHD should be considered because higher rates of AD are observed in ADHD and comorbidities of AD.

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Paediatrics and Child Health (Canada). 2015;20:200-02.

MISDIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: 'NORMAL BEHAVIOUR' AND RELATIVE MATURITY.

Ford-Jones PC.

Attention deficit hyperactivity disorder (ADHD) is one of the most frequently diagnosed disorders in children, yet it remains poorly understood. Substantial controversy exists regarding correct diagnosis of ADHD, and areas of subjectivity in diagnosis have been identified. Concerns for appropriate diagnosis are critical in terms of children's educational outcomes, as well as health concerns associated with the use and potential overuse of stimulant medications. There exists a relative-age effect in which children who are relatively younger than their peers and born closest to the school start age cut-off are more frequently diagnosed and treated for ADHD. Additionally, substantial variation exists in ADHD diagnosis between boys and girls, with boys often presenting with more stereotypical symptoms. Both the relativeage effect and variation in sex diagnosis, as well as the challenges of early preschool diagnosis, emphasize the importance of considering relative maturity in ADHD diagnosis of children. Implications and knowledge translation strategies for practitioners, parents and the education system are presented.

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Patient. 2015;8:269-81.

UNMET NEEDS ASSOCIATED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN EIGHT EUROPEAN COUNTRIES AS REPORTED BY CAREGIVERS AND ADOLESCENTS: RESULTS FROM QUALITATIVE RESEARCH.

Sikirica V, Flood E, Dietrich CN, et al.

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by inattention, impulsivity, and hyperactivity, the levels of which are inappropriately high for an individualnulls developmental age.
Objective: The objective of this study was to explore the unmet needs of children/adolescents with ADHD and their caregivers in eight European countries.
Methods: Semi-structured interviews with 38 caregivers of children/adolescents (aged 6null17 years) with ADHD and no or less serious comorbidities and 28 adolescents (aged 13null17 years) with ADHD and no or less serious comorbidities were conducted, audio-recorded, transcribed into English, and coded for analysis.
Results: Caregivers reported their own ADHD-related issues, including making personal accommodations, such as limiting activities and spending extra time/effort caring for their child/adolescent, social impacts, and strained relationships. Medication was generally considered helpful; however, most children experience core ADHD symptoms while on medication (reported by 88 % of caregivers and 100 % of adolescents). Adolescents often reported schoolwork difficulties (96 %) and peer issues (75 %), while caregivers reported school issues (84 %) and peer difficulties (79 %). Caregivers reported minimal ADHD education and community support. Caregivers (29 %) and adolescents (54 %) desired medication that better controlled symptoms but had concerns about being oversubdued. Caregivers reported concerns about adverse effects (21 %).
Conclusions: European caregivers of children/adolescents with ADHD identified multiple unmet needs, which persist despite treatment. Adolescents noted impacts on school and social interactions consistent with caregivers. Future research is needed to quantify the study findings, and, ultimately, ease the impact of ADHD on patients and their caregivers.

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PeerJ. 2015;2015.

LONGITUDINAL RELATIONS AMONG INATTENTION, WORKING MEMORY, AND ACADEMIC ACHIEVEMENT: TESTING MEDIATION AND THE MODERATING ROLE OF GENDER.

Gray SA, Rogers M, Martinussen R, et al.

Introduction: Behavioral inattention, working memory (WM), and academic achievement share significant variance, but the direction of relationships across development is unknown. The aim of the present study was to determine whether WMmediates the pathway between inattentive behaviour and subsequent academic outcomes.
Methods: 204 students from grades 1-4 (49.5% female) were recruited from elementary schools. Participants received assessments of WM and achievement at baseline and one year later.WMmeasures included a visual-spatial storage task and auditory-verbal storage and manipulation tasks. Teachers completed the SWAN behaviour rating scale both years.Mediation analysis with PROCESS (Hayes, 2013) was used to determine mediation pathways.
Results: Teacher-rated inattention indirectly influenced math addition fluency, subtraction fluency and calculation scores through its effect on visual-spatial WM, only for boys. There was a direct relationship between inattention and math outcomes one year later for girls and boys. Children who displayed better attention had higherWMscores, and children with higherWMscores had stronger scores on math outcomes. Bias-corrected bootstrap confidence intervals for the indirect effects were entirely below zero for boys, for the three math outcomes.WMdid not mediate the direct relationship between inattention and reading scores.
Discussion: Findings identify inattention and WM as longitudinal predictors for math addition and subtraction fluency and math calculation outcomes one year later, with visual-spatialWMas a significant mediator for boys. Results highlight the close relationship between inattention andWMand their importance in the development of math skills.

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PLoS ONE. 2015;10.

INTERVAL TIMING DEFICITS ASSESSED BY TIME REPRODUCTION DUAL TASKS AS COGNITIVE ENDOPHENOTYPES FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hwang-Gu S-L, Gau SSF.

The literature has suggested timing processing as a potential endophenotype for attention deficit/hyperactivity disorder (ADHD); however, whether the subjective internal clock speed presented by verbal estimation and limited attention capacity presented by time reproduction could be endophenotypes for ADHD is still unknown. We assessed 223 youths with DSM-IV ADHD (age range: 10-17 years), 105 unaffected siblings, and 84 typically developing (TD) youths using psychiatric interviews, intelligence tests, verbal estimation and time reproduction tasks (single task and simple and difficult dual tasks) at 5-second, 12-second, and 17-second intervals. We found that youths with ADHD tended to overestimate time in verbal estimation more than their unaffected siblings and TD youths, implying that fast subjective internal clock speed might be a characteristic of ADHD, rather than an endophenotype for ADHD. Youths with ADHD and their unaffected siblings were less precise in time reproduction dual tasks than TD youths. The magnitude of estimated errors in time reproduction was greater in youths with ADHD and their unaffected siblings than in TD youths, with an increased time interval at the 17-second interval and with increased task demands on both simple and difficult dual tasks versus the single task. Increased impaired time reproduction in dual tasks with increased intervals and task demands were shown in youths with ADHD and their unaffected siblings, suggesting that time reproduction deficits explained by limited attention capacity might be a useful endophenotype of ADHD.

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Psychiatr Psychol Klin. 2014;14:277-83.

THE MEASUREMENT OF THE SYMPTOMS OF ADHD IN THE NICHQ VANDERBILT ASSESSMENT SCALE FOR PARENT (VADPRS) AND FOR TEACHER (VADTRS).

Kadziela-Olech H.

The presence of several inattentive or hyperactive, impulsive symptoms in two or more situations (at home, school, in other activities) is required for the diagnosis of attention deficit hyperactivity disorder. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning. The National Initiative for Children's Healthcare Quality, American Academy of Pediatrics, recommended a toolkit with standardized assessment scales: NICHQ Vanderbilt Assessment Scale - Parent Informant (VADPRS) and NICHQ Vanderbilt Assessment Scale - Teacher Informant (VADTRS), each divided into two sections: symptoms and performance. The aim of the research was to determine whether there is a correlation between categorial symptoms of attention deficit hyperactivity disorder and results obtained in the assessment scales: VADPRS and VADTRS, and a comparative analysis of assessments made by parents and teachers regarding the symptoms and performance of children diagnosed with attention deficit hyperactivity disorder. The study group comprised 132 children (87.1% of boys, 12.9% of girls) with attention deficit hyperactivity disorder, aged between 6 and 12 years (mean age: 9.29 years; SD 1.96) who had been referred for specialized psychiatric diagnosis and therapy to the Day Care Psychiatric Unit. Diagnoses of attention deficit hyperactivity disorder were conducted pursuant to DSM-IV criteria. Each child with attention deficit hyperactivity disorder was assessed by its parent and teacher using the VADPRS and VADTRS. The statistical analysis (based on Statistica, StatSoft 10) revealed high correlations between categorial DSM-IV symptoms and VADPRS/VADTRS. These tools can be helpful in diagnosis, treatment and evaluation of the effects of therapy in children with attention deficit hyperactivity disorder.

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Psychiatry, Psychology and Law. 2015;22:407-16.

ADULT ATTENTION DEFICIT DISORDER AND AGGRESSIVE BEHAVIOUR: AN EXPLORATION OF RELATIONSHIPS BETWEEN BROWN ATTENTION-DEFICIT DISORDER SCALES AND THE AGGRESSION QUESTIONNAIRE.

Byrne K, Parletta N, Webster DG, et al.

Aggressive and violent behaviour is often associated with a diagnosis of attention-deficit hyperactivity disorder (ADHD). This article investigates the relationship between adult attention deficit disorder (ADD) and aggressive cognitions. The Aggression Questionnaire and the Brown Attention-Deficit Disorder Scales were administered to two samples: a nulllow-risk samplenull comprising university students (n = 60), and a nullhigh-risk samplenull of prison inmates (n = 117). The prevalence of nullprobable ADDnull was found to be higher in the prison sample (33%), compared with the university sample (20%). There were moderate correlations >r =.5 (p < .01) between total ADHD and Aggression Questionnaire scores in both groups. There were also moderate to strong correlations between subscales of both measures, including cognitive processes such as attention and memory and various forms of aggression, which were particularly apparent in the prison sample. The relationship between ADHD and aggressive behaviour suggests that the treatment of adult ADHD may aid in the management of aggressive behavior.

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Psychol Assess. 2015.

PARENT AND TEACHER RATINGS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS: FACTOR STRUCTURE AND NORMATIVE DATA.

Dupaul GJ, Reid R, Anastopoulos AD, et al.

Comprehensive assessment of attention-deficit/hyperactivity disorder (ADHD) symptoms includes parent and teacher questionnaires. The ADHD Rating Scale-5 was developed to incorporate changes for the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013). This study examined the fit of a correlated, 2-factor structure of ADHD (i.e., DSM-5 conceptual model) and alternative models; determined whether ADHD symptom ratings varied across teacher and child demographic characteristics; and presented normative data. Two samples were included: (a) 2,079 parents and guardians (1,131 female, 948 male) completed ADHD symptom ratings for children (N = 2,079; 1,037 males, 1,042 females) between 5 and 17 years old (M = 10.68; SD = 3.75) and (b) 1,070 teachers (766 female, 304 male) completed ADHD symptom ratings for students (N = 2,140; 1,070 males, 1,070 females) between 5 and 17 years old (M = 11.53; SD = 3.54) who attended kindergarten through 12th grade. The 2-factor structure was confirmed for both parent and teacher ratings and was invariant across child gender, age, informant, informant gender, and language. In general, boys were higher in symptom frequency than girls; older children were rated lower than younger children, especially for hyperactivity-impulsivity; and non-Hispanic children were rated higher than Hispanic children. Teachers also rated non-Hispanic African American children higher than non-Hispanic White, Asian, and Hispanic children. Non-Hispanic White teachers provided lower hyperactivity-impulsivity ratings than non-Hispanic, African American, and Hispanic teachers. Normative data are reported separately for parent and teacher ratings by child gender and age. The merits of using the ADHD Rating Scale-5 in a multimodal assessment protocol are discussed.

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Sleep Medicine Clinics. 2015;10:143-49.

ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND SLEEP IN CHILDREN.

Herman JH.

Basic assumptions about ADHD in children and sleep are not supported by research. It is unclear that children with hyperactivity or inattention have disrupted sleep. Parents of children with ADHD consistently report more bedtime resistance, but there is no objective evidence that sleep is subsequently disrupted. Treatment of ADHD with stimulants may disrupt sleep. Studies of comorbid sleep or psychiatric disorders consistently show that they disrupt sleep. Melatonin is an effective treatment of sleep problems in children

with ADHD. Before any child is placed on stimulants, the pediatrician or other health care professional should insure that the child is obtaining adequate sleep.

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Therapeutic Drug Monitoring. 2014;37:347-52.

PLASMA METHYLPHENIDATE LEVELS IN YOUTHS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER TREATED WITH OROS FORMULATION.

Yorbik O, Mutlu C, Ozilhan S, et al.

Background: There are limited studies investigating the relationship between oral release osmotic system-methylphenidate (OROS-MPH) doses and plasma methylphenidate (MPH) concentrations in children and adolescents. The aim of this study was to investigate the relationship between the doses of OROS-MPH and the plasma levels of the drug. We also examined the effects of the other drugs including aripiprazole, risperidone, fluoxetine, and sertraline on the levels of the MPH in the plasma.

Methods: The files of 100 attention deficit hyperactivity disorder (ADHD) subjects (76 male, 24 female) who were diagnosed as ADHD according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition criteria, were screened. The ages of subjects were between 6 and 18 years (mean 11.5 (plus or minus) 3.8 years). Plasma MPH levels were determined by high-performance liquid chromatography-tandem mass spectrometry assay.

Results: Daily mean OROS-MPH dose used in ADHD children was 0.7 (plus or minus) 0.2 mg/kg (range: 0.3-1.3 mg/kg). The mean plasma OROS-MPH was 11.6 (plus or minus) 7.3 ng/mL (range: 0.5-43.4 ng/mL). There was no group difference in the mean plasma MPH and dose-related MPH levels between the groups that used any additional drug including aripiprazole (n 25), risperidone (n 10), fluoxetine (n 16), sertraline (n 10), and did not use these drugs ($P > 0.05$). There was a positive correlation between the OROS-MPH doses (mg/kg) and the blood MPH levels (Pearson correlation 0.40; $P < 0.001$). The plasma levels of MPH were found to be less than 13 ng/mL in 65% of the subjects.

Conclusions: Our findings point to the fact that plasma levels of MPH show a wide range of changes at similar doses, correlate positively with the doses and, as expected, are not affected by using risperidone, sertraline, fluoxetine, and aripiprazole. Therapeutic drug monitoring may help to optimize MPH dose in patients not responding to treatment or in those experiencing serious side effects, but not in routine clinical practice. The presence of intermediate dose formulations such as 45-mg tablets for OROS-MPH may contribute to the optimization.

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ATOMOXETINE VERSUS OROS METHYLPHENIDATE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SIX-MONTH FOLLOW UP STUDY FOR EFFICACY AND ADVERSE EFFECTS.

Cetin FH, Tas TY, Isik TY.

Objective: Attention deficit hyperactivity disorder (ADHD) is one of the most frequently seen neuropsychiatric disorders in childhood. The aim of this study is to compare the efficacy and the adverse effects of two FDA-approved agents, atomoxetine (ATX) and osmotic release oral system methylphenidate (OROS-MPH), in the treatment of ADHD.

Material and Methods: This research was designed as a randomized, open label, prospective and follow-up study. The study was performed by 120 cases between ages 7-16 years who were diagnosed as ADHD for the first time and given prescription. The cases were divided into two by randomization. One group was given ATX (n=59) while the other was given OROS-MPH (n=61) were evaluated prospectively by clinical examination and Connernulls Comprehensive Behavior Rating Scale-Teacher (CRS-T) at the 2nd, 4th, and 6th months. Efficacy of treatment was regarded as a 40% reduction in CRS-T scores when compared to baseline values, and the adverse effects were questioned in every follow up visit.

Results: The efficacy was 55.7% in CRS-T hyperactivity score, 63.9% in the attention deficit score, and 55.7% in the behavior problems score in OROS-MPH group. Those values were 47.5%, 69.5% and 57.6%

respectively in ATX group. Adverse effects were seen in 27.1% (n=16) of the patients in the ATX group, and in 31.1% (n=19) of the patients in the OROS-MPH group. Two groups were not found significantly different for the frequency of adverse effects as well as the efficacy of the medication, at the follow-up evaluations which were performed at 2nd, 4th and 6th months.
Conclusion: In this study, ATX and OROS-MPH were compared for their efficacy and adverse effects for the treatment of ADHD, and two agents were found similar for their efficacies and adverse effect profiles. ATX and OROSMPH have similar efficacies in the treatment of ADHD and adverse effect profiles are similar.

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Value Health. 2015;18:A122-A123.

CAREGIVERS' PREFERENCES FOR TREATMENT OPTIONS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A LATENT CLASS ANALYSIS.

Ng X, Bridges JF, Ross MM, et al.

OBJECTIVES: To elicit caregivers' preferences for evidence-based treatment options for their child's attention deficit hyperactivity disorder (ADHD), and to identify segments of caregivers who display similar preferences.
METHODS: Caregivers with a child aged 4-14 and in care for ADHD were recruited from outpatient clinics and advocacy groups. All caregivers completed a self-administered survey that included socio-demographic information, and a best-worst scaling (BWS) instrument assessing treatment preferences. The BWS instrument comprised 18 choice tasks, each displaying seven treatment attributes: medication, therapy, school involvement, caregiver behavior training, physician management, provider communication and out-of-pocket costs. Every attribute was operationalized into 3 possible levels. Within each task, caregivers selected one best and one worst attribute. A scaleadjusted latent-class (SALC) analysis was conducted to account for variability in the consistency of responses.
RESULTS: Our study population of 164 caregivers were on average 42 years old (SD 8.7), predominantly female (95%), white (65%), married (61%), college-educated (73%), and 20% had a child who was diagnosed with ADHD for (less-than or equal to) 1year. Based on the aggregate results, using medication everyday was the most preferred treatment attribute (coefficient= 2.41, p< 0.001). Three latent classes (i.e. segments) that best described the data were identified, and the scale factor included in the model was significant (p< 0.001). The 3 segments comprised 28%, 27%, and 45% of our study population. Segment 1 has the strongest preference for 'medication' (coefficients= 3.69 -4.34, all p< 0.001) while Segment 2 displayed the least preference for medication (coefficients= -1.49 - -3.36, all p< 0.001). Segment 3 was most costavoidant (coefficients= -2.13 - -6.11, all p< 0.001) but had the strongest preference for 'school involvement' (coefficients= 0.63 - 2.58, all p< 0.05).
CONCLUSIONS: This study demonstrated variation in caregivers' priorities for ADHD treatment attributes. A better understanding of preferences for evidence-based treatment options can enhance patient-centered care. By utilizing SALC, our study reduces the likelihood of misclassification error.

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Value Health. 2015;18:A257-A258.

COST-EFFECTIVENESS OF A BEHAVIORAL PSYCHOSOCIAL TREATMENT INTEGRATED ACROSS HOME AND SCHOOL FOR PEDIATRIC ADHD-INATTENTIVE TYPE.

Tran JL, Sheng R, Esonwune-Chukwudi P, et al.

OBJECTIVES: Our clinical trial compared two behavioral psychosocial interventions tailored for children with ADHD-inattentive type (ADHD-I) which varied in intensity and outcomes. We evaluated cost-effectiveness of the Child Life and Attention Skills (CLAS) program, which has parent, teacher and child sessions, and the parentfocused treatment (PFT), which includes only parent sessions, both compared with traditional community treatment (TAU).
METHODS: We used our recent clinical trial for data on resources used and treatment outcomes. Our CEA outcome was cost per ADHD case avoided as measured by the Child Symptom Inventory. Costs for CLAS

and PFT included clinician, parent, and teacher time, supplies, and childcare. TAU costs included only supplies. Salaries were from Bureau of Labor Statistics in 2011 USD. Savings were calculated from reductions in parent time spent on homework and lost leisure and work time based on surveys taken before and 7 months post-treatment. Sensitivity analyses assessed the impact of altering CLAS structure, including having personnel of varying educational background lead group sessions.
RESULTS: Total cost per patient for CLAS, PFT, and TAU were $1,655.04, $795.03, and -$9.37, respectively. CLAS, the costliest, was also more effective than PFT and TAU; 39, 34, and 11 cases avoided. The incremental cost-effectiveness ratio (ICER) was $4,368.63 per disordered case avoided for CLAS compared to TAU. PFT compared to TAU was lower at $2,564.56. The ICER of CLAS compared to PFT was $12,684.49. Reducing the number and length of group meetings resulted in an ICER of $3,333.05 for CLAS compared to TAU.
CONCLUSIONS: PFT is the more cost-effective treatment option for children with ADHD-I given delivery based on our clinical trial. However, CLAS may be comparably cost-effective by decreasing number and length of group meetings. Current studies are looking at the efficacy of a streamlined CLAS structure with reduced and centralized group sessions.

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Value Health. 2015;18:A128-A129.

PHYSICIAN CARE-PROVIDING BEHAVIOR IN TREATING ATTENTION-DEFICIT HYPERACTIVE CHILDREN AND ADOLESCENTS.

Patel A, Chen H, Aparasu R, et al.

OBJECTIVES: This study aims to explore physician care-providing behavior in treating children and adolescents with Attention-deficit/hyperactivity disorder (ADHD).
METHODS: The study was conducted using the GE electronic medical records (GE-EMR) 1995-2010. The cohort consisted of all children and adolescents (age(less-than or equal to) 18 years), who were prescribed either stimulants or atomoxetine hydrochloride and had at least two physician visits. Incident ADHD cases, defined as those who have not been diagnosed with ADHD or received ADHD prescription in the last 6 months, were followed for a period of 12 months to observe their physician careproviding behavior.
RESULTS: Approximately 5% of children in the GE-EMR were diagnosed with ADHD. 74% of the cases were identified by primary care physicians (PCPs), 5% by a mental health specialist, and the remaining cases had missing provider specialties. 52% (N= 101,516) of ADHD cases were prescribed pharmacotherapy immediately following the first ADHD diagnosis, while 43% (N= 35,069) had delayed prescriptions with median time to treatment of 55 days (IQR: (21-171 days)). ADHD cases first identified by PCPs were more likely to receive immediate pharmacotherapy than those identified by mental health specialists (58% vs 41%, P= < 0.0001). The majority of the children who received pharmacotherapy were prescribed stimulants (89%), about 10% were prescribed atomoxetine and less than 1% were on a combination of the two. The most commonly prescribed concurrent non-ADHD medications were antidepressants (11%) and atypical antipsychotics (4.6%). During the one year follow-up, children with ADHD had an average of six office visits with the first follow-up visit at an average of 51 days after treatment initiation. Only 0.39% (N= 318) of children received concurrent psychotherapy.
CONCLUSIONS: As compared to mental health specialists, PCPs are more likely to prescribe pharmacotherapy immediately after the ADHD cases were identified. Medication concurrent psychotherapy is low in patients seen by either PCPs or mental health specialists.

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Value Health. 2015;18:A120.

PRESCRIPTION MEDICATION COSTS ASSOCIATED WITH CHILDHOOD ATTENTION DEFICIT HYPERACTIVITY DISORDER IN AMBULATORY CARE VISITS IN 2010.

McConeghy RO, Pawar AM, Kogut S.

OBJECTIVES: To estimate the national costs of prescription medications for childhood attention deficit hyperactivity disorder (ADHD) in the United States (U.S.) in 2010 and to identify differences in diagnosis and costs by gender and racial/ethnic background.
METHODS: To determine childhood ADHD diagnosis and prescription medication use, we used ICD-9 and drug ID codes recorded from pediatric visits in the 2010 National Ambulatory Medical Care Survey (NAMCS). Our analysis included all formulations of the following medications: amphetamine salts, atomoxetine, dextroamphetamine, dexmethylphenidate, and methylphenidate. To calculate the costs of medication use, we multiplied the 2010 average wholesale price (AWP) by a presumed usual number of yearly doses and weighed these costs to reflect national estimates. We compared differences in overall medication cost by gender and race using the student's t test and evaluated differences in the proportion of patients diagnosed with ADHD using the chi-square test.
RESULTS: Among pediatric visits in 2010, we found that 5.70% (n= 7,201,548) were associated with a diagnosis of ADHD and, of those diagnosed, 67.29% (n= 4,846,163) had a mention of a prescribed ADHD medication. The nationally weighted sum of ADHD medication cost was $6.62 billion (mean= $1,336, SD= $1,220). Amphetamine salts prescriptions were associated with the highest overall cost ($3.67 billion). Overall drug expenditure did not differ by gender or race. We found a higher proportion of males were diagnosed with ADHD than females (7.97% vs. 3.48%, P < 0.001). Diagnosis with ADHD was less frequent among white children as compared with African-American children (5.79% vs. 7.09%, P = 0.012).
CONCLUSIONS: We found that 5.70% of 2010 U.S. pediatric visits had a mention of ADHD diagnosis. We estimated that in 2010 U.S. expenditure for ADHD medications was $6.62 billion. Diagnosis of ADHD was more frequent among males and African-American children and less frequent among females and whites.

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Value Health. 2015;18:A263-A264.

RELATIVE AGE IN CLASS AND ADHD IN SCHOOL CHILDREN - DIAGNOSIS AND MEDICATION PATTERNS - INTRA-ANNUAL AND INTER-ANNUAL DISPARITY.

Hoshen MB, Benis A, Keyes KM, et al.

OBJECTIVES: Diagnosis of children with attention-deficit/hyperactivity disorder (ADHD) is increasing. Recent studies have shown a tendency for younger children in a school cohort being diagnosed with the condition, suggesting the diagnosis is associated with immaturity. Given potential sequelae of treatment, there is a great need to evaluate potential misdiagnosis. The present study sought to identify characteristics and treatment patterns of children with ADHD, compare younger to older children within single age cohorts, and find seasonality and trends in disparity of diagnosis and pharmacotherapy, within a non-selective real-world setting.
METHODS: Children aged 6-11 who were members of Clalit Health Services January 2010. Diagnosis (ICD-9 314.[0,1,2,8,9]) and medication (ATC codes 'N06BAx') were extracted from the Clalit Health Services database. Calendar months of first diagnosis (2003-2011) and months of drug purchases (2010-2011) were compared by month of birth. Trends of diagnosis and treatment were determined for the various sub-cohorts, and population sector differences were compared.
RESULTS: Of total population (400,828 children, 51% male), 40467 (10.1%) were diagnosed with ADHD and 33188 (8.3%) were treated (usually methylphenidate). Diagnosis levels for younger (Y: Aug-Nov) children (10.9%) were lower than older (O: Dec, Jan-March) children (9.2%, RR 1.18 CI 1.16 to 1.21). The rate disparity was higher beginning school-year (September-December; RR 1.21 CI 1.17-1.26). Any-purchase dispensing RR was 1.19 (CI 1.16 to 1.22), while monthly RR was 1.18 (1.17-1.19). RR for dispensing was stable between age-cohorts (1.17-1.22) without trend. Among children purchasing drugs, the seasonal variation in drug purchases (adherence) is similar Y:O
CONCLUSIONS: ADHD diagnosis and medication are common in the primary school population. The increased incidence and prevalence among younger children in a cohort questions the appropriateness of both diagnosis and medication, suggesting behavioral treatment may often be more suitable to avoid long term costs and deleterious effects, than pharmacological intervention.

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Value Health. 2015;18:A120-A121.

COST EFFECTIVENESS ANALYSIS OF DIFFERENT TREATMENT ALTERNATIVES IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

El-Hamamsy M, Elsayed BM, Eid EM.

OBJECTIVES: to determine the cost effectiveness of three treatment alternatives (medication, behavioral, and combined treatment of Atomoxetine and behavioral therapy) for attention deficit hyperactivity disorder in children from payer perspective with time horizon: 12 weeks

METHODS: a prospective trial based economic evaluation was conducted on children in psychiatric out patients clinic at Abasseya Mental Hospital (AMH), Cairo ,Egypt who are 6 to 12 years of age (boys or girls), and had a clinical diagnoses of ADHD as defined in the Diagnostic and statistical Manual fourth edition (DSM-IV). Patients were classified into three groups: (Depended on psychiatric recommendation and parents preferences) medication only group (group I), behavioral therapy group (group II), and combined medication and behavioral therapy group (group III). Each treatment had both a cost and an outcome associated with it. Cost effectiveness ratio comprising the average total cost per child per unit of outcome three months-Quality Adjusted Life Years nullQALYnull in each of the three groups.

RESULTS: The combined therapy was associated with the highest cost effective ratio C/E Ratio of 7695.524 LE per QALY, medication therapy was 4381.927 LE per QALY, While C/E Ratio of behavioral therapy was 3337.339 LE per QALY. According to base-case analysis, combined therapy resulted in greatest health benefits but at the same time it was the most expensive treatment option. Behavioral therapy was the least effective and cheapest option. The sensitivity analyses: show that the utility values of all health states are crucial determinants of the cost-effectiveness results.

CONCLUSIONS: combined therapy resulted in greatest health benefits but at the same time it was the most expensive treatment option. Behavioral therapy was the least effective and cheapest option.

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Z Kinder- Jugendpsychiatr Psychother. 2015;43:185-93.

THE COMORBIDITY OF LEARNING DIFFICULTIES AND ADHD SYMPTOMS IN PRIMARY-SCHOOL-AGE CHILDREN.

Schuchardt K, Fischbach A, Balke-Melcher C, et al.

Children having difficulties in acquiring early literacy and mathematical skills often show an increased rate of inattention, hyperactivity, and impulsivity. This study provides data on the comorbidity rates of specific learning difficulties and ADHD symptoms. We analyzed the data of 273 children with learning difficulties despite an at least average IQ, 57 children with low IQ, and 270 children without learning difficulties and average IQ (comparison group). We assessed children's IQ and school achievement using standardized achievement tests. ADHD symptoms were assessed via parents' ratings. Our results showed that only 5% of both the control group and the group with solely mathematical difficulties fulfilled the criteria of an ADHD subtype according to the DSM-IV based on parents' ratings. In contrast, this was the case in even 20% of the children with difficulties in reading/writing and of those with low IQ. Compared to girls, boys in the control group had a 150% higher risk for matching the criteria of one of the ADHD subtypes in parents' ratings, whereas boys with learning difficulties and those with low IQ had an even 200% to 600% higher risk for it. The relationship between learning difficulties and ADHD symptoms can be found predominantly in the inattentive type. Possible reasons for the results are discussed.

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Overlap Between Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorder: Searching for Distinctive/Common Clinical Features

Francesco Craig, Anna Linda Lamanna, Francesco Margari, Emilia Matera, Marta Simone, and Lucia Margari

Recent studies support several overlapping traits between autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD), assuming the existence of a combined phenotype. The aim of our study was to evaluate the common or distinctive clinical features between ASD and ADHD in order to identify possible different phenotypes that could have a clinical value. We enrolled 181 subjects divided into four diagnostic groups: ADHD group, ASD group, ASD+ADHD group (that met diagnostic criteria for both ASD and ADHD), and control group. Intelligent quotient (IQ), emotional and behavior problems, ADHD symptoms, ASD symptoms, and adaptive behaviors were investigated through the following test: Wechsler Intelligence Scale for Children, Wechsler Preschool and Primary Scale of Intelligence or Leiter International Performances Scale Revised, Child Behavior Checklist, Conners' Rating Scales-Revised, SNAP-IV Rating Scale, the Social Communication Questionnaire, Vineland Adaptive Behavior Scales. The ASD+ADHD group differs from ADHD or ASD in some domains such as lower IQ mean level and a higher autistic symptoms severity. However, the ASD+ADHD group shares inattention and hyperactivity deficit and some emotional and behavior problems with the ADHD group, while it shares adaptive behavior impairment with ASD group. These findings provide a new understanding of clinical manifestation of ASD+ADHD phenotype, they may also inform a novel treatment target. ***Autism Res*** *2015, 8: 328–337*. © 2015 International Society for Autism Research, Wiley Periodicals, Inc.

Keywords: autism spectrum disorders; attention deficit hyperactivity disorder; overlapping; intelligent quotient; emotional and behavior problems; ADHD symptoms; ASD symptoms; adaptive behaviors

Introduction

Autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD) are childhood-onset neurodevelopmental disorders, with prevalence, respectively, of 1% and 5% in the pediatric population [American Psychiatric Association, 2013]. According to the Diagnostic and Statistical Manual of Mental Disorders—4th edition—Text Revision (DSM-IV-TR) criteria, a diagnosis of ADHD cannot be made if the symptoms of inattention and hyperactivity occur exclusively during the course of a pervasive developmental disorder (PDD). However, epidemiological, clinical and neuroimaging findings have led a revision of the ADHD exclusion criteria in the recent publication of the DSM-5 [American Psychiatric Association, 2013]. In fact, autism is no longer an exclusion criteria and both ASD and ADHD can be diagnosed together [DSM-5, 2013]. Although there are some important differences (e.g., core symptom definition and recommended treatment), ASD and ADHD share many similar impairments in different domains that could complicate a differential diagnosis. Researchers have shown an increased interest in the overlapping features between these disorders, including attention deficit [Mayes et al., 2011; Sturm, Fernell, & Gillberg, 2004], behavior problems [Mayes et al., 2011], and difficulty in social skills [de Boo & Prins, 2007]. Moreover, several studies have shown high rates of ADHD comorbidity in children with ASD [Gadow et al., 2006; Holtmann, et al., 2007; Lee & Ousley, 2006; Simonoff et al., 2008; Wozniak & Biederman, 2012; Yoshida & Uchiyama, 2004]. On the other hand, several studies observed elevated rates of autistic symptoms in children with ADHD [Grzadzinski et al., 2011; Kotte et al., 2013; Reiersen et al., 2007;

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Santosh & Mijovic, 2004]. Recent studies on biological risk factors, neuropsychological domains, and brain imaging support several overlapping traits between ASD and ADHD. In a review study, Taurines et al. (2012) suggests that comorbidity is caused by overlapping genetic or non-genetic biological risk factors [Taurines et al., 2012]. Family and twin studies provide support for the hypothesis that ADHD and ASD originate partly from similar familial/genetic factors [Reiersen, Constantino, Volk, & Todd, 2007; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008]. Only a few candidate gene studies, linkage studies, and Genome-Wide Association (GWA) studies have specifically addressed this co-occurrence, pointing to some promising pleiotropic genes, loci, and single-nucleotide polymorphisms (SNPs) [Freitag et al., 2012; Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010; Taurines et al., 2012]. The specific nongenetic biological risk factors associated with overlapping between ASD and ADHD seem to include maternal psychotropic medications, preterm birth, maternal pre-eclampsia, maternal autoimmune disease, and maternal infection disease [Cohen et al., 2011; Croen et al., 2011; Kroger et al., 2011; Lyall et al., 2012; Taurines et al., 2012].

Moreover, neuropsychological impairments, as attention and executive function (EF), were frequently reported in individuals with ASD and ADHD. A meta-analysis study of the EF in ADHD children found that response inhibition, vigilance, working memory, and planning were the strongest and most consistent deficits found across studies [Willcutt et al., 2005]. However, executive functions deficits are also detected in children with ASD who reported deficits in the areas of planning and cognitive flexibility [Hill, Berthoz, & Frith, 2004; Kenworthy et al., 2005; Ozonoff et al., 2004], response selection/monitoring [Happé et al., 2006], and task initiation/task shifting [Hill & Bird, 2006]. These impairments are due to the fact that ASD and ADHD are neurodevelopmental disorders affecting key fronto-striatal and fronto-parietal circuits that are important for executive functions. Neuroimaging findings describe common gray matter reductions in the left medial temporal lobe and increased gray matter volumes in the left inferior parietal cortex in both disorders [Brieber et al., 2007]. Recently, Christakou et al. (2013) compared ASD children and ADHD children using functional magnetic resonance imaging (fMRI) during a parametrically modulated vigilance task with a progressively increasing load of sustained attention demonstrating that ADHD and ASD boys had significantly reduced activation relative to controls in bilateral striato-thalamic regions, left dorsolateral prefrontal cortex (DLPFC), and superior parietal cortex [Christakou et al., 2013]. Despite the fact that there have been an increasing amount of molecular genetic and imaging studies about the overlapping of ASD and ADHD, there are no definitive findings.

These literature data highlight the need for further studies on the overlap between ASD and ADHD, assuming the existence of a combined phenotype. For this reason, the aim of our study was to evaluate the common or distinctive clinical features between ASD and ADHD in order to identify possible different phenotypes that could have a clinical value.

Method

The sample consisted of 181 subjects referred to University Hospital of Bari. Participants were divided into four groups: ADHD group, ASD group, ASD+ADHD group, and a control group. The ADHD group comprised 51 children/adolescents, the ASD group comprised 43 children/adolescents, and the ASD+ADHD group comprised 31 children/adolescents. These patients were enrolled at the Child Neuropsychiatry Unit and clinical diagnoses were made by clinical experts according to DSM-IV-TR. The diagnoses were based on the developmental histories of the children, taken from clinical interviews with the parents, observations and extended neuropsychological testing of the children themselves. To be eligible for the current study, ASD patients had to present the typical triad of symptoms of autism: social deficits, communication impairment, and rigid ritualistic interests. The clinical diagnosis of ASD was supported by the Autism-Diagnostic Interview-Revised [Rutter et al., 2003b] and the Autism Diagnostic Observation Scale [Lord et al., 1999]. ADHD patients had to present the typical core symptoms of inattention, hyperactivity, and impulsivity. ADHD children that were included in our sample had received the DSM subtype diagnosis. The ASD+ADHD patients met DSM-IV-TR diagnostic criteria for both ASD and ADHD.

Exclusion criteria were the presence of any genetic or medical condition underlying ADHD or ASD symptoms. Considering the difficulty in recruiting healthy children, the control group comprised 56 children/adolescents enrolled at the Pediatric Surgery Unit, admitted for mild surgical diseases (hernia, ingrown nails, appendicitis, hemorrhoids, syndactylia, phimosis), in which neurological and psychiatric disorders were excluded. All participants were consecutively examined in the period between September 2010 and February 2014.

Parental informed consent was obtained for all participants and the study was approved by the local ethical committee of the "Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari."

Assessment

In order to evaluate the common or distinctive clinical features in ASD, ADHD, ASD+ADHD, and the control groups we investigated intelligent quotient (IQ),

emotional and behavior problems, ADHD symptoms, ASD symptoms, and adaptive behaviors.

In ASD, ADHD, ASD+ADHD patients, the IQ was assessed according to the age through Wechsler Intelligence Scale for Children (WISC-III) [Wechsler, 1991], Wechsler Preschool and Primary, Scale of Intelligence (WPPSI) [Wechsler, 2002], and Leiter International Performances Scale Revised (Leiter-R) [Roid & Miller, 1997] alternatively to WISC-III, in nonverbal subjects. The control group was not assessed for IQ.

Emotional and behavior problems, ADHD symptoms, ASD symptoms, and adaptive behaviors were investigated through the following scales: Child Behavior Checklist (CBCL), Conners' Rating Scales-Revised (CRS-R), SNAP-IV Rating Scale, the Social Communication Questionnaire (SCQ), Vineland Adaptive Behavior Scales (VABS).

The CBCL [Achenbach & Rescorla, 2001] is a common tool used to assess emotional and behavioral problems in children. The first section of the scale includes 20 items related to the child's social competency, as rated by parents. These items address the child's participation in sports, hobbies, games, activities, organizations, jobs, chores, friendships, social interactions during play, independent work, and school functioning. The second section consists of 120 items on behavior or emotional problems during the past 6 months as rated on a three-point scale. The main areas of this construct are aggression, hyperactivity, bullying, conduct problems, defiance, and violence. The following behavioral and emotional problems are also measured: aggressive behavior, anxious/depressed, attention problems, delinquent rule-breaking behavior, social problems, somatic complaints, thought problems, withdrawal, externalizing, internalizing, and total problems. Lower scores indicate lower functioning on the academic performance and adaptive functioning scales [Achenbach & Rescorla, 1991]. Higher scores indicate higher levels of maladaptive behavior on the syndrome, total problems, externalizing and internalizing scales. The instrument has an internal validity of 0.90–0.91 for the scales of internalizing disorders and of 0.95–0.96 for externalizing disorders. Cronbach's coefficient alpha was 0.95 and 0.96, respectively.

CRS [Conners, 1997] is used as part of a comprehensive examination and is designed to be easily administered and scored. Conners' Rating Scales-Revised (CRS-R) is an assessment for children aged 3 through 17 years designed to measure cognitive, behavioral, and emotional problems from teacher and parent perspectives. CRS-R are available in long and short versions for both parents and teachers. We used the long version for parents [Conners et al., 1998] that consisted of 80 items in the following subscales: oppositional, social problems, cognitive problems/inattention, psychosomatic, hyperactivity, DSM-IV symptom subscales, anxious-shy, ADHD Index, perfectionism, Conners' Global Index. Conners' Global Index includes 10 items related to problem behavior critically associated with the severity of childhood problems. Each of the column scores can then be converted to a T-score. T-scores are standardized scores with a mean of 50 and a standard deviation of 10. These can be further converted to percentile scores, when needed. As a rule, T-scores above 60 are cause for concern and have interpretive value. Interpretable scores range from a low T-score of 61 (mildly atypical) to above 70 (markedly atypical).

The SNAP-IV Rating Scale [Swanson et al., 2001] is a revision of the Swanson, Nolan, and Pelham (SNAP) Questionnaire (Swanson, 1983). The 26 items of the SNAP-IV include the 18 ADHD symptoms (nine for inattentive, nine for hyperactive/impulsive) and eight ODD symptoms specified in the DSM-IV. The SNAP-IV is based on a 0 to 3 rating scale: Not at All = 0, Just A Little = 1, Quite A Bit = 2, and Very Much = 3. Subscale scores on the SNAP-IV are calculated by summing the scores on the items in the subset and dividing by the number of items in the subset.

The SCQ [Rutter, et al., 2003a] is a 40-item, parent completed, screening questionnaire, based on the initial mandatory probes from the original Autism Diagnostic Interview [Le Couteur et al., 1989]. It includes the areas of communication, reciprocal social interactions, and restricted and repetitive behaviors and interests. Each item is checked as "yes" or "no," and is assigned a rating point of "1" (presence of abnormal behavior) or "0" (absence of abnormal behavior). Total scores are compared to a cut off of $\geq$15 for ASD. A lower cut-off score of $\geq$12 has been suggested for children under the age of 5 years. There are two different versions of the SCQ: 1) a "current" version designed for children under the age of 5 years and 2) a "lifetime" version designed for children of 5 years of age or older, with all questions based on lifetime or past behavior.

The VABS [Sparrow et al., 1984] is a semistructured parental interview that evaluates adaptive functioning in four domains: communication, daily living skills, socialization, and motor skills. Age-equivalent scores and standard scores are provided for each domain. Scores across domains can be combined to create an overall adaptive behavior composite standard score.

Statistical Analysis

All demographic and clinical variables were subjected to statistical analysis. Descriptive analysis was conducted for sociodemographics featuring of the four samples. Raw scores obtained from each subscale of the CSR, CBCL, SNAP-IV, SCQ, and VABS were transformed into *t*-scores to allow for consideration of how an individual's response compares with that of the population

Table 1. Sociodemographic Characteristics and IQ of ASD, ADHD, ASD+ADHD, and Control Groups

	ASD ($N = 43$)	ASD+ADHD (N=31)	ADHD ($N = 51$)	Control ($N = 56$)	P Value
Gender (N)					
Male	36	26	46	43	.323
Female	7	5	5	13	
Age (years)					
Range	5.6–8.6	7.05–9.5	7.2–9.8	7.6–9.5	—
Mean ± SD	7.11 ± 4.7	8.28 ± 3.3	8.54 ± 3.9	8.6 ± 3.46	.26
IQ (Mean ± SD)	72.09 ± 36.7	59.03 ± 34.5	85.17 ± 19.7	—	*ASD+ADHD vs ASD *ASD+ADHD vs ADHD
IQ level					
Borderline	27%	13%	19%	—	—
Mild	11%	22%	12%	—	—
Moderate	9%	16%	5%	—	—
IQ measures					
WISC-III	30%	3%	72%	—	—
WPPSI	16%	13%	20%	—	—
Leiter-R	54%	84%	8%	—	—

Autism Spectrum Disorders (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Intelligence Quotient (IQ), borderline (IQ 71-84), mild (IQ 50–70), moderate (IQ 35–49), Wechsler Intelligence Scale for Children (WISC-III), Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Leiter International Performances Scale Revised (Leiter-R); *P <.005.

norms. For CBCL, the borderline (t-score > 65) and clinical (t-score > 70) scores were put together. In line with the interpretive guidelines from CRS-R, participants with a t-score of 66 on a subscale represent individuals who score much above the average and were categorized as symptomatic for that trait. Analysis of variance (ANOVA) test was used to evaluate the differences of the means of the CBCL, CRS-R, SNAP-IV, SCQ, and VABS scales among overlap, ASD, ADHD and control groups. Additionally, Bonferroni correction was used to conduct the post hoc analysis. A P-value of less than. 05 was considered as statistically significant. For statistical processing, we used the data processing program the Statistical Package for Social Science version 20.0.

Results

Socio-demographic characteristics of ASD, ADHD, ASD+ADHD and Control groups are summarized in Table 1. No statistical differences among the four groups in age ($P = .26$) and gender ($P = .323$) were found. Among the ASD participants in our study, 72% met the DSM-IV-TR diagnostic criteria for pervasive developmental disorder not otherwise specified (PDD-NOS), 14% for Autistic Disorder, and 14% for Asperger's Syndrome. Among the ADHD patients, 8% met the DSM-IV-TR diagnostic criteria for the inattentive subtype of ADHD and 92% met the criteria for the combined subtype. Among the ASD+ADHD patients, 68% met the DSM-IV-TR diagnostic criteria for PDD-NOS+ADHD combined subtype, 19% for Autistic Disorder + ADHD combined subtype, and 13% for Asperger's disorder + ADHD combined subtype.

Intelligent Quotient

A statistically significant difference was found between the groups in IQ mean score ($F = 7.27$; $P < .001$). The post-hoc analysis showed that ASD+ADHD groups had lower IQ mean score, compared with ASD ($P = .023$) and ADHD ($P = .001$) groups. No statistical difference was found between the ADHD and the ASD group. Results about IQ are summarized in Table 1.

Emotional and Behaviors Problems

Emotional and behaviors problems assessed with CBCL (Table 2) showed a statistically significant difference between the groups in internalizing ($F = 8.32$, $P < .001$), externalizing ($F = 20.04$, $P < .001$), and total problems ($F = 19.9$, $P < .001$). ADHD and ASD+ADHD groups showed higher Internalizing scores compared with the control group. ADHD and ASD+ADHD groups showed higher Externalizing and Total problems scores compared with the ASD and control groups.

Emotional and behaviors problems assessed with CRS-R (Table 3) showed a statistically significant difference between the groups in all subscales ($P < .05$). The ADHD group had higher ODD, cognitive problems, anxiety, perfectionism, social problems, somatic complain and CGI total scores compared with the ASD and Control groups. The ASD+ADHD group had higher ODD, cognitive problems, anxiety, perfectionism, social problems, somatic complaints, CGI emotional lability, and CGI total scores compared with the ASD group. The ASD+ADHD group had higher ODD, cognitive problems, perfectionism, social problems, CGI

Table 2. Significant Differences in CBCL Symptom Scores Between Groups

	ASD ($N = 43$)		ASD+ADHD ($N = 31$)		ADHD($N = 51$)		Control ($N = 56$)				
	%>Cut-off	M ± SD	%>Cut-off	M ± SD	%>Cut-off	M ± SD	%>Cut-off	M ± SD	F	*P* Value	Bonferroni's Test
Internalizing problems	59.7%	60.4±8.8	78.6%	64.7±7.2	84.9%	66.1±8.4	49.9%	53.9 ±16.4	8.3	<.001	ASD+ADHD=ASD=ADHD>*Control
Externalizing problems	32.7%	56.5±8.2	67.9%	63.9±9.3	86.8%	69.6±10.3	21.6%	53.5±9.3	20	<.001	ADHD=ASD+ADHD>*ASD=Control
Total Problems	53.3%	59.7±8.2	92.8%	69±8.1	90.1%	70.1±9.8	34.9%	56.2±8.8	19.9	<.001	ADHD=ASD+ADHD>*ASD=Control
Mood symptoms	25.2%	58.1±7.3	23.4%	62.5±8	49.8%	65±8.6	28.5%	58.7±7.4	5.9	.001	ADHD>*ASD=Control
Social Withdraw	75.6%	69.2±12.1	62.3%	68.4±9.8	60.6%	65.3±7	17.1%	57.7±6	11.7	<.001	ASD+ADHD=ASD=ADHD>*Control
Somatic Complain	9.4%	55±7	22.6%	57.3±6.9	45.5%	62.4±9.3	14.1%	56.7±6.2	6.3	.001	ADHD>*ASD+ADHD=ASD=Control
Attention deficit	37.2%	62.5±7.3	80.6%	71.3±7.9	78.8%	70.7±8.3	22.9%	59.9 ± 7.5	18.5	<.001	ASD+ADHD=ADHD>*ASD=Control
Aggressive problem	28.1%	56.6±7	48.4%	64.4 ±8.7	68.3%	71.4±10.7	8.4%	55.9±7.6	24.5	<.001	ADHD>*ASD+ADHD>*ASD=Control
Depression	34.4%	60.6±9.7	48.4%	67.2±9.6	69.7%	67.1±6.5	17.2%	57.8±7.2	11	<.001	ADHD=ASD+ADHD>*ASD=Control
Anxiety	25%	57.8±7.2	70%	66.1±8	65.3%	65.9±7.7	40%	61.3±8	8.5	<.001	ADHD>*ASD+ADHD=ASD
ADHD	18.3%	59±6.7	65.5%	67.8±7.3	78.9%	69.8±7.8	17.2%	57.8±6.8	24.4	<.001	ADHD=ASD+ADHD>*ASD=Control
ODD	6.2%	55.5±5.5	16.8%	61.1 ±7.7	64.6%	68.1 ±8.8	12%	55.1±6.6	24.1	<.001	ADHD>*ASD+ADHD>*ASD=Control

Autism Spectrum Disorders (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional defiant disorder (ODD), Mean (M), standard deviation (SD), Child Behavior Checklist (CBCL); *$P < .05$.

Table 3. Significant Differences in CRS-R Scores Between Groups

	ASD ($N = 43$)		ASD+ADHD ($N = 31$)		ADHD ($N = 51$)		Control (N=56)				
	%>Cut-off	M ± SD	%>Cut-off	M ± SD	%>Cut-off	M±SD	%>Cut-off	M±SD	F	*P* Value	Bonferroni's Test
ODD	9.8%	46 ± 12.9	41.9%	60.7 ± 13	82.9%	74.8 ± 17.9	18.9%	51.5 ± 9.3	36	<.001	ADHD>*ASD+ADHD>*ASD=Control
Cogntive problems	46.3%	60 ± 13.1	80.6%	74.4 ± 15	88.6%	74.8 ± 9.6	43.4%	59.8 ± 14.3	16.1	<.001	ADHD=ASD+ADHD>*ASD=Control
Hyperactivity	19.5%	54.6 ± 9.2	83.9%	73.7 ± 12.6	88.6%	77.8 ± 13.9	20.8%	52.3 ± 11.3	49.3	<.001	ADHD=ASD+ADHD>*ASD=Control
Anxiety	19.5%	49.4 ± 9.2	41.4%	60.2 ± 13.9	57.1%	62.3 ± 15	32.1%	54.9 ± 11.9	8.1	<.001	ADHD=ASD+ADHD>*ASD; ADHD>*Control
Perfeczionism	12.2%	49.7 ± 8.9	64.5%	64.6 ± 15.1	54.3%	64.3 ± 13.6	11.3%	46.9 ± 9.2	26.4	<.001	ADHD=ASD+ADHD>*ASD=Control
Social problems	41.5%	60.9 ± 14.8	80.6%	77.4 ± 18.9	70.6%	73.3 ± 20.1	17%	52.8 ± 9.5	21.5	<.001	ADHD=ASD+ADHD>*ASD=Control
Psychosomatic	9.3%	49.9 ± 9.5	29%	58.7 ± 14.3	51.4%	65 ± 16.5	15.1%	51.3 ± 9.4	12.6	<.001	ADHD=ASD+ADHD>*ASD; ADHD>*Control
ADHD INDEX	46.3%	60.4 ± 10.3	90.3%	77 ± 12	89.7%	76.5 ± 9	41.5%	58.7 ± 12.3	32	<.001	ADHD=ASD+ADHD>*ASD=Control
CGI restlessness	29.3%	56.2 ± 8.2	71%	68.4 ± 12.4	82.9%	75.1 ± 12.6	22.6%	54.9 ± 10.9	31.4	<.001	ADHD=ASD+ADHD>*ASD=Control
CGI emotional lability	22%	51 ± 10.4	58.1%	66.4 ± 16.4	80%	67.3 ± 13.5	9.4%	48.4 ± 9.1	27	<.001	ADHD=ASD+ADHD>*ASD=Control
CGI total	19.5%	54.8 ± 8	71%	70 ± 13.3	88.6%	75.7 ± 12.6	11.3%	53.3 ± 9.9	42	<.001	ADHD=ASD+ADHD>*ASD=Control
DSM-IV inattention	36.6%	59.8 ± 11.3	83.9%	73.7 ± 14.4	91.4%	75.6 ± 9.4	39.6%	58.4 ± 12.9	22.1	<.001	ADHD=ASD+ADHD>*ASD=Control
DSM-IV hyperactivity	22%	54.4 ± 10.8	83.9%	72.2 ± 12.7	85.7%	76.3 ± 11.5	26.4%	53.4 ± 11	43.3	<.001	ADHD=ASD+ADHD>*ASD=Control
DSM-IV ADHD	34.1%	57.6 ± 9.7	96.8%	81.9 ± 33.3	91.4%	78.6 ± 10.5	32.1%	56.2 ± 11.2	23.7	<.001	ADHD=ASD+ADHD>*ASD=Control

Autism Spectrum Disorders (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional defiant disorder (ODD), Conners Global Impairment (CGI), Diagnostic and Statistical Manual of Mental Disorders (DSM), Mean (M), standard deviation (SD), Conners' Rating Scales-Revised (CRS-R); *$P < .05$.

emotional lability, and CGI total scores, compared with the control group.

ADHD Symptoms

ADHD symptoms assessed with SNAP-IV (Table 4) showed a statistically significant difference among the groups in inattention scores ($F = 51.4$, $P < .001$) and hyperactivity scores ($F = 75.4$, $P < .001$). ADHD and ASD+ADHD groups had higher SNAP-IV inattention score compared with ASD and control groups; ASD groups had higher SNAP-IV inattention score compared with the Control group. ADHD and ASD+ADHD groups had higher SNAP-IV hyperactivity score compared with ASD and Control groups; ASD groups had higher SNAP-IV hyperactivity score compared with the control group.

ADHD symptoms assessed with CRS-R (Table 3) showed a statistically significant difference among the groups in Hyperactivity ($F = 49.3$, $P < .001$); ADHD Index ($F = 32$, $P < .001$); Restlessness-Impulsivity ($F = 31.4$, $P < .001$); DSM-IV inattention ($F = 22.1$, $P < .001$); DSM-IV Hyperactivity ($F = 43.3$, $P < .001$), DSM-IV ADHD Total ($F = 23.7$, $P < .001$). The Bonferroni test showed that ADHD and ASD+ADHD groups had higher hyperactivity, ADHD index, restlessness-impulsivity, DSM-IV inattention, DSM-IV hyperactivity, DSM-IV ADHD total scores, compared with ASD ($P < .001$ for every scales) and Control groups ($P < .001$ for every scales). No differences were found between ASD and control groups.

ADHD symptoms assessed with CBCL (Table 2) showed a statistically significant difference between the groups in ADHD scores ($F = 24.4$, $P < .001$) and attention deficit scores ($F = 18.5$, $P < .001$). The Bonferroni test showed that ASD+ADHD and ADHD groups had higher ADHD symptoms and attention deficit scores, compared with ASD and control groups. No differences were found between ASD and control groups.

ASD Symptoms

All four groups differed significantly from each other in SCQ total scores ($F = 47.7$, $P < .001$). The ASD+ADHD group had higher SCQ score (Table 4) compared with ASD ($p = .009$), ADHD ($P < .001$) and Control ($P < .001$) groups. The ASD group had higher score compared with ADHD ($P = .023$) and control ($P < .001$) groups. The ADHD group had higher score compared with the control ($P < .001$) group.

Adaptive Behaviors

Adaptive behaviors assessed with VABS (Table 4), showed a statistically significant difference among the groups in communication skills ($F = 13.6$, $P < .001$), daily living skills ($F = 15.4$, $P < .001$), social skills

Table 4. Significant Differences in SNAP-IV, SCQ, VABS Scores Between Groups

	ASD (N=43)		ASD+ADHD (N=31)		ADHD(N=51)		Control (N=56)				
	%>Cut-off	M±SD	%>Cut-off	M±SD	%>Cut-off	M±SD	%>Cut-off	M±SD	F	p-value	Bonferroni's Test
SNAP-IV											
Inattentive	45%	1.5 ± 0.6	96.8%	2.3 ± 0.3	89%	2.2 ± 0.5	7.5%	1.1 ± 0.5	51.4	<.001	ADHD=ASD+ADHD>*ASD>Control
Hyperactive/impulsive	25%	1.1 ± 0.4	93.1%	2.1 ± 0.4	91.7%	2.2 ± 0.6	11.3%	0.7 ± 0.6	75.4	<.001	ADHD=ASD+ADHD>*ASD>Control
ODD	2.5%	1 ± 1.2	54.8%	1.6 ± 0.9	65.7%	2 ± 0.7	9.4%	0.7 ± 0.5	18.5	<.001	ADHD=ASD+ADHD>*ASD=Control
SCQ	62.5%	15.4 ± 7.7	87.1%	20 ± 6.8	25.7%	11.4 ± 4.9	1.9%	4.9 ± 4.3	47.7	<.001	ASD+ADHD>*ASD>*ADHD>*Control
VABS											
Communication skills	—	52.1 ± 44.7	—	59 ± 39.7	—	86 ± 28	—	101.3 ± 37.7	13.6	<.001	ASD+ADHD=ASD<*ADHD=Control
Daily living skills	—	48.2 ± 37.8	—	41.7 ± 22.9	—	71 ± 30.7	—	93.4 ± 46.2	15.4	<.001	ASD+ADHD=ASD<*ADHD=Control
Social skills	—	42.2 ± 28.6	—	35.2 ± 19.2	—	60.8 ± 33.3	—	99.3 ± 48.1	25.5	<.001	ASD+ADHD=ASD<*ADHD<*Control
Motor skills	—	38.7 ± 18.3	—	42.7 ± 12.6	—	56.4 ± 14	—	69.6 ± 36.7	13.7	<.001	ASD+ADHD=ASD<*ADHD=Control

Autism Spectrum Disorders (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional defiant disorder (ODD), Mean (M), standard deviation (SD), Swanson, Nolan and Pelham (SNAP), Social Communication Questionnaire (SCQ), Vineland Adaptive Behavior Scales (VABS); *$P < .05$.

(F = 25.5, $P < .001$.), and motor skills (F = 13.7, $P < .001$). ASD+ADHD and ASD groups had lower communication skills, daily living skills, socialization skills, and motor skills compared with ADHD and control groups.

Discussion

Comparative studies between ASD, ADHD, and ASD+ADHD disorders are rare. Scheirs and Timmers investigated the IQ differentiating among children with PDD-NOS, ADHD, and those with a combined diagnosis on the basis of WISC-III [Scheirs & Timmers, 2009]. The authors found that the mean IQ score did differ among the three groups, in particular the PDD-NOS group attained the highest scores, whereas the scores of the ADHD and combined diagnosis groups were lower and highly similar to one another. Statistically significant differences were found only between the PDD-NOS and the ADHD group. The authors conclude that a distinction between the PDD-NOS and ADHD diagnoses can be validated on the basis of IQ scores; however, the existence of a distinct combined diagnosis group could not be warranted. In the current study, we found that the ASD+ADHD group (where the 68% met the DSM-IV-TR diagnostic criteria for PDD-NOS) was characterized by a statistically significant lower IQ mean score compared with ASD and ADHD groups. These findings suggest that the assessment of IQ could help to identify distinctive characteristics in ASD+ADHD phenotype. Further studies, which take these variables into account, will need to be undertaken.

In literature data, studies regarding psychiatric comorbid disorders that compare children with ASD and ADHD are lacking. Recently, van Steensel et al. (2013) found that children with ASD did not differ from children with ADHD with respect to their overall comorbidity rate, however, anxiety disorders were more often present in children with ASD compared to children with ADHD [van Steensel et al., 2013]. To our knowledge, only the study of Yerys et al. (2009) investigated emotional and behavior problems comparing children with ASD+ADHD, children with ASD without ADHD and a typically developing control group. The authors found that the ASD+ADHD group received significantly higher ratings for externalizing problems, attention problems, and hyperactivity than the ASD and Control groups [Yerys et al., 2009]. An advantage of our study, in comparison with previous research, was the use of a four-sample design including ADHD vs. ASD vs. ASD+ADHD vs. control. We found that ADHD, ASD, and ASD+ADHD groups showed higher internalizing and externalizing scores compared with the control group; ADHD and ASD+ADHD groups showed higher externalizing scores and ADHD symptoms compared with ASD and control groups. These findings suggest that ADHD and ADHD+ASD phenotypes are characterized in equal measure by externalizing behavior problems and ADHD symptoms. Moreover, ASD phenotype reported more ADHD symptoms than the Control group confirming previous studies which found that inattentive and hyperactive symptoms are often reported in individuals with ASD [Lord et al., 2000; Leyfer et al., 2006]. Further study is needed to extend the analysis of differences between groups of patients on the clinical aspects.

Regarding the prevalence of ASD symptoms, we found that the ASD+ADHD group reported more ASD symptoms than ASD, ADHD, and control groups. These results are in accordance with Sprenger et al. (2013) who reported that patients with ASD and ADHD symptoms showed more strongly expressed autistic symptoms than children with ASD with no additional ADHD symptoms. Therefore, in ASD+ADHD phenotype, the inattentive and hyperactive symptoms may exacerbate the severity of ASD. However, another possible explanation for the greater severity of autistic symptoms may be the fact that we found a lower IQ in the ADHD+ASD group, compared to the other groups. We also found that ADHD phenotype reported more ASD symptoms than healthy children. The presence of ASD symptoms in individuals with a primary diagnosis of ADHD has been increasingly noted [Hattori et al., 2006; Nijmeijer et al., 2008, 2009]. Several studies have shown social deficits, peer relationship and empathy problems are common in ADHD children [Gillberg et al., 2004; Kadesjö & Gillberg, 2001]. Recently, Cooper et al. (2014) investigated whether higher levels of autistic traits, indicated a more severe presentation in a large sample of children with ADHD symptoms, and suggested that ADHD children reported elevated ratings of core ASD traits not accounted for by ADHD or behavioral problems [Cooper et al., 2014].

Although studies have shown adaptive behavioral difficulties in children diagnosed with ASD and in children with ADHD, it remains poorly investigated whether ASD+ADHD children share similar adaptive functioning impairments. Studies comparing ASD and ADHD groups reported that adaptive functioning is generally impaired in both disorders, but individuals with ASD show more severe impairments [Happé, Booth, Charlton, & Hughes, 2006; Saulnier & Klin, 2008]. Yeyrs et al. (2009) detected that both ASD and ASD+ADHD groups received significantly lower adaptive functioning ratings on the communication, daily living skills, and socialization domains relative to the healthy children group, but the ASD+ADHD group exhibited a more severe impairment in daily living skills compared to the ASD group [Yeyrs et al., 2009]. Recently, Mattard-Labrecque, Ben Amor, & Couture (2013) investigated adaptive behaviors in children with

a dual diagnosis of ASD+ADHD compared with children with ADHD or ASD alone. The authors found that children with ASD+ADHD had a lower performance in all of the adaptive functions except home/school living than children with ADHD [Mattard-Labrecque et al., 2013]. In the present study, no statistically significant difference in adaptive functions between ASD+ADHD and ASD group was found. However, ASD+ADHD and ASD groups reported more impairment in communication, daily living skills, and motor skills compared to ADHD and control groups. These findings suggest that the presence of ADHD does not lead to a greater impairment in adaptive functions, but impairments in these domains may results from increased neurocognitive deficits related to the autism phenotype characterized by difficulties in executive function, organization, and planning skills [Kenworthy et al., 2005]. However, ASD+ADHD, ASD, and ADHD children reported a lower score in social skills compared with the control group. These findings, suggest that the Social skills deficit could be due to impairments in social perception and/or difficulties in emotion recognition, which characterize both ASD and ADHD disorders.

Conclusion

In conclusion, the ASD+ADHD phenotype differs from ADHD or ASD phenotypes in some domains such as IQ and autistic symptoms severity. However, the ASD+ADHD phenotype maintains some clinical aspects that characterize ASD or ADHD phenotypes. In fact, the ASD+ADHD phenotype shares inattention and hyperactivity deficit and emotional and behavior problems with the ADHD phenotype, while it shares the adaptive behavior impairment with the ASD phenotype.

The findings in this study provide some new understanding of the clinical manifestation of the ASD+ADHD phenotype, and it represents a starting point for future research that needs to investigate aspects such as treatment response, neuropsychological measures, etiopathogenesis, and developmental trajectories of the ASD+ADHD phenotype.

Conflict of Interest

All authors declare that they have no conflicts of interest.

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CHILDHOOD AND ADOLESCENT HEADACHE (S EVERS, SECTION EDITOR)

Headache and ADHD in Pediatric Age: Possible Physiopathological Links

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Abstract Primary headache and attention-deficit/hyperactivity disorder (ADHD) are common disorders in children and adolescences, frequently associated to severe cognitive, emotional, and behavioral impairments. They both are a disabling condition with consequences on family and child's quality of life. Literature data on their association are contrasting. Dopaminergic system dysfunction, brain iron deficiency, and sleep disturbance should be considered to better understand headache and ADHD overlap. In this review, we analyze the complex association between these two diseases and the potential impact on child neurodevelopment.

Keywords Migraine · Headache · Hyperactivity · Inattention · ADHD · Comorbidity

Introduction

Literature data on attention-deficit/hyperactivity disorder (ADHD) and primary headache overlap in children are lacking and contradictory. Both the diseases often become disabling for children and families and are accompanied by poor academic performance [1, 2], low cognitive and emotional functioning [3–6], and wrong sleep habits [7, 8], leading to severe impairments of the child's quality of life [9, 10].

Primary headache is common in pediatric population [11], and particularly, migraine is among the most frequent chronic conditions with an estimated prevalence of 10–28 % in children and adolescents [9]. ADHD is the most commonly diagnosed neurodevelopmental disorder in childhood. Diagnoses of ADHD are made based on developmentally inappropriate behavioral symptoms, which have been categorized into three subtypes, inattentive, impulsive, and hyperactive, and a combined type. The DSM-IV-TR reported that 3–7 % of school-aged children have ADHD. However, most recent surveys have estimated significantly increased prevalence rates, from 6.9 % in 1998 to 9.0 % in 2009, shown in children aged 5–17 years [12, 13]. ADHD has been associated to epilepsy [14••], learning disability [15], and behavioral problems [16, 17].

Concentration difficulties and hyperactivity are psychological predictors of headaches [18], and at the same time, frequent headaches may increase distractibility and are associated with impaired attention span [19] and hyperactivity-impulsivity disease [20, 21].

A recent study has found significant high incidence of hyperactivity and impulsivity symptoms in children with headache, compared with healthy controls [22]. Strine et al. [23] evidenced an odds ratio of 2.6 to have inattention and hyperactivity in children who referred headache, and Genizi et al. showed that learning disabilities and ADHD are more common in children and adolescents who are referred for neurological assessment for primary headaches than those described in the general pediatric population [1], while Arruda et al. demonstrated that migraine and TTH are not comorbid to ADHD overall but are comorbid to hyperactive-impulsive behavior [20].

It has been shown that ADHD and migraine have a comorbid connection with mood and anxiety disorders [24–26] with evidences for the involvement of dopaminergic systems in the

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pathophysiology of all three categories of disorders [27]. However, the association between attention deficit disorder and headache type remains controversial. Riva et al. showed a significant association between attention-related problems and headaches in both conditions—migraine and tension-type headache. Headache children compared to healthy controls had more frequently atypical score at Conners' continuous performance test with mean scores in hit reaction time significantly different from those of controls and with no differences between migraine and tension-type headache [28]. Villa et al. [29] described impaired visual attention in children with migraine and suggested that it depends on neurotransmitters such as dopamine and noradrenalin. These same neurotransmitters are involved in the pathophysiology of migraine; therefore, they suggested that it may dispose those children to attention deficit.

Some authors suggested that migraine and tension headache form a continuum that may share the same pathophysiological mechanisms and that the cerebral circuits subserving headache, personality profile, and attention may overlap [30].

Pathogenesis

Structural and functional abnormalities in brain networks have been found to be central in both headache and ADHD pathophysiology. It will be crucial to gain a better understanding of how subcortical-cortical and cortico-cortical network development is altered during the onset of the disorders.

The pathophysiology of primary headaches involves the neurovascular system with the cortical spreading depression and trigeminovascular activation, followed by transmission through the thalamus to higher cortical structures [31, 32]. Studies on headaches and epilepsy comorbidity had given an important support to better understand headache pathogenetic pathways. Many data demonstrated the hypothesis of excessive neocortical cellular excitability as the main pathological mechanism underlying the onset of attacks in both diseases [33]. Indeed, since hypo-excitation and hyper-excitation in migraine occur sequentially as rebound phenomena (during a spreading depression), the term *dys-excitability* may better describe migraine pathophysiology than hyper-excitability [34, 35].

Cortical spreading depression (CSD) can be considered as the link between headache and epilepsy. It is characterized by a slowly propagating wave of sustained strong neuronal depolarization that generates transient intense spike activity, followed by neural suppression, which may last for minutes. The depolarization phase is associated with an increase in regional cerebral blood flow, whereas the phase of reduced neural activity is associated with a reduction in blood flow. On the other hand, CSD activates the trigeminovascular system, inducing the cascade release of numerous inflammatory molecules and neurotransmitters, which results in pain during the migraine attack [36••].

Both migraine and epilepsy have an important genetic component, with strong evidence pointing to a shared genetic basis between headache and epilepsy emerging from clinical/EEG and genetic studies on familial hemiplegic migraine (FHM) [37, 38]. In addition, glutamate metabolism [39], serotonin metabolism [40], dopamine metabolism [41], and ion channel (sodium, potassium, and chloride) function might be impaired in both epilepsy and migraine [36••, 42].

Despite extensive research, the pathophysiological mechanisms underlying ADHD are not completely understood [43]. Neuronal deficits in attention and executive function processing networks have been frequently reported in ADHD, using structural and functional neuroimaging approaches [44, 45]. ADHD is considered one of the most hereditable disorders with an estimated mean heritability of 75 % [46]. Besides the genetic component, ADHD also has neurobiological and environmental underpinnings. The etiology of this highly inhomogeneous disorder is still unknown. Apart from the behavioral symptoms that are used for diagnostic measurements, both children and adults with ADHD have been found to have impairments in neural networks associated with sensory and cognitive processing functions. For instance, neuronal deficits inattention and executive function processing networks have been frequently reported in both children and adults with ADHD, using sophisticated structural and functional neuroimaging approaches. Neuroimaging studies have demonstrated global cortical maturation delay based on reduced cortical thickness and reduced gray matter (GM) and white matter (WM) volumes, specifically in the frontal lobe [47]; regional WM microstructural abnormalities in the frontal, temporal, and parietal lobes [48–50]; and aberrant neuronal activations in the inter-regional functional connectivity of these cortical areas [51, 52]. In addition, spontaneous low-frequency functional activities have been reported in multiple brain regions, which formed the default mode network (DMN), during wakeful resting-state functional magnetic resonance imaging (fMRI) acquisition. Patients with ADHD have been reported to have both structural and functional abnormalities associated with the DMN [51, 53].

All these structural and functional abnormalities in the brain have been associated with impaired cognitive, affective, and motor behaviors seen in ADHD approaches.

Sleep disorders may be considered one of the possible mechanisms to explain headache and ADHD overlap. Epidemiologic and physiopathology studies showed that headache, ADHD, and sleep disorders seem to be related to dysfunction in the same brain structure, involved in the control of the sleep–wake cycle as well as in the arousal generation during sleep and modulation of pain.

More than 70 % of children with ADHD have been reported as having mild to severe sleep problems including bedtime

resistance, sleep-onset difficulties, night awakenings, difficulties with morning awakenings, sleep-disordered breathing, and daytime sleepiness [54]. Five sleep phenotypes may be identified in ADHD: one characterized by a hypo-arousal state, a phenotype associated with delayed sleep-onset latency and a higher risk of bipolar disorder, a phenotype associated with sleep-disordered breathing (SDB), a phenotype related to restless leg syndrome (RLS) and/or periodic limb movements (PLMs), and lastly, a phenotype related to epilepsy or EEG interictal discharges [55•, 56]. Each sleep phenotype is characterized by sleep alterations expressed by either an increased or decreased level of arousal during sleep. Both an increase and a decrease in arousal are linked to executive dysfunctions controlled by prefrontal cortical regions and arousal system, which may be hyperactivated or hypoactivated depending on the form of ADHD/sleep phenotype [55•, 57].

It is known that sleep is related to the occurrence of some headache syndromes, while headache may cause sleep disruption and several sleep disturbances. Headache episodes are known to occur in relationship with various sleep stages, and on the other hand, a bad quality or inadequate duration of sleep can trigger headache [7, 8].

The hypothalamus is connected with anatomical structures involved in the control of the sleep–wake cycle as well as in the modulation of pain [58] (limbic system, pineal gland, noradrenergic locus coeruleus, and serotoninergic dorsal raphe), with serotoninergic and dopaminergic system playing an important role in the relationship between headache and sleep. Dysfunctional hypothalamic activity, in particular of the ventrolateral part of the periaqueductal gray matter (PAG), might contribute to both altered sleep–wake function and altered pain processing via its orexinergic neurons [59]. Orexin can stimulate neurons in the ventrolateral part of the PAG, inhibiting antinociceptive activity in the trigeminal nucleus caudalis, thus facilitating trigeminal nociception and triggering a migraine attack.

There is initial evidence that the use of melatonin in children with both ADHD and headache is grounded on a pathophysiological rationale.

Melatonin is a chronobiotic substance, and its chronobiological production alteration, associated to damaged serotoninergic and dopaminergic pathways which characterize both migraine and sleep disease, could play a role from the early period of life and tend to persist during childhood and adolescence, leading to disorders of the sleep–wake rhythm in infancy and determination of the comorbidity between neurodevelopment and headache [60]. Melatonin genetic pathways have been found to be abnormal in children with ADHD, a delay in dim-light melatonin onset (DLMO) has been reported in children with ADHD, and at the same time, it has been related to headache through different ways [57].

Melatonin showed an antinociceptive effect, and it acts as a free radical scavenger reducing macromolecular damage and inhibits the production of pro-inflammatory cytokines. It is involved in membrane stabilization as well as inhibition of the activity of nitric oxide synthase. It can decrease dopamine and glutamate release and can also potentiate the receptor-mediated response of GABA and the opioid immune response [57].

The hypothalamus is involved in the prodromal symptoms of migraine, such as hunger, fatigue, mood changes, and sensory and visual distortions, which are commonly considered as dopaminergic premonitory symptoms [61, 62]. Individuals susceptible to migraine appear to have genetic polymorphisms in the dopamine D_2 gene, with an increased responsiveness to dopamine, or defects in tyrosine hydroxylase, which inhibits dopamine metabolism. At the same time, this imbalance of the dopaminergic system with altered modulation of synaptic potentiation and pruning by dopamine during development, resulting in altered patterns of cortico-cortical connectivity, has been linked to the structural and functional connectivity deficits of the ADHD [63].

Between the variety of phenomena that can disrupt the sleep macrostructure and can impact its restorative function, the PLM disorder can be considered as the most powerful. PLM has also been associated to both headache and ADHD. A dopaminergic dysfunction and iron deficiency (ID) may be the neuroanatomical substrate linking migraine, ADHD, and PLM [64]. Iron is a coenzyme necessary for the synthesis and catabolism of monoaminergic neurotransmitters, which are implicated in ADHD pathophysiology [65]; ID is associated with decreased dopamine transporter expression [66]; variation in the corresponding dopamine transporter gene has been linked to genetic vulnerability for ADHD [67], and finally, ID may lead to dysfunction in the basal ganglia [68], which have been implicated in the pathophysiology of ADHD [69]. Cortese et al. [70] suggested that it is low brain iron, not necessarily peripheral iron, to increase the risk for ADHD, due to dysfunction in the blood–brain barrier, which regulates the entry of iron into the brain. It has been shown by an MRI study that there increased iron depositions in the periaqueductal gray matter in migraineurs, suggestive of a disturbed central antinociceptive neuronal network. Iron is essential in oxygen carrier proteins and in many metabolic enzymes. Brain tissue is characterized by a high iron utilization, given the elevated oxygen consumption (up to 25 % of total oxygen consumption of the body). Non-heme iron, primarily stored inside the non-toxic ferritin protein, can also be present in an unshielded, soluble form, becoming toxic through the formation of free radicals, which can lead to DNA, protein, and neuronal cell damage [71, 72].

Transferrin receptor binding is proportional to the metabolic activity of the neuron and, in turn, may be influenced by nociceptive function [73], so repeated migraine attacks are associated with increased iron concentration/accumulation in multiple deep nuclei that are involved in central pain processing and migraine pathophysiology [74, 75••, 76].

Conclusion

Literature data are still controversial about the epidemiological association between headache and ADHD. The same brain network seems to be involved in their pathogenesis, and this, of particular interest, is a functional brain RMN study, focusing on the importance of the hypothalamic structure and the dopaminergic and serotoninergic system. These study confirms the involvement of the same brain structure that acts in control of the sleep–wake cycle as well as in the arousal generation during sleep and modulation of pain, explaining the link between sleep structure alteration and both headache and ADHD. Iron brain metabolism abnormalities may be also involved, in particular, considering the known link between its deficiency and sleep disorders related to both ADHD and headache. Future research is needed to better define this complex association and its impact on neurocognitive and behavioral child development.

Compliance with Ethics Guidelines

Conflict of Interest Maria Chiara Paolino, Alessandro Ferretti, Maria Pia Villa, and Pasquale Parisi each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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