NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD OTTOBRE 2018

ADHD Atten Deficit Hyperact Disord. 2018.

EFFECT OF PHYSICAL EXERCISES ON ATTENTION, MOTOR SKILL AND PHYSICAL FITNESS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW .

***Jeyanthi S, Arumugam N, Parasher RK*.**

Children with attention deficit hyperactivity disorder (ADHD) are educated in classrooms along with typically developing children. Those with ADHD, however, find it difficult to participate in routine educational and recreational activities as they encounter problems associated with behaviour, attention, motor skills and physical endurance. Traditionally, the management of children with ADHD has focussed primarily on problems with cognition and has been heavily dependent on pharmaceutical interventions and, to a lesser extent, on non-pharmaceutical measures. More recently, experts have increasingly advocated the use of exercises in alleviating symptoms associated with ADHD. The primary objective of this review was to summarize research that examined the role of exercises on deficits related to attention, motor skills and fitness in children with ADHD. A search of the available literature was conducted using a combination of relevant key words in the following databases: PubMed, MEDLINE, Google Scholar, Embase and Cochrane review. The search filtered 3016 studies of potential relevance, of which 2087 were excluded after screening titles and abstracts as per the inclusion criteria. Thirty-four (34) studies were analysed in greater depth, and 16 were excluded after detailed consideration as they did not match the inclusion (PEDro score > 4) and exclusion criteria. Three (3) additional studies were excluded as they lacked exercise prescription details such as intensity, duration and frequency of exercise. Finally, 15 studies were analysed with a focus on the effects of physical exercises on attention, hyperactive behaviour, motor skills and physical fitness in ADHD children. Overall, the studies reviewed were of moderate-to-high quality and reported benefits of a variety of exercise programmes in improving motor skills, physical fitness, attention and social behaviour in children with ADHD. However, there was limited information regarding school-based programmes, the effects of structured exercise programmes independently or in combination with cognitive-based therapies, and the long-term benefits of exercises in alleviating behavioural problems in these children

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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. 2018.

INDIVIDUAL DIFFERENCES IN TENDENCIES TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND EMOTIONALITY: EMPIRICAL EVIDENCE IN YOUNG HEALTHY ADULTS FROM GERMANY AND CHINA.

Wernicke J, Li M, Sha P, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is characterized by inattention, hyperactivity, and impulsivity but also by negative emotionality. The aim of the present study was to investigate whether subclinical ADHD tendencies are associated with negative emotionality in healthy adult samples. The present study is of special interest since it investigated negative emotionality with a questionnaire anchored in Neuroscience Theory the Affective Neuroscience Personality Scales (ANPS). Furthermore, through the investigation of samples in two countries, namely Germany and China, the study aims to replicate the results across different cultures. German (n = 377; age: M = 23.25, SD = 8.47; 117 males) and Chinese (n = 389; age: M = 20.74, SD = 2.47; 279 males) subjects completed ANPS (primary emotional traits) and ASRS (ADHD tendencies) questionnaires in an online survey. Principal component analysis of the ANPS revealed one factor for negative emotionality and one factor for positive emotionality. Partial correlations between ANPS and ASRS (controlled for age) were conducted separately for nation and gender. The same correlation patterns between ADHD tendencies and negative emotionality could be found in male and female German/Chinese participants (range r =.189 to r =.352). Higher negative emotionality was always significantly associated with more inattentive, hyperactive/impulsive, or combined tendencies. However, significant negative correlations between ADHD tendencies and positive emotionality could only be observed in Chinese males (range r = .264 to r = .296). The results are in line with former findings in children and show that also in healthy adults, associations between negative emotionality and ADHD tendencies are robustly visible. The results were independent of the cultural background, indicating a general association between ADHD tendencies and negative emotionality, even in healthy adults

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Am Econ Rev. 2018 Apr;108:1214-52.

FAMILY RUPTURES, STRESS, AND THE MENTAL HEALTH OF THE NEXT GENERATION.

Persson P, Rossin-Slater M.

This paper studies how in utero exposure to maternal stress from family ruptures affects later mental health. We find that prenatal exposure to the death of a maternal relative increases take-up of ADHD medications during childhood and anti-anxiety and depression medications in adulthood. Further, family ruptures during pregnancy depress birth outcomes and raise the risk of perinatal complications necessitating hospitalization. Our results suggest large welfare gains from preventing fetal stress from family ruptures and possibly from economically induced stressors such as unemployment. They further suggest that greater stress exposure among the poor may partially explain the intergenerational persistence of poverty

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Am J Epidemiol. 2018;187:1896-906.

ASSOCIATION OF MATERNAL EXPOSURE TO CHILDHOOD ABUSE WITH ELEVATED RISK FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN OFFSPRING.

Roberts AL, Liew Z, Lyall K, et al.

Children whose mothers experienced childhood abuse are more likely to suffer various neurodevelopmental deficits. Whether an association exists specifically for attention deficit hyperactivity disorder (ADHD) is unknown. We examined the association of maternal experience of childhood abuse with ADHD in offspring, assessed bymaternal report of diagnosis and validated with the ADHD Rating Scale-IV in a subsample, in the Nurses' Health Study II (n = 49,497 mothers; n = 7,607 case offspring; n = 102,151 control offspring). We examined whether 10 adverse perinatal circumstances (e.g., prematurity, smoking) or socioeconomic factors accounted for a possible association. Exposure to abuse was associated with greater prevalence of ADHD in offspring (8.7% of offspring of women exposed to severe abuse vs. 5.5% of offspring of women not abused, P = 0.0001) and with greater risk for ADHD when the model was adjusted for demographic factors (male offspring, risk ratio (RR) = 1.6, 95% confidence interval (CI): 1.3, 1.9; female offspring, RR = 2.3, 95% CI:

1.7, 3.0). After adjustment for perinatal factors, the association of maternal childhood abuse with ADHD in offspring was slightly attenuated (male offspring, RR = 1.5, 95%CI: 1.2, 1.8; female offspring, RR = 2.1, 95%CI: 1.6, 2.8). We identified an association betweenmaternal experience of childhood abuse and risk for ADHD in offspring, which was not explained by several important perinatal risk factors or socioeconomic status

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Am J Med Genet Part B Neuropsychiatr Genet. 2018.

LIKE PARENT, LIKE CHILD: ATTENTION DEFICIT HYPERACTIVITY DISORDER-LIKE CHARACTERISTICS IN PARENTS OF ADHD CASES.

Trejo S, Matute E, de LRR-Da, et al.

The objective of this study was to characterize an attention deficit hyperactivity disorder (ADHD) endophenotype in non-affected parents of adolescents with a history of ADHD, based on the relationship between performance on a sustained attention test (continuous performance task, or CPT) and polymorphisms of the DRD4 gene. In a sample of 25 non-affected parents of adolescents with ADHD history obtained from a longitudinal study of a nonclinical population, and 25 non-affected parents of adolescents with no ADHD history, four groups were evaluated with respect to the presence or absence of the long allele polymorphism of the DRD4 gene (i.e., over seven repeats). Comparisons of CPT performance among the four study groups included the number of commission errors, the number of omission errors, mean reaction time on correct responses (MRT), and reaction time (RT) variability (mean standard deviation of RT in each block [SDRT, as variability], and the sigma and tau components of the ex-Gaussian approach). The group of non-affected parents of adolescents with ADHD history and at least one long allele of the DRD4 gene showed greater RT variability (measured by SDRT), which is best explained by the greater frequency of abnormally slow responses (measured by tau). An association between the presence of the long allele of the DRD4 gene polymorphism and ADHD-like failure in CPT performance was evident in the non-affected parents of adolescents with ADHD in childhood. These findings suggest that certain traits of CPT performance could be considered an ADHD endophenotype

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Ann Neurol. 2018;84:S366.

AUTOIMMUNE GLIAL FIBRILLARY ACIDIC PROTEIN ASTROCYTOPATHY FOLLOWING HERPES SIMPLEX VIRUS ENCEPHALITIS IN A PEDIATRIC PATIENT.

Maureen H, Takacs D, Hong W, et al.

Objective: To describe a case of pediatric autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy following herpes simplex virus (HSV) encephalitis, presenting with predominantly psychiatric manifestation and cognitive decline. This follows a recent case report describing an adult case of GFAP astrocytopathy after HSV encephalitis.

Methods: Cerebrospinal fluid (CSF), serum studies, magnetic resonance imaging, electroencephalogram, were performed according to routine institutional protocol. Prior neuropsychological test reports were obtained with parents' written consent. We performed a systematic literature search in PubMed and EMBASE on GFAP astrocytopathy.

Results: A 13 year old with history of ADHD developed mood and behavioral changes a few months after recovering from HSV encephalitis. His symptoms include anxiety, impulse control difficulties such as disinhibition and hypersexuality, hoarding, emotional lability, and aggression, which progressively worsened prior to his hospital admission. Neuropsychological testing revealed significant declines in neurocognitive and behavioral functioning. MRI brain did not reveal new signal abnormalities other than evolution of cystic encephalomalacia from his prior HSV encephalitis. His CSF was positive for antibody against GFAP, and he was diagnosed with GFAP astrocytopathy. He was started on immunotherapy with intravenous corticosteroids and immunoglobulins, and is currently being monitored for improvement.

Conclusions: Autoimmune GFAP astrocytopathy is a novel autoimmune disease which can present in children with primary neurocognitive and psychiatric manifestations. This is the first pediatric case suggesting

a link between GFAP astrocytopathy and a viral trigger such as HSV encephalitis, as has been described in anti-N-methyl-d-aspartate receptor encephalitis

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Ann Neurol. 2018;84:S368.

HOME-BASED, THERAPIST-ASSISTED, THERAPY FOR YOUNG CHILDREN WITH PRIMARY COMPLEX MOTOR STEREOTYPIES.

Singer H, Rajendran S, Waranch H, et al.

Objective: Complex motor stereotypies (CMS) begin before age 3 years and include rhythmic, repetitive, fixed movements that last for seconds-minutes, and stop with distraction. Our goal was to evaluate the effectiveness of a homebased, parent-provided therapy accompanied by telephone calls with a therapist, in 5-7 year-olds with primary CMS.

Methods: Eligible families received an instructional DVD, written instructions, and scheduled telephone contacts with a therapist-at baseline (DVD receipt), 1, 3, and 8 weeks later. At each call, parents completed outcome measures and received feedback. Outcome scales (Stereotypy Severity Scale (SSS) Motor and Impairment scales and a Stereology Linear Analogue Scale (SLAS) were also completed via the internet (REDCap)-at screening, 1 and 2 months post baseline call. At study conclusion, participants were divided into an Intent-to-Treat (ITT; had at least one call) or a Lost-to-Follow-up (LFT) group.

Results: 38 children (m=5 years + 11 months) were enrolled. The LTF (n=14) had significantly higher scores, than the ITT (n=28) group, on all ADHD ratings ($p<0.01$), but not stereotypy severity. Primary outcome scores, acquired by telephone and REDCap, showed a significant reduction in SSS Motor and Impairment scores between the initial and the last completed evaluation ($p<0.001$). Calculated change ratios were SSS Motor-0.23/-0.30 (call/REDCap); SSS Impairment-0.31/-0.32; and SLAS-0.54 (REDCap). Clinical improvement was further supported by results from a parent improvement scale and end of study questionnaires.

Conclusions: Home-based, parent-administered behavioral therapy supplemented by telephone contact with a therapist is effective in reducing complex motor stereotypies in children

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Ann Neurol. 2018;84:S360.

NEUROLOGICAL AND PSYCHOLOGICAL VULNERABILITIES IN PEDIATRIC CELIAC DISEASE.

Parker M, Coburn S, Sady M, et al.

Objective: This study aimed to examine the neurological, neuropsychological and psychological vulnerabilities in children with Celiac Disease (CD) to inform clinical care models.

Methods: Ninety-six parents of children ages 2-18, with biopsy proven CD, completed a pre clinical Redcap survey on neurological, cognitive, and psychological symptoms. Current psychosocial experiences were reported using visual analogue scales (0=none, 100=extreme). In addition, 32 patients with CD had structured face to face interviews with a neurologist, neuropsychologist and psychologist to assess symptoms.

Results: Parents reported child headaches (40.0%), fatigue (44.0%), cognitive/learning/attention problems (36.0%), sleep difficulties (21.3%), and emotional or behavioral difficulties (2.7%). Forty-three percent reported a psychological diagnosis, compared to 17.9% in the general pediatric population (NIMH, 2015). Most common conditions included ADHD (22.2%), anxiety disorder (16.7%), developmental delay (8.3%), and learning disorder (5.6%). In structured interviews, 56% of patients reported neurologic symptoms with headaches ranked highest (37.5%). Other complaints include neuropathy (18.8%) and fatigue (15.6%). Thirty-two percent screened positive for school problems, specifically difficulty with organization, memory, staying focused, completing work on time, impulsivity/hyperactivity, and understanding new material. Mood disorder (43.7%) and primarily anxiety (43%) were the most common psychological concerns, followed by depression (15.6%). Thirty-seven percent also screened positive for behavioral concerns; with anger and distress most widely recognized.

Conclusions: Neurological, cognitive, and mental health vulnerabilities were reported and observed frequently and at higher rates than the general population. Therefore, neurological, neuropsychological, and psychological services should be incorporated into medical treatment for CD. Multi-disciplinary care is an ideal environment for CD treatment

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Ann Neurol. 2018;84:S319.

HEALTHCARE EXPENDITURES ASSOCIATED WITH TIC DISORDERS IN U.S. CHILDREN, 2013.

Bitsko R, Gupta P, Danielson M, et al.

Objective: To describe healthcare expenditures associated with tic disorders (TDs).

Methods: Truven Health MarketScanR data comprised convenience samples of U.S. children aged 6-17 years in 2013 with public (Medicaid or Children's Health Insurance Program, n=2,202,883) or commercial insurance (n=4,318,446). TDs were defined as having one inpatient claim or two outpatient claims at least seven days apart with ICD-9-CM code 307.2x. Outpatient, inpatient, drug, and total expenditures were calculated for children with and without TDs, matched on age, sex, and insurance type (capitated vs. fee-for-service). Log total expenditures from matched samples were adjusted for the presence of five co-occurring disorders (attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, autism spectrum disorder, anxiety disorder, and communication and language disorder), using the same algorithm as for TDs.

Results: Children with TDs had higher median total expenditures compared to those without ($1,648 vs. $477 for commercial insurance; $1,787 vs. $450 for public). Children with TDs had higher overall, drug, and inpatient expenditures, but lower outpatient expenditures. Children with TDs had incremental costs of $1,037 (commercial) and $1,001 (public) after matching. Co-occurring disorders were present in 70.9% (public) and 57.7% (commercial) of children with TDs. The incremental cost for TDs, after adjusting for co-occurring disorders, was $386 for commercial insurance; there was no longer a cost difference for Medicaid.

Conclusions: Higher overall healthcare expenditures among children with TDs compared to those without TDs were driven by higher drug and inpatient expenditures. Co-occurring disorders contributed a significant portion of the expenditures, and fully accounted for incremental costs of TDs in the Medicaid sample

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Ann Neurol. 2018;84:S318.

COMPLEXITIES OF TOURETTE SYNDROME: DIAGNOSIS, SEVERITY, IMPAIRMENT, AND TREATMENT.

Wolicki S, Bitsko R, Danielson M, et al.

Objective: Describe the diagnosis, impairment, and treatment of Tourette syndrome (TS).

Methods: We analyzed data from the 2014 National Survey of the Diagnosis and Treatment of ADHD and Tourette Syndrome (NS-DATA). NS-DATA is a follow-back survey of parents/caregivers who reported yes on the 2011-2012 National Survey of Children's Health to has a doctor or other health care provider ever told you that your child had [attention-deficit/hyperactivity disorder or TS Descriptive analyses include percentages or means and standard deviations (SD). We calculated Fisher's exact tests for severity comparisons.

Results: In this sample of 115 children ever diagnosed with TS (by parent report), the mean age of reported tic onset was 6.3 years (SD=2.6), mean age of TS diagnosis was 7.7 years (SD=2.7), and mean age when TS symptoms were worst was 9.3 years (SD=2.9). Most children (84.6%) had one or more cooccurring mental or developmental disorder(s). Most (77.2%) children had ever received any type of TS treatment; of those, 48.9% had received both medication and behavioral treatment. Three-quarters (73.0%) of parents/caregivers reported worst TS severity as mild or moderate, versus severe (27.0%). Tic-related impairment and treatment were associated with severity (figure 1, $p<0.05$). Experiences and activities had varying effects on tics (figure 1).

Conclusions: TS symptoms begin in childhood, are associated with varying impairment, and are influenced by cooccurring disorders and the environment. These findings support other research to increase understanding of TS and potential complexities regarding how best to support those living with TS and their families

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Appl Neuropsychol Child. 2018 Oct;7:366-73.

DEVELOPING ADHD IN PRESCHOOL: TESTING THE DUAL PATHWAY MODEL OF TEMPERAMENT.

Kerner auch Koerner J, Gust N, Petermann F.

The dual pathway model of Attention Deficit Hyperactivity Disorder (ADHD) suggests that effortful control and positive approach, or surgency, are independent pathways leading to ADHD. This model has been proven on the basis of temperament in school children, however not in preschool children. In this study we tested whether the dual pathway model of ADHD can be replicated in preschool children using temperamental measures. One hundred and nineteen children (59 girls, M-age = 4.97 years, SD = 0.96) participated in a study. Parents rated temperament on the Child Behavior Questionnaire (CBQ) and parents and teachers rated ADHD symptoms (SDQ). We found that effortful control and surgency independently predicted preschool ADHD symptoms but there were no moderations or mediations. Our findings support the dual pathway model of temperament but not compensatory models of ADHD. Ratings of temperament might be an important predictor of which child is at risk to develop clinical ADHD later on and therefore an important part of prevention

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Appl Neuropsychol Child. 2018 Oct;7:287-97.

NOVEL READING INDEX FOR IDENTIFYING DISORDERED READING SKILL DEVELOPMENT: A PRELIMINARY STUDY.

Mohl B, Ofen N, Jones LL, et al.

Children with ADHD are at high risk of developing a Reading Disability (RD), although the reasons remain unclear. ADHD-associated impairments, including processing speed, can complicate clinical evaluation for a co-occurring RD diagnosis. We propose a novel metric to (a) assess reading development and (b) provide an alternative method to classifying readers that may aid investigations for etiologies of RD in ADHD. Specifically, as both phonological decoding and word recognition skills are important precursors of reading fluency, we propose a new quantitative method comparing these skills after accounting for variations in perception, motor response, or processing speeds. Forty boys (14 control, 15 ADHD, 11 ADHD/ + RD) completed a lexical decision task testing decoding and another assessing word recognition. Response time data was modeled using a Drift Diffusion approach to estimate the underlying reading skills. Using these reading skill estimates, we calculated a novel Reading Tendency Index and classified participants into three reading groups (Decoders, Balanced Readers, and Sight Readers). The reading and cognitive performance of these groups were consistent with theoretical predictions and subsequently provided external validity for the novel Reading Tendency Index classification. Our findings demonstrate a potential classification tool for readers based on individual's developed, reading tendencies

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Archivos Venezolanos de Farmacologia y Terapeutica. 2018;37:205-11.

NEUROFEEDBACK EFFECTS ON COGNITIVE PERFORMANCE IN CHILDREN WITH ATTENTION DEFICIT.

Riaño-Garzón ME, et al.

The objective of this research was to analyze the effects of an intervention program through neurofeedback, on the cognitive performance in children with inattention indicators. A quasi-experimental pretest-posttest study was used under a positivist epistemology, with a comparative analysis for each evaluated cognitive process. A sample of 29 cases was intentionally selected from a group of children and young adolescents with low performance indicators from a Therapeutic Center from Cucuta-Colombia. The neurofeedback program was developed in 20 sessions with the purpose of increase low-beta waves (12-16 Hz) and inhibition

theta waves (4-7 Hz). A comparative statistically analysis with five months of difference was carried out using Wilcoxon test, finding significant differences between the pretest and the posttest in neuropsychological tests of auditory-visual attention, encoding memory and planning. The results are discussed with empirical backgrounds that have shown positive effects in this type of interventions

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Asian J Psychiatry. 2018.

UNDERSTANDING PARENTAL CAUSAL EXPLANATIONS AND HELP SEEKING IN ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER: PERSPECTIVES FROM A DEVELOPING ASIAN NATION.

Shah R, Sharma A, Chauhan N, et al.

Introduction: Research on parental understanding of causation and help-seeking for ADHD comes from ethnic minorities in developed nations; research from Asia is scarce. Our purpose was to explore perceptions of Indian parents regarding causation and diagnosis of problematic childhood behaviors diagnosed as ADHD or hyperkinetic disorder, and to understand the process of decision making and help seeking using a qualitative study design.

Method: In-depth, semi-structured interviews were conducted with 52 parents (33 mothers and 19 fathers), focusing on initial emotional reactions and cognitive appraisals, decision making, parental causal explanations and perceptions regarding diagnosis and symptom labeling.

Results: Mothers were decision makers for seeking professional help either singly or jointly in 76.1% of cases. Initial reactions ranged from those with negative valence (negative emotional reactions and cognitive appraisals) to ambi-valence (recognition of problems, but at the same time not accepting completely) and positive valence (sense of relief and hopefulness). Psycho-social explanations (63.46%) were more common than biological explanations (51.82%), with 19.23% reporting both explanations. Biological explanations included illness model (e.g. brain problem, obstetric complications), hereditary and intellectual disability. Psycho-social explanations included psychological (e.g. lack of motivation) and social (e.g. problems with disciplining at home) causations. Irrespective of initial reactions and causal explanations, a significant majority of parents were aware of the diagnosis and labeled problems as symptoms attributable to ADHD.

Conclusion: Our findings provide insights for development of culturally sensitive psycho-social interventions; from understanding of causal attributions, process of decision making and help seeking

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Basic and Clinical Pharmacology and Toxicology. 2018;123:22.

CONCOMITANT USE OF PSYCHOTROPIC DRUGS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Ruiz-Antor+ín B, Javaloyes L, Maresca MIP, et al.

Objectives: To describe the profile of current drug therapy use in paediatric patients diagnosed of ADHD in specialized health care and its evolution from 2011 to 2017. To analyse the concomitant use of medicines associated with stimulants for the treatment of ADHD with/without psychiatric- comorbidity.

Methods: Retrospective, longitudinal drug utilizationstudy. We included all patients with electronic medical records, seen at the paediatrics Northwestern mental health area of Madrid, between 2011 and 2017 with a diagnosis of ADHD (ICD10: F90.0-F90.9).

Results: Of the 7070 pediatric patients attended in the Mental Health Area, 3416 with ADHD, 44% had associated psychiatric-comorbidities. The analysis showed a progressive increase in the percentage of patients diagnosed, from 28.4% (2011) to 59.6% (2017). The percentage of ADHD with psychiatric-comorbidity remained stable. The overall percentage of treated patients increased from 74% (2011) to 87% (2017). There were no significant differences in relation to patients who had associated comorbidity (2017: 86.2% vs. 86.9%). The frequency of prescription for each pharmacological group is shown in Table 1. (Table presented)

Conclusions: The diagnosis of ADHD has increased between the years 2011-2017. The percentage of ADHD patients with pharmacological treatment remained stable. There is concomitant use of other psychotropic drugs, particularly antidepressants and antipsychotics, in a 6-8% percentage of ADHD patients without other psychiatric diagnoses

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Bioanalysis. 2018 Jun;10:839-50.

NOVEL AND RAPID LC-MS/MS METHOD FOR QUANTITATIVE ANALYSIS OF METHYLPHENIDATE IN DRIED BLOOD SPOTS.

Gandhi A, Beekman C, Parker R, et al.

AIM: Development and validation of a novel, sensitive, specific and rapid dried blood spots (DBS)-LC-MS/MS method for methylphenidate (MPH), an attention-deficit hyperactivity disorder drug.

Methodology & results: Protein precipitation with acetonitrile was used to extract MPH from the DBS cards. Chromatographic separation was achieved on a Zorbax C18 column using an isocratic mobile phase composed of acetonitrile and 5 mM ammonium formate buffer (20:80, v/v) at a flow rate of 0.5 ml/min. MPH was quantified over a linear range of 200-25,000 pg/ml.

CONCLUSION: The clinical DBS-LC-MS/MS method was successfully validated as per the US FDA's Bioanalytical Method Validation Guidance to support an ongoing pediatric pharmacokinetic study

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Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2018;3:927-36.

PRESCHOOL EXECUTIVE FUNCTION PREDICTS CHILDHOOD RESTING-STATE FUNCTIONAL CONNECTIVITY AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND DEPRESSION.

Hawkey EJ, Tillman R, Luby JL, et al.

Background: Measures of executive function (EF), such as the Behavior Rating Inventory of Executive Function, distinguish children with attention-deficit/hyperactivity disorder (ADHD) from control subjects, but less work has examined relationships to depression or brain network organization. This study examined whether early childhood EF predicted new onset or worsening of ADHD and/or depression and examined how early childhood EF related to functional connectivity of brain networks at school age.

Methods: Participants included 247 children who were enrolled at 3 to 6 years of age from a prospective study of emotion development. The Behavior Rating Inventory of Executive Function Global Executive Composite score was used as the measure of EF in early childhood to predict ADHD and depression diagnoses and symptoms across school age. Resting-state functional magnetic resonance imaging network analyses examined global efficiency in the frontoparietal, cingulo-opercular, salience, and default mode networks and six hub seed regions selected to examine between-network connectivity.

Results: Early childhood EF predicted new onset and worsening of ADHD and depression symptoms across school age. Greater EF deficits in preschool predicted increased global efficiency in the salience network and altered connectivity with four regions for the dorsal anterior cingulate cortex hub and one region with the insula hub at school age. This altered connectivity was related to increasing ADHD and depression symptoms.

Conclusions: Early executive deficits may be an early common liability for risk of developing ADHD and/or depression and were associated with altered functional connectivity in networks and hub regions relevant to executive processes. Future work could help clarify whether specific EF deficits are implicated in the development of both disorders

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BJPsych Open. 2017;3:141-46.

SMOKING, ALCOHOL AND DRUG USE IN YOUTH AND ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Osland S, Hirsch L, Pringsheim T.

Background Previous research suggests a relationship between attention-deficit hyperactivity disorder (ADHD) and smoking, alcohol and illicit drug use, however most studies have focused on adolescents or young adults, or clinically ascertained samples.

Aims To analyse population-based data on the relationship between ADHD and at-risk health behaviours in adolescents and adults.

Method Data were derived from a Statistics Canada population-based health survey. The association between the diagnosis of ADHD and smoking, alcohol use, and illicit drug use was examined.

Results Individuals with ADHD started smoking at a younger age. They consumed more alcoholic drinks on drinking days, and women with ADHD were more likely to engage in binge drinking. Women over the age of 25 and men with ADHD were more likely to meet alcohol-dependence lifetime criteria. People with ADHD were at a greater risk of drug misuse and dependence.

Conclusions People with ADHD are more likely to partake in at-risk behaviours

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BMC Med Educ. 2018 Jul;18:164.

ASSOCIATIONS BETWEEN SYMPTOMS OF ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER AND LIFE SATISFACTION IN MEDICAL STUDENTS: THE MEDIATING EFFECT OF RESILIENCE.

Shi M, Liu L, Sun X, et al.

BACKGROUND: Research on symptoms of attention-deficit/hyperactivity disorder (ADHD) in medical students is rather scant. Studying the disorder in this population, especially its associations with positive psychological constructs can further the understanding of mental health in future physicians. The objectives of the present study were to investigate the prevalence of ADHD symptoms in medical students, to examine the relationships between ADHD symptoms and life satisfaction, and to explore the mediating role of resilience on the associations.

METHODS: This cross-sectional study was carried out at one medical university in China, in June 2016. Self-reported questionnaires consisting of Adult ADHD Self-Report Scale (ASRS), Wender Utah Rating Scale (WURS), Conner-Davidson Resilience Scale (CD-RISC), Satisfaction With Life Scale (SWLS), and socio-demographic characteristics, were distributed to the students. Hierarchical linear regression analyses were used to examine the effects of ADHD symptoms on life satisfaction, and asymptotic and resampling strategies were used to explore the mediating role of resilience.

RESULTS: A total number of 521 medical students became final subjects. Based on the cutoffs of the scales, 1.54% of the medical students were highly likely to have ADHD, and 6.91% of the students were likely to have ADHD. Only inattention was negatively correlated with life satisfaction in the students. Resilience functioned as a mediator in the relationship between inattention and life satisfaction.

CONCLUSIONS: The prevalence of ADHD symptoms among Chinese medical students could be relatively high. Inattention is significantly related to life satisfaction among the students. Early identification of medical students with ADHD symptoms should be warranted. Resilience intervention programs might be undertaken to enhance life satisfaction in medical students, especially for those with inattention symptoms

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BMC Neurol. 2018;18.

COMORBIDITY OF MIGRAINE WITH ADHD IN ADULTS 11 MEDICAL AND HEALTH SCIENCES 1117 PUBLIC HEALTH AND HEALTH SERVICES 17 PSYCHOLOGY AND COGNITIVE SCIENCES 1701 PSYCHOLOGY.

Hansen TF, Hoeffding LK, Kogelman L, et al.

Background: Migraine and Attention Deficit and Hyperactivity Disorder (ADHD) have been found to be associated in child and adolescent cohorts; however, the association has not been assessed in adults or otherwise healthy population. Assessing the comorbidity between ADHD and migraine may clarify the

etiopathology of both diseases. Thus, the objective is to assess whether migraine (with and without visual disturbances) and ADHD are comorbid disorders.
Methods: Participants from the Danish Blood Donor Study (N = 26,456, age 18-65, 46% female) were assessed for migraine and ADHD using the ASRS ver 1.1 clinically validated questionnaire and self-reported migraine in a cross-sectional study. Logistic regression was used to examine the comorbidity between migraine and ADHD, and their associated endophenotypes.
Results: Migraine was strongly associated with ADHD (OR = 1.8, 95% CI = 1.5-2.1), (238/6152 vs 690/19,376). There was a significant interaction between age and gender, with comorbidity increasing with age and female sex. Post-hoc analysis showed that migraine with visual disturbance was generally associated with a marginally higher risk of ADHD and this was independent of ADHD endophenotypes.
Conclusion: Migraine and ADHD were demonstrated to be comorbid disorders; the association with ADHD was most prominent for participants with migraine with visual disturbances. Future studies will elucidate which genetic and environmental factors contribute to migraine-ADHD comorbidity

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BMC Psychiatry. 2018;18.

THE MODERATING ROLES OF BEDTIME ACTIVITIES AND ANXIETY/DEPRESSION IN THE RELATIONSHIP BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND SLEEP PROBLEMS IN CHILDREN.

Tong L, Ye Y, Yan Q.

Background: Children with attention-deficit/hyperactivity disorder (ADHD) often experience sleep problems, but the comorbidity mechanism has not been sufficiently studied. This study aimed to determine the comorbidity of ADHD symptoms and sleep problems as well as the moderating effects of bedtime activities and depression/anxiety symptoms on the relationship between ADHD symptoms and sleep problems.
Methods: We recruited 934 primary students from third to fifth grade and their parents by stratified random sampling from three primary schools in Shanghai, China. This study used parent-reported versions of the ADHD Rating Scale-IV, Children's Sleep Habits Questionnaire, and Achenbach Child Behavior Checklist. We used hierarchical linear regression analysis to clarify the moderating effects of bedtime activities and depression/anxiety symptoms.
Results: We found that children with more ADHD symptoms had shorter sleep durations and more sleep problems on weekdays. Screen time before bedtime strengthened the relationship between ADHD symptoms and sleep-disordered breathing. Children with more screen time were more likely to have sleep onset delay, while those with less screen time had more sleep onset problems with increasing ADHD symptoms. The high bedtime eating group experienced more night waking with increasing ADHD symptoms compared with the low bedtime eating group. Anxiety/depression exacerbated total sleep problems and further interacted with ADHD symptoms to predict sleep length and sleep duration problems.
Conclusions: Bedtime activities and emotional problems had important moderating effects on the relationship between ADHD symptoms and sleep problems. These findings indicate that appropriate bedtime management and emotional management may reduce sleep problems and improve sleep duration for children with ADHD symptoms

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BMC Psychiatry. 2018;18.

EFFECTS OF LONG-TERM METHYLPHENIDATE USE ON GROWTH AND BLOOD PRESSURE: RESULTS OF THE GERMAN HEALTH INTERVIEW AND EXAMINATION SURVEY FOR CHILDREN AND ADOLESCENTS (KIGGS).

McCarthy S, Neubert A, Man KKC, et al.

Background: Concerns have been raised over the safety of methylphenidate (MPH), with regard to adverse effects on growth and blood pressure. Our study investigates whether, and to what extent, methylphenidate use in boys with ADHD is associated with having low body mass index (BMI), having low height, and increased systolic and diastolic blood pressure.
Methods: Data used for this study stem from the German KiGGS dataset. Three different groups of boys aged 6-15 years were included in the analysis: ADHD patients who used MPH for less than 12 months;

ADHD patients who used MPH for 12 months or more; and ADHD patients without current MPH treatment. Each of these three groups was compared to a non-ADHD control group regarding low weight (BMI 3rd percentile), low height (Γëñ3rd percentile) and raised systolic and diastolic blood pressure. For growth outcomes, boys were categorized according to age (< 11 years/ΓëÑ11 years, to account for pubertal maturation). Multivariable logistic regression was conducted to test for associations.
Results: 4244 boys were included in the study; MPH < 12 months: n = 65 (n = 36 < 11 years), MPH ΓëÑ 12 months: n = 53 (n = 22 < 11 years), ADHD controls: n = 320 (n = 132 < 11 years), non-ADHD controls: n = 3806 (n = 2003 < 11 years). Pre-pubertal boys with MPH use less than 12 months and pubertal/postpubertal boys with MPH use of 12 months or greater were significantly more likely to have a BMI 3rd percentile compared to non-ADHD controls. Boys from the ADHD control group were significantly less likely to have a raised systolic blood pressure compared to non-ADHD controls. Beyond that, no significant between group differences were observed for any other growth and BP parameter.
Conclusion: The analyses of the KiGGS dataset showed that MPH use in boys with ADHD is associated with low BMI. However, this effect was only observed in certain groups. Furthermore, our analysis was unable to confirm that MPH use is also associated with low height (Γëñ3rd percentile) and changes in blood pressure

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BMC Res Notes. 2018 Jun;11:366.

TRAINING, EXECUTIVE, ATTENTION AND MOTOR SKILLS (TEAMS) TRAINING VERSUS STANDARD TREATMENT FOR PRESCHOOL CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A RANDOMISED CLINICAL TRIAL.

Vibholm HA, Pedersen J, Faltinsen E, et al.

OBJECTIVE: This study compared the effectiveness of manualised training, executive, attention, and motor skills (TEAMS) training versus standard treatment in preschool children with attention deficit hyperactivity disorder (ADHD). We conducted a randomised parallel group, single-blinded, superiority trial. The primary outcome was ADHD symptoms and the secondary outcome was functionality. Parents and primary school teachers assessed outcomes at pretreatment, posttreatment, and at one, three, and 6 months follow-up.
RESULTS: In total, 67 children (aged 3-6 years) were randomised. In the TEAMS group, 32 out of 33 (97%) participants completed the total 8-week program, compared with only 7 out of 26 (27%) in the control group. The repeated-model analyses showed no significant change between the two interventions for ADHD symptoms and functionality levels over time. The mean difference in ADHD symptoms between TEAMS versus standard treatment at posttreatment was 2.18 points (95% confidence interval - 8.62 to 13.0; trial sequential analysis-adjusted confidence interval - 19.3 to 23.7).
Trial registration Clinical Trials identifier: NCT01918436 (Retrospectively registered). Registered on 7 August 2013

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BMJ Case Rep. 2018;2018.

FETISHISM IN ADHD: AN IMPULSIVE BEHAVIOUR OR A PARAPHILIC DISORDER?

Masiran R.

A boy with attention deficit and hyperactivity disorder (ADHD) presented with a fetish for and the subsequent stealing of female undergarments. He was predominantly inattentive and had been a slow learner. Psychological tests showed that he had significant cognitive and inattention problems without significant hyperactivity, and was at risk of dyslexia as well as conduct disorder

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BMJ Open. 2018 Mar;8:e019700.

COMORBID PSYCHIATRIC DISORDERS IN A CLINICAL SAMPLE OF ADULTS WITH ADHD, AND ASSOCIATIONS WITH EDUCATION, WORK AND SOCIAL CHARACTERISTICS: A CROSS-SECTIONAL STUDY.

Anker E, Bendiksen B, Heir T.

OBJECTIVES: Adults with attention-deficit hyperactive disorder (ADHD) report high rates of comorbid disorders, educational and occupational failure, and family instability. The aim of this study was to examine the prevalence of comorbid psychiatric disorders in a clinical population of adults with ADHD and to examine associations between educational level, work participation, social characteristics and the rates of psychiatric comorbidity.

METHODS: Out of 796 patients diagnosed with ADHD in a specialised outpatient clinic in Oslo, Norway, 548 (68%) agreed to participate in this cross-sectional study: 277 women and 271 men. ADHD was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. Comorbid disorders were diagnosed using the Mini-International Neuropsychiatric Interview.

RESULTS: In this clinical sample, 53.5% had at least one current comorbid psychiatric disorder. The most prevalent disorders were major depression, substance use disorders and social phobia. Women had more eating disorders than men, whereas men had more alcohol and substance use disorders. Education above high school level (>12 years) and work participation were associated with lower rates of comorbid disorders (adjusted ORs 0.52 and 0.63, respectively). Gender, age, marital status, living with children or living in a city were not associated with comorbidity.

CONCLUSIONS: Adult ADHD is associated with high rates of comorbid psychiatric disorders, irrespective of gender and age. It appears that higher education and work participation are related to lower probability of comorbidity

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BMJ Open. 2018 Mar;8:e018959.

NINETEEN AND UP STUDY (19UP): UNDERSTANDING PATHWAYS TO MENTAL HEALTH DISORDERS IN YOUNG AUSTRALIAN TWINS.

Couvy-Duchesne B, O'Callaghan V, Parker R, et al.

PURPOSE: The Nineteen and Up study (19Up) assessed a range of mental health and behavioural problems and associated risk factors in a genetically informative Australian cohort of young adult twins and their non-twin siblings. As such, 19Up enables detailed investigation of genetic and environmental pathways to mental illness and substance misuse within the Brisbane Longitudinal Twin Sample (BLTS).

PARTICIPANTS: Twins and their non-twin siblings from Queensland, Australia; mostly from European ancestry. Data were collected between 2009 and 2016 on 2773 participants (age range 18-38, 57.8% female, 372 complete monozygotic pairs, 493 dizygotic pairs, 640 non-twin siblings, 403 singleton twins).

FINDINGS TO DATE: A structured clinical assessment (Composite International Diagnostic Interview) was used to collect lifetime prevalence of diagnostic statistical manual (4th edition) (DSM-IV) diagnoses of major depressive disorder, (hypo)mania, social anxiety, cannabis use disorder, alcohol use disorder, panic disorder and psychotic symptoms. Here, we further describe the comorbidities and ages of onset for these mental disorders. Notably, two-thirds of the sample reported one or more lifetime mental disorder.In addition, the 19Up study assessed general health, drug use, work activity, education level, personality, migraine/headaches, suicidal thoughts, attention deficit hyperactivity disorder (ADHD) symptomatology, sleep-wake patterns, romantic preferences, friendships, familial environment, stress, anorexia and bulimia as well as baldness, acne, asthma, endometriosis, joint flexibility and internet use.The overlap with previous waves of the BLTS means that 84% of the 19Up participants are genotyped, 36% imaged using multimodal MRI and most have been assessed for psychological symptoms at up to four time points. Furthermore, IQ is available for 57%, parental report of ADHD symptomatology for 100% and electroencephalography for 30%.

FUTURE PLANS: The 19Up study complements a phenotypically rich, longitudinal collection of environmental and psychological risk factors. Future publications will explore hypotheses related to disease onset and development across the waves of the cohort. A follow-up study at 25+years is ongoing

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BMJ Open. 2018 Feb;8:e018053.

TOWARDS HIGH-QUALITY, USEFUL PRACTICE GUIDELINES FOR CHILD AND YOUTH MENTAL HEALTH DISORDERS: PROTOCOL FOR A SYSTEMATIC REVIEW AND CONSENSUS EXERCISE.

Bennett K, Duda S, Brouwers M, et al.

INTRODUCTION: The quality of clinical practice guidelines (PGs) has not been evaluated in child and youth mental health (CYMH). To address this gap, we will: (1) conduct a systematic review (SR) to answer the question 'among eligible PGs relevant to the prevention or treatment of CYMH conditions, which PGs meet criteria for minimum and high quality?'; (2) apply nominal group methods to create recommendations for how CYMH PG quality, completeness and usefulness can be strengthened.

METHODS AND ANALYSIS: SR: Potentially eligible PGs will be identified in 12 databases using a reproducible search strategy developed by a research librarian. Trained raters will: (1) apply prespecified criteria to identify eligible PGs relevant to depression, anxiety, suicidality, bipolar disorder, behaviour disorder (attention-deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder) and substance use disorder; (2) extract descriptive data and (3) assess PG quality using the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool. Scores on three AGREE II domains (rigour of development, stakeholder involvement, editorial independence) will designate PGs as minimum (>/=50%) or high quality (>/=70%). Nominal group: Four CYMH PG knowledge user groups (clinicians, mental health service planners, youth and adult family members) will participate in structured exercises derived using nominal group methods to generate recommendations to improve PG quality, completeness and usefulness.

ETHICS AND DISSEMINATION: Ethics approval is not required. Study products will be disseminated as follows. A cross-platform website will house eligible CYMH PGs and their quality ratings. Twitter and Facebook tools will promote it to a wide variety of PG users. Data from Google Analytics, Twitonomy and Altmetrics will inform usage evaluation. Complementary educational workshops will be conducted for CYMH professionals. Print materials and journal articles will be produced.

PROSPERO REGISTRATION NUMBER: CRD42017060738

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Braz J Med Biol Res. 2018 Oct;51:e7653.

LATENT CLASS ANALYSIS OF ATTENTION AND WHITE MATTER CORRELATION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Rossi ASU, Moura LM, Miranda MC, et al.

This study aimed to explore attentional patterns among children with inattentive attention-deficit/hyperactivity disorder (ADHD-I) and children with typical development (TD), using a latent class analysis (LCA). Patterns of brain connectivity were also explored. The sample comprised 29 ADHD-I and 29 TD matched children. An LCA was conducted to reclassify subjects according to their attentional performance, considering cognitive measures of attention and behavioral symptoms, regardless of group of origin. The new clusters were then compared in respect to brain white matter measurements (extracted from diffusion tensor imaging). Participants were rearranged in 2 new latent classes, according to their performance in an attention task and the results of behavioral scales, resulting in groups with more homogeneous attentional profiles. A comparison of the 2 new classes using the white matter measurements revealed increased fractional anisotropy in the left inferior fronto-occipital fasciculus and left inferior longitudinal fasciculus for the class composed by participants with a higher risk of attentional problems. The findings indicated that it was possible to observe variability regarding neuropsychological profile, accompanied by underpinning neurobiological differences, even among individuals with the same disorder subtype - inattentive ADHD. This specific data-driven clustering analysis may help to enhance understanding of the pathophysiology of the disorder's phenotypes

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British Journal of Dermatology. 2018;179:933-39.

EVIDENCE OF THE HIGH PREVALENCE OF NEUROLOGICAL DISORDERS IN NONSYNDROMIC X-LINKED RECESSIVE ICHTHYOSIS: A RETROSPECTIVE CASE SERIES.

Rodrigo-Nicolàís B, et al.

Background: X-linked recessive ichthyosis (XLI) is a relatively common type of ichthyosis caused by a deficiency in the steroid sulfatase (STS) enzyme. It is the only type of ichthyosis that can be both syndromic and nonsyndromic. Typical clinical features include dark-brown scale of variable size favouring the extensor surfaces of the extremities.

Objectives: To characterize clinically nonsyndromic XLI, with a particular focus on extracutaneous manifestations.

Methods: This was a multicentre retrospective review of clinical findings from a case series of patients with a clinical and genetic diagnosis of XLI.

Results: We identified 30 patients with XLI belonging to 25 different families carrying a deletion in the STS locus. All patients had dark scales of variable size on the extensor surfaces of the extremities. Lack of flexural involvement and pruritus were common but inconsistent findings, whereas palmoplantar hyperlinearity was absent in all but one patient. A history of orchiopexy was present in 10% and thus was more common than expected vs. the general population (3%). Neurological disorders including epilepsy (13%) and attention deficit hyperactivity disorder (ADHD; 30%) were over-represented in patients with XLI.

Conclusions: This was a retrospective study with a limited number of patients. In the absence of confirmatory genetic testing and family history of the disease, dark-brown scale of the extensor surfaces and the absence of palmoplantar hyperlinearity appear to be the most reliable clinical findings supporting a diagnosis of XLI. Dermatologists should be aware of the high prevalence of ADHD and epilepsy in patients with nonsyndromic XLI

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Cereb Cortex. 2018 Sep;28:3176-83.

X-CHROMOSOME EFFECTS ON ATTENTION NETWORKS: INSIGHTS FROM IMAGING RESTING-STATE NETWORKS IN TURNER SYNDROME.

Green T, Saggar M, Ishak A, et al.

Attention deficit hyperactivity disorder (ADHD) is strongly affected by sex, but sex chromosomes' effect on brain attention networks and cognition are difficult to examine in humans. This is due to significant etiologic heterogeneity among diagnosed individuals. In contrast, individuals with Turner syndrome (TS), who have substantially increased risk for ADHD symptoms, share a common genetic risk factor related to the absence of the X-chromosome, thus serving as a more homogeneous genetic model. Resting-state functional MRI was employed to examine differences in attention networks between girls with TS (n = 40) and age- sex- and Tanner-matched controls (n = 33). We compared groups on resting-state functional connectivity measures from data-driven independent components analysis (ICA) and hypothesis-based seed analysis. Using ICA, reduced connectivity was observed in both frontoparietal and dorsal attention networks. Similarly, using seeds in the bilateral intraparietal sulcus (IPS), reduced connectivity was observed between IPS and frontal and cerebellar regions. Finally, we observed a brain-behavior correlation between IPS-cerebellar connectivity and cognitive attention measures. These findings indicate that X-monosomy contributes affects to attention networks and cognitive dysfunction that might increase risk for ADHD. Our findings not only have clinical relevance for girls with TS, but might also serve as a biological marker in future research examining the effects of the intervention that targets attention skills

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Child Dev. 2018 Sep;89:1839-55.

A METHYLOME-WIDE ASSOCIATION STUDY OF TRAJECTORIES OF OPPOSITIONAL DEFIANT BEHAVIORS AND BIOLOGICAL OVERLAP WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Barker ED, Walton E, Cecil CAM, et al.

In 671 mother–child (49% male) pairs from an epidemiological birth cohort, we investigated (a) prospective associations between DNA methylation (at birth) and trajectories (ages 7–13) of oppositional defiant disorder (ODD), and the ODD subdimensions of irritable and headstrong; (b) common biological pathways, indexed by DNA methylation, between ODD trajectories and attention deficit hyperactivity disorder (ADHD); (c) genetic influence on DNA methylation; and (d) prenatal risk exposure associations. Methylome-wide significant associations were identified for the ODD and headstrong, but not for irritable. Overlap analysis indicated biological correlates between ODD, headstrong, and ADHD. DNA methylation in ODD and headstrong was (to a degree) genetically influenced. DNA methylation associated with prenatal risk exposures of maternal anxiety (headstrong) and cigarette smoking (ODD and headstrong)

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Child Neuropsychol. 2018.

WRITTEN EXPRESSION IN BOYS WITH ADHD: THE MEDIATING ROLES OF WORKING MEMORY AND ORAL EXPRESSION.

Eckrich SJ, Rapport MD, Calub CA, et al.

The written expression difficulties experienced by children with ADHD are widely recognized; however, scant empirical evidence exists concerning the cognitive mechanisms and processes underlying these deficiencies. The current study investigated the independent and potentially interactive contributions of two developmentally antecedent cognitive processes–viz., working memory (WM) and oral expression–hypothesized to influence written expression ability in boys. Thirty-three boys with ADHD-Combined Presentation and 27 neurotypical (NT) boys 8–12-áyears of age were administered standardized measures of oral and written expression, and multiple counterbalanced tasks to assess WM central executive (CE) processes, WM phonological short-term memory (PH STM), and WM visuospatial short-term memory (VS STM). Bias-corrected bootstrapped mediation analyses revealed a significant mediation effect, wherein the independent and interactive effects of PH STM and oral expression collectively explained 76% of the diagnostic status to written expression relation. The implications of the obtained results for clinical practice suggest that children with ADHD may benefit by incorporating a blended approach that simultaneously strengthens PH STM capacity and oral expression abilities as antecedents to engaging in writing-related activities

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Child Psychiatry Hum Dev. 2018 Oct;49:822-32.

THE EFFECT OF NEUROCOGNITIVE FUNCTION ON MATH COMPUTATION IN PEDIATRIC ADHD: MODERATING INFLUENCES OF ANXIOUS PERFECTIONISM AND GENDER.

Sturm A, Rozenman M, Piacentini JC, et al.

Predictors of math achievement in attention-deficit/hyperactivity disorder (ADHD) are not well-known. To address this gap in the literature, we examined individual differences in neurocognitive functioning domains on math computation in a cross-sectional sample of youth with ADHD. Gender and anxiety symptoms were explored as potential moderators. The sample consisted of 281 youth (aged 8–15 years) diagnosed with ADHD. Neurocognitive tasks assessed auditory-verbal working memory, visuospatial working memory, and processing speed. Auditory-verbal working memory speed significantly predicted math computation. A three-way interaction revealed that at low levels of anxious perfectionism, slower processing speed predicted poorer math computation for boys compared to girls. These findings indicate the uniquely predictive values of auditory-verbal working memory and processing speed on math computation, and their differential moderation. These findings provide preliminary support that gender and anxious perfectionism may influence the relationship between neurocognitive functioning and academic achievement

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Child Health Care. 2018.

BULLYING AND OSTRACISM IN YOUTH WITH AND WITHOUT ADHD: IMPLICATIONS FOR RISK AND RESILIENCE .

Fonseca A, Kral MC, Lally MD, et al.

Objective: This study compared bullying experiences, psychosocial adjustment, and resiliency in youth with and without ADHD.

Method: Participants included 73 youth ages 12–17 with and without ADHD. Participants and their caregivers completed the Bullying and Ostracism Screening Scale, Pediatric Symptom Checklist, and Fitness and Flourish Scale.

Results: There were no significant group differences in youth self-report for rates of bullying experiences or psychosocial adjustment. In contrast, caregivers reported significantly higher levels of victimization experiences (bullying and ostracism) and psychosocial maladjustment for youth with ADHD. Youth who reported increased victimization experiences also reported significantly more internalizing symptoms and lower levels of resilience, irrespective of ADHD diagnosis.

Conclusion. The diagnosis of ADHD did not confer increased risk for bullying or ostracism according to youth self-report. In contrast, caregivers of youth with ADHD reported increased risk for victimization and higher rates of psychosocial maladjustment. Potential reasons for these inter-rater differences are discussed

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Chinese Journal of Medical Genetics. 2018;35:587-90.

ASSOCIATION OF GPER GENE POLYMORPHISM WITH SOCIAL FUNCTION OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Xiao G, Zhou X, Huang J, et al.

Objective: To assess the association of G protein-coupled estrogen receptor (GPER) gene polymorphism with social function of children with attention deficit hyperactivity disorder (ADHD).

Methods: The social function of 135 children with ADHD were assessed by Weiss Functional Impairment Scale-Parent form (WFIRS-P). The coding region of GPER gene of all patients was subjected to Sanger sequencing. The association of polymorphisms with the social function of the ADHD children was analyzed.

Results: In the case group, the social function scores of Learning and School and Risky Activities of boys were significantly higher than those of girls {t = 2. 704, P=0. 008) t=2. 289, P=0. 027). No significant difference was found in the genotypic frequencies of the c. - 9T/C and c. 789G/A loci between different genders. But the learning and school scores of those with a TC genotype for the c. - 9T> C locus were significantly higher than those with a TT genotype (t = 2. 159, P = 0. 033).

Conclusion: For children with ADHD, the social function of Learning and School of those with a TC genotype of the GPER gene c. - 9T/C locus is more severely damaged compared with those with a TT genotype

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Clin Dysmorphol. 2018 Oct;27:113-15.

SHANK3 VARIANT AS A CAUSE OF NONSYNDROMAL AUTISM IN AN 11-YEAR-OLD BOY AND A REVIEW OF PUBLISHED LITERATURE.

Kanani F, Study D, Balasubramanian M.

Autism spectrum disorder (ASD) encompasses a spectrum of pervasive neuropsychiatric disorders characterized by deficits in social interaction, communication, unusual and repetitive behaviours. The aetiology of ASD is believed to involve complex interactions between genetic and environmental factors; it can be further classified as syndromic or nonsyndromic, according to whether it is the primary diagnosis or secondary to an existing condition where both common and rare genetic variants contribute to the development of ASD or are clearly causal. The prevalence of ASD in children is increasing with higher rates of diagnosis and an estimated one in 100 affected in the UK. Given that heritability is a major contributing factor, we aim to discuss research findings to-date in the context of a high-risk autism candidate gene, SHANK3 (SH3 and multiple ankyrin repeat domain 3), with its loss resulting in synaptic function disruption. We present a 10-year-old patient with a pathogenic de novo heterozygous c.1231delC, p.Arg411Val frameshift variant in SHANK3. He presented with severe autism, attention deficit hyperactivity disorder and

pathological demand avoidance, on a background of developmental impairment and language regression. The number of genes associated with autism is ever increasing. It is a heterogeneous group of disorders with no single gene conferring pathogenesis in the majority of cases. Genetic abnormalities can be detected in ~15% of ASD and these range from copy number variants in 16p11.2 and 15q13.2q13.3 to several well-known genetic disorders including tuberous sclerosis and fragile X syndrome. Further, high confidence autism genes include but are not limited to NRXN, NLGN3, NLGN4, SHANK2 and SHANK3

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Clin Neuropharmacol. 2018 Jan;41:23-27.

PRESCRIBING TRENDS OF ATYPICAL ANTIPSYCHOTIC DRUGS IN AN OUTPATIENT UNIT OF A CHILD AND ADOLESCENT CLINIC IN TURKEY.

Yektas C, Tufan AE.

OBJECTIVE: Use of antipsychotic agents in the management of various psychopathologies in Child and Adolescent Psychiatric practice is gradually increasing. This study aimed to evaluate the sociodemographic and clinical features of children and adolescents who applied to an outpatient clinic of child and adolescent psychiatry department in Turkey and were prescribed atypical antipsychotics.

METHOD: Patients with prescription codes of ATC N05A (except N05AN lithium) were accepted to denote those with atypical antipsychotic treatment. Sociodemographic and clinical variables, pharmacological mechanisms and groups and use of multiple agents for 212 patients with atypical antipsychotic treatment were collected and recorded.

RESULTS: Patients (6.6%) evaluated within a year were prescribed antipsychotic agents (APs). The majority of the sample consisted of adolescents and especially females. The most common diagnoses managed with atypical antipsychotic were attention-deficit/hyperactivity disorder, MDD, and mental retardation/intellectual disability in decreasing frequency. Males with attention-deficit/hyperactivity disorder, CD, and autism spectrum disorders and females with MDD and PTSD were more frequently prescribed APs. Most common indications were irritability, impulsivity, and self-harming behaviors. Most common agents were risperidone, aripiprazole, and quetiapine in decreasing order of frequency. Most common adverse effects were reported as sedation, increased appetite, and hyperprolactinemia.

CONCLUSIONS: Our results support the prevalence of off-label use of AP agents in managing various childhood psychopathologies also in Turkey. Further studies from multiple centers and using reliable and valid measurements are needed to determine the extent and predictors of AP use in outpatient samples from different child and adolescent centers

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Clin EEG Neurosci. 2018;49:NP32-NP33.

DIFFERENTIAL ADHD EFFECTS ON COGNITIVE CONTROL.

Albrecht B, Brandeis D, Sandersleben HUV, et al.

Flexible adaptation to conflicting task demands plays an important role in everyday life and is impaired in many psychiatric disorders. As a prerequisite, cognitive control comes into play when task demands conflict, which may be reflected in brain electrical activity as enhanced N2 amplitude under conflict (monitoring) in various tasks. Cognitive control may also play a role in attention deficit/hyperactivity disorder (ADHD), but studies on N2-Enhancement revealed mixed results. The current study contrasts three task demands tapping conflict monitoring and cognitive control and their relation to ADHD. This was done in a sample of 94 children with ADHD in comparison with 43 controls, aged 8 to 15 years using a Flanker-Task paradigm by contrasting processing of congruent and incongruent stimuli, and in Continuous Performance Tests by contrasting Go-Nogo demands and processing of additionally presented incongruent stimuli. All 3 demands for cognitive control revealed significant N2-Enhancement, but differential ADHD effects thereon: N2-Enhancements in the CPT regarding Go-Nogo and processing of additional incongruent Flankers was similar in ADHD and Controls, while Flanker-Task Congruency revealed medium-sized ADHD effects. The current results indicate that children with ADHD have mediumsized difficulties with cognitive control during some particular demand (eg, with Flanker-Task Congruency that requires frequent responding) but not on others (eg, during

response-control in CPTs that require responding in only 10% of all trials). This highlights the importance of clinical studies for understanding cognitive control in different demands, and it may also indicate that moderators like arousal may play an important role for ADHD deficits

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Clin EEG Neurosci. 2018;49:NP36.

TRUST IS GOOD, CONTROL IS BETTER: EEG QUALITY CONTROL IN A MULTICENTER EEG STUDY OF CHILDREN, ADOLESCENTS, AND ADULTS WITH ADHD.

Kaiser A, Holtmann M, Fallgatter A, et al.

Quality of the raw data crucially affects the validity of analyses and interpretation of scientific results obtained from electroencephalography (EEG). Therefore, regular assessments of EEG data quality are essential to ensure that established standards are met, particularly for multicenter studies. EEG data were collected from N = 68 patients within an ongoing multicenter study ESCAlife (involving Bochum, Homburg, Koln, Mainz, Mannheim, Marburg, Oldenburg, Rostock, Tubingen, Wurzburg) of children, adolescents, and adults (6-45 years) with attention deficit hyperactivity disorder (ADHD) in the ESCAbrain subproject. Resting state eyes open and eyes closed (4 minutes) EEG data are collected to identify potential predictors of treatment response. The EEG is recorded using a 22-channel EEG cap (Brain Products) and a sampling rate of 256 Hz (DC-70 Hz). As ADHD patients are prone to EEG artifacts, a regular data quality assessment focused on typical artifacts was conducted. For data processing, the software BrainVision Analyzer (Brain Products) is used. The percentage of artifact-free epochs is calculated for each data set as an index of data quality. Furthermore, the percentage of blink-artifactrelated ICA-components is determined and compared across study centers and participants. Age of the participants, ADHD symptom severity, as well as the different study sites (comprising potentially relevant variables such as the electromagnetic environment, the training, and the experience of the staff with EEG recordings) are explored as relevant factors that might influence data quality. Finally, corrective actions are discussed that were adopted to improve data quality. Funding. This work was supported by the research consortium on ADHD, ESCALife, funded by the German Federal Ministry of Education and Research (FKZ 01EE1408E)

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Cochrane Database Syst Rev. 2018 Jun;6:CD007990.

PHARMACOLOGICAL TREATMENT FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN WITH COMORBID TIC DISORDERS.

Osland ST, Steeves TD, Pringsheim T.

BACKGROUND: This is an update of the original Cochrane Review published in Issue 4, 2011.Attention deficit hyperactivity disorder (ADHD) is the most prevalent of the comorbid psychiatric disorders that complicate tic disorders. Medications commonly used to treat ADHD symptoms include stimulants such as methylphenidate and amphetamine; non-stimulants, such as atomoxetine; tricyclic antidepressants; and alpha agonists. Alpha agonists are also used as a treatment for tics. Due to the impact of ADHD symptoms on the child with tic disorder, treatment of ADHD is often of greater priority than the medical management of tics. However, for many decades, clinicians have been reluctant to use stimulants to treat children with ADHD and tics for fear of worsening their tics.

OBJECTIVES: To assess the effects of pharmacological treatments for ADHD in children with comorbid tic disorders on symptoms of ADHD and tics.

SEARCH METHODS: In September 2017, we searched CENTRAL, MEDLINE, Embase, and 12 other databases. We also searched two trial registers and contacted experts in the field for any ongoing or unpublished studies.

SELECTION CRITERIA: We included randomized, double-blind, controlled trials of any pharmacological treatment for ADHD used specifically in children with comorbid tic disorders. We included both parallel-group and cross-over study designs.

DATA COLLECTION AND ANALYSIS: We used standard methodological procedures of Cochrane, in that two review authors independently selected studies, extracted data using standardized forms, assessed risk of bias, and graded the overall quality of the evidence by using the GRADE approach.
MAIN RESULTS: We included eight randomized controlled trials (four of which were cross-over trials) with 510 participants (443 boys, 67 girls) in this review. Participants in these studies were children with both ADHD and a chronic tic disorder. All studies took place in the USA and ranged from three to 22 weeks in duration. Five of the eight studies were funded by charitable organizations or government agencies, or both. One study was funded by the drug manufacturer. The other two studies did not specify the source of funding. Risk of bias of included studies was low for blinding; low or unclear for random sequence generation, allocation concealment, and attrition bias; and low or high for selective outcome reporting. We were unable to combine any of the studies in a meta-analysis due to important clinical heterogeneity and unit-of-analysis issues.Several of the trials assessed multiple agents. Medications assessed included methylphenidate, clonidine, desipramine, dextroamphetamine, guanfacine, atomoxetine, and deprenyl. There was low-quality evidence for methylphenidate, atomoxetine, and clonidine, and very low-quality evidence for desipramine, dextroamphetamine, guanfacine and deprenyl in the treatment of ADHD in children with tics. All studies, with the exception of a study using deprenyl, reported improvement in symptoms of ADHD. Tic symptoms also improved in children treated with guanfacine, desipramine, methylphenidate, clonidine, and a combination of methylphenidate and clonidine. In one study, tics limited further dosage increases of methylphenidate. High-dose dextroamphetamine appeared to worsen tics in one study, although the length of this study was limited to three weeks. There was appetite suppression or weight loss in association with methylphenidate, dextroamphetamine, atomoxetine, and desipramine. There was insomnia associated with methylphenidate and dextroamphetamine, and sedation associated with clonidine.
AUTHORS' CONCLUSIONS: Following an updated search of potentially relevant studies, we found no new studies that matched our inclusion criteria and thus our conclusions have not changed.Methylphenidate, clonidine, guanfacine, desipramine, and atomoxetine appear to reduce ADHD symptoms in children with tics though the quality of the available evidence was low to very low. Although stimulants have not been shown to worsen tics in most people with tic disorders, they may, nonetheless, exacerbate tics in individual cases. In these instances, treatment with alpha agonists or atomoxetine may be an alternative. Although there is evidence that desipramine may improve tics and ADHD in children, safety concerns will likely continue to limit its use in this population

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Crim Behav Ment Health. 2018 Aug;28:313-23.

LEARNING TO BLAST A WAY INTO CRIME, OR JUST GOOD CLEAN FUN? EXAMINING AGGRESSIVE PLAY WITH TOY WEAPONS AND ITS RELATION WITH CRIME.

Smith S, Ferguson CJ, Beaver KM.

BACKGROUND: Researchers, such as Bandura, have proposed that children's mere exposure to the use of play weapons encourages deviant displays of aggression, but there is very little research to support this hypothesis of 20 years. AIM: To examine the relationship between amount of weapon play and concurrent aggression as well as later violent juvenile crime, while controlling for other variables possibly influencing criminal pathways.
METHOD: Using longitudinal survey data collected from mothers and children (n = 2019) from age 5, with follow-up at age 15, correlations between children's play with toy weapons and juvenile criminality were examined. Multivariate regression analyses were employed to determine to what extent early childhood aggression, symptoms of attention deficit hyperactivity disorder, and symptoms of depression were antecedents of juvenile crime.
RESULTS: For bivariate analysis between toy weapon play and juvenile criminality, the effect size was small and not significant. The relationship remained not significant once control variables were introduced into the model.
CONCLUSIONS AND IMPLICATIONS: The act of pretending to be aggressive in childhood thus plays little role in predicting later criminality after other factors, such as gender, attention deficit hyperactivity disorder or depression, have been taken into account. Involvement in imaginative play with toy gun use in early

childhood is unlikely to be useful as a risk marker for later criminal behaviour. Play fighting and war toy games may even be considered necessary components within the frame of normal development.

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Curr Obes Rep. 2018 Mar;7:19-26.

A Review of Childhood Behavioral Problems and Disorders in the Development of Obesity: Attention Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, and Beyond.

Matheson BE, Eichen DM.

PURPOSE OF REVIEW: Given the high rates of pediatric and adult obesity, it is imperative to identify early risk factors that might contribute to excess weight gain. This review aims to investigate the relationship between childhood behavioral problems with the development and persistence of obesity. Specifically, this review highlights the association of obesity with (1) neurocognitive constructs, such as executive functioning and inhibition/impulsivity, and (2) disorders commonly diagnosed in childhood, including attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).

RECENT FINDINGS: Consistent evidence supports a relationship between childhood behavioral problems, executive functioning, inhibition/impulsivity, ADHD, and ASD with obesity across the lifespan. Longitudinal studies suggest behavior problems, neurocognitive functioning deficits, and ADHD symptoms in childhood predict weight gain over time. Identifying risk factors in childhood that promote obesity may help develop targeted intervention and prevention programs. Additional research should elucidate mechanisms that account for these relationships

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Cyberpsychol Behav Soc Netw. 2018 May;21:281-86.

Smoking, ADHD, and Problematic Video Game Use: A Structural Modeling Approach.

Lee HJ, Tran DD, Morrell HER.

Problematic video game use (PVGU), or addiction-like use of video games, is associated with physical and mental health problems and problems in social and occupational functioning. Possible correlates of PVGU include frequency of play, cigarette smoking, and attention deficit hyperactivity disorder (ADHD). The aim of the current study was to explore simultaneously the relationships among these variables as well as test whether two separate measures of PVGU measure the same construct, using a structural modeling approach. Secondary data analysis was conducted on 2,801 video game users (Mage = 22.43 years, standard deviation [SD]age = 4.7; 93 percent male) who completed an online survey. The full model fit the data well: chi(2) (2) = 2.017, p > 0.05; root mean square error of approximation (RMSEA) = 0.002 (90% CI [0.000-0.038]); comparative fit index (CFI) = 1.000; standardized root mean square residual (SRMR) = 0.004; and all standardized residuals <|0.1|. All freely estimated paths were statistically significant. ADHD symptomatology, smoking behavior, and hours of video game use explained 41.8 percent of variance in PVGU. Tracking these variables may be useful for PVGU prevention and assessment. Young's Internet Addiction Scale, adapted for video game use, and the Problem Videogame Playing Scale both loaded strongly onto a PVGU factor, suggesting that they measure the same construct, that studies using either measure may be compared to each other, and that both measures may be used as a screener of PVGU

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Dan Med J. 2018 Apr;65.

Tourette syndrome in a longitudinal perspective. Clinical course of tics and comorbidities, coexisting psychopathologies, phenotypes and predictors.

Groth C.

INTRODUCTION: Tourette syndrome (TS) is a childhood onset neurodevelopmental disorder characterised by motor and vocal tics and frequent associated comorbidities. The developmental trajectory of tic shows tic-onset in the age of 4-6, peak in the age of 10-12 and decline during adolescence, although only few and small longitudinal studies form the basis of this evidence. Recent studies suggest that comorbid obsessive-

compulsive disorder (OCD), attention deficit-hyperactivity disorder (ADHD) and coexisting psychopathologies tend to persist and become more dominant in adolescence. This large prospective follow-up study want to examine the clinical course of TS: tic and comorbidities during adolescence, the prevalence of coexisting psychopathologies, the tic-related impairment, development in phenotype expression and find predictors for the expected course of TS.
Method: This study is examining a large clinical cohort recruited at the Danish National Tourette Clinic during the period 2005-2007 and 2011-2013. At baseline, 314 participants aged 5-19 years were included and at follow-up 6 years later 227 participated, aged 11-26. All participants were uniformly clinically examined at basis and follow-up with a clinical interview and validated measurements to assess comorbidities. The Yale Global Tic Severity Scale was used to asses tic severity and tic-related impairment. At follow-up a cross-sectional diagnostic evaluation was made with the Development and Well-Being Assessment to assess coexisting psychopathologies.
Results: A significant decline in tic and the most frequent comorbidities OCD and ADHD was found although some variation existed and some subclinical and partial remissions persisted. Tic-related impairment was not reflected in the tic-decline as expected but influenced by several parameters. The phenotype expression was found to be dynamic but overall changed toward TS without comorbidities. Several predictors were found to predict the clinical course of TS in adolescence and early adulthood. Childhood tics, OCD and ADHD severity were the strongest predictors for future symptoms of the respectively diagnoses. Comorbidities and coexisting psychopathologies were found in 63% at follow-up, whereas 37% had pure TS.
Conclusion: The clinical course of TS during adolescence was confirmed, with solid evidence, with decline in tics, OCD and ADHD severity. We provide evidence of considerable coexisting psychopathologies requiring clinical support and partial remissions and subthreshold symptoms requiring monitoring and clinical guidance to assist the young adults in promoting a healthy transition into early adulthood. Furthermore we provide predictors for the clinical course of TS to be used in the preventive efforts, early intervention and allocation of resources improving quality of life for the children and their families

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Dev Psychol. 2018 Jun;54:1099-110.

PREDICTORS OF EATING BEHAVIOR IN MIDDLE CHILDHOOD: A HYBRID FIXED EFFECTS MODEL.

Bjorklund O, Belsky J, Wichstrom L, et al.

Children's eating behavior influences energy intake and thus weight through choices of type and amount of food. One type of eating behavior, food responsiveness, defined as eating in response to external cues such as the sight and smell of food, is particularly related to increased caloric intake and weight. Because little is known about the potential determinants of such behavior, we focus herein on child and parent predictors of food responsiveness in a large community sample of Norwegian 6-year-olds, followed up at ages 8 and 10. To measure children's food responsiveness, parents completed the Children's Eating Behavior Questionnaire. Potential predictors were children's inhibition and symptoms of attention-deficit/hyperactivity disorder and depression, and parents' instrumental and controlling feeding practices as well as parental restrained eating. After accounting for children's initial levels of food responsiveness within a hybrid fixed effects method that takes into consideration all unmeasured time-invariant confounders, more child attention-deficit/hyperactivity disorder symptoms and greater restrained eating by parents predicted more food responsiveness at both ages 8 and 10. These results may provide important insights for efforts to prevent overeating

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Dev Psychopathol. 2018 Aug;30:1107-28.

IDENTIFYING THE CONTRIBUTION OF PRENATAL RISK FACTORS TO OFFSPRING DEVELOPMENT AND PSYCHOPATHOLOGY: WHAT DESIGNS TO USE AND A CRITIQUE OF LITERATURE ON MATERNAL SMOKING AND STRESS IN PREGNANCY.

Rice F, Langley K, Woodford C, et al.

Identifying prenatal environmental factors that have genuinely causal effects on psychopathology is an important research priority, but it is crucial to select an appropriate research design. In this review we explain why and what sorts of designs are preferable and focus on genetically informed/sensitive designs. In the field of developmental psychopathology, causal inferences about prenatal risks have not always been based on evidence generated from appropriate designs. We focus on reported links between maternal smoking during pregnancy and offspring attention-deficit/hyperactivity disorder or conduct problems. Undertaking a systematic review of findings from genetically informed designs and "triangulating" evidence from studies with different patterns of bias, we conclude that at present findings suggest it is unlikely that there is a substantial causal effect of maternal smoking in pregnancy on either attention-deficit/hyperactivity disorder or conduct problems. In contrast, for offspring birth weight (which serves as a positive control) findings strongly support a negative causal effect of maternal smoking in pregnancy. For maternal pregnancy stress, too few studies use genetically sensitive designs to draw firm conclusions, but continuity with postnatal stress seems important. We highlight the importance of moving beyond observational designs, for systematic evaluation of the breadth of available evidence and choosing innovative designs. We conclude that a broader set of prenatal risk factors should be examined, including those relevant in low- and middle-income contexts. Future directions include a greater use of molecular genetically informed designs such as Mendelian randomization to test causal hypotheses about prenatal exposure and offspring outcome

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Dev Med Child Neurol. 2018.

STRUCTURAL AND FUNCTIONAL NEUROIMAGING IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Albajara SA, Villemonteix T, Massat I.

Over the last decade, there has been a dramatic increase in the number of neuroimaging studies in attention-deficit/hyperactivity disorder (ADHD). In terms of brain structure, magnetic resonance imaging (MRI), and diffusion tensor imaging studies have evidenced differences in volume, surface-based measures (cortical thickness, surface area, and gyrification), and white matter integrity in different cerebral regions, in children and adults with ADHD compared to population norms. Abnormalities in the basal ganglia, prefrontal structures, and the corpus callosum have been the most consistently reported findings across studies. Hemodynamic (functional MRI, functional near-infrared spectroscopy, positron emission tomography, single-photon emission computed tomography) and magnetoencephalography measurements have also shown differences in neural activity during the execution of neuropsychological tasks and during rest, in widespread regions of the brain. Importantly, multimodal studies combining structural and functional methods have shown an intercorrelation between structural and functional abnormalities in ADHD. Further longitudinal studies are needed to clarify the effects of age and medication on brain structure and function in individuals with ADHD

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Drug Alcohol Depend. 2018 Jul;188:135-40.

HOW TREATMENT IMPROVEMENT IN ADHD AND COCAINE DEPENDENCE ARE RELATED TO ONE ANOTHER: A SECONDARY ANALYSIS.

Levin FR, Choi CJ, Pavlicova M, et al.

BACKGROUND: Attention-deficit hyperactivity disorder (ADHD) is overrepresented among individuals seeking treatment for substance use disorders. We previously reported that treatment with extended release mixed amphetamine salts (MAS-XR) increased abstinence, compared to placebo, among patients with co-occurring ADHD and cocaine dependence. This secondary analysis investigates the temporal relationship between ADHD improvement and cocaine abstinence in the first six weeks of the trial.

METHODS: The study was a three-arm, randomized, double-blinded, placebo-controlled, 14-week trial comparing MAS-XR (60mg or 80mg daily) versus placebo among 126 participants with ADHD and cocaine dependence. An autoregressive cross-lagged structural equation model was fit and evaluated weekly ADHD improvement (defined as >/=30% reduction in the Adult ADHD Investigator Symptom Rating Scale) and urine-confirmed abstinence over the first six weeks.
RESULTS: The proportion of patients with each of the possible overall patterns of response was: ADHD improves before cocaine abstinence: 24%; Cocaine abstinence occurs before ADHD improvement: 12%; ADHD improvement and abstinence occur during the same week: 6%; ADHD improves but abstinence never achieved: 34%; Abstinence achieved but ADHD never improves: 6%; Neither ADHD improvement nor abstinence: 18%. A significant cross-lagged association was found; subjects with ADHD improvement at week 2 had significantly higher odds of cocaine abstinence at week 3 (p=.014).
CONCLUSION: When treating co-occurring ADHD and cocaine dependence with stimulant medication, abstinence is most likely preceded by improvement in ADHD, which tends to occur early with medication treatment. Other observed temporal patterns suggest the potential complexity of the relationship between ADHD and cocaine dependence

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Drug Alcohol Depend. 2018 Jul;188:281-87.

CIGARETTE USE TRAJECTORIES IN YOUNG ADULTS: ANALYSES OF PREDICTORS ACROSS SYSTEM LEVELS.

Berg CJ, Haardorfer R, Vu M, et al.

BACKGROUND: Cigarette smoking escalates most in early to middle young adulthood. However, little research has examined a range of multilevel factors in relation to smoking trajectories during this time.
METHODS: We examined: 1) trajectories of cigarette smoking among 2967 US college students (aged 18-25) in a two-year, six-wave longitudinal study (using growth mixture modeling); and 2) intrapersonal- (i.e., other substance use, depressive symptoms, ADHD symptoms,); interpersonal- (i.e., adverse childhood events, social support, parental tobacco and marijuana use), and community-level (i.e., type of college, rural vs. urban setting) predictors of differing trajectories (using multinomial logistic regression).
RESULTS: We identified three trajectory classes: 1) Dabblers, who used cigarettes at one point in their life or not at all (85.6%); 2) College Onset Smokers, who began smoking regularly during the college years (6.2%); and 3) Later Onset Smokers, who began smoking during the mid- to late-20s (8.2%). Multinomial regression (with Dabblers as the reference group) showed that predictors of being College Onset Smokers included being male (p=.031); Asian (p=.001) but not Black (p=.008; Ref: White); early onset smokers (i.e., initiation before age 15; p=.006); past 30-day users of little cigars/cigarillos (p=.024), alcohol (p<.001), and marijuana (p=.008); children of tobacco users (p=.050); and public (p=.031) or a technical college students (p<.001; Ref: private college); predictors of being Later Onset Smokers were being male (p=.019) and technical college students (p=.005).
CONCLUSIONS: Despite some young adults' smoking initiating/escalating in middle young adulthood, few risk factors were documented. This understudied period warrants greater examination to inform intervention

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Early Intervent Psychiatry. 2018;12:93.

PSYCHOPATHOLOGY IN 7-YEAR-OLD CHILDREN WITH FAMILIAL HIGH RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER - THE DANISH HIGH RISK AND RESILIENCE STUDY - VIA 7; A POPULATION-BASED COHORT STUDY.

Ellersgaard D, Plessen KJ, Jepsen JRM, et al.

Introduction: For both schizophrenia and bipolar disorder the single largest risk factor for developing the disorder is a positive family history. Therefore early antecedents of schizophrenia and bipolar disorder can be identified by studying children of parents with these disorders. We aimed to compare psychopathological profiles of children aged 7 with familial high risk for developing schizophrenia (FHRSZ) or bipolar disorder (FHR-BP).
Methods: Nationwide Danish registers were used to establish a population based cohort of 7-year-old children with FHR-SZ (N = 202), FHR-BP (120) and controls (200). Psychopathology of the children was

assessed both categorically and dimensionally and from multiple informants including children, parents and teachers. Lifetime diagnoses and psychotic like experiences (PLEs) were ascertained through the Schedule for Affective Disorders and Schizophrenia for School- Age Children - Present and Lifetime Version (K-SADS-PL). Psychopathology was assessed dimensionally with the Child Behavior Checklist (CBCL), the Teacher's Report Form (TRF), the ADHD-Rating Scale, the Test Observation Form (TOF) and the State-Trait Anxiety Inventory for Children (STAI-CH). Current level of functioning was assessed with the Children's Global Assessment Scale (CGAS).
Results: We found marked differences between the three groups in several domains of psychopathology including PLEs and level of functioning. Results will be presented at the meeting.
Conclusion: Children with familial risk of especially schizophrenia but also bipolar disorder have a higher prevalence of a broad spectrum of psychiatric disorders and psychopathological symptoms including PLEs already at age 7 compared with controls. The results emphasize the need for research on early intervention strategies towards these children

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Early Intervent Psychiatry. 2018;12:125.

IMPLICATION OF ATTENTION-DEFICIT AND HYPERACTIVITY DISORDER IN THE APPEARANCE OF EARLY PSYCHOSIS: SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Tesn NM, et al.

Recent studies show a relationship between symptoms of Attentiondeficit/ Hyperactivity Disorder (ADHD) during childhood and subsequent psychotic disorders. Moreover the first episode of psychosis (FEP) is typically preceded by a prodrome with deficits in attention. There are only 2 previous studies in FEP that evaluate the presence of ADHD in these patients and their impact on clinical presentation. The objective of our study is to examine the prevalence of ADHD in a sample of 130 patients with an incipient psychotic (IP) disorder, treated at the Early Intervention Service of Reus, aged between 14 and 28. The Structured Diagnostic Interview of ADHD in adults (DIVA) was administered. The data were analyzed using SPSS version 20,0 for Windows. Sample consisted in 97 FEP and 33 ARMS. Mean age of sample was 24.36, 63.84% were men and 37.39% of subjects met criteria for ADHD. In the FEP subgroup 32.97% fulfills diagnostic criteria for ADHD (versus 51.72% in ARMS, 51,72% of men), 90.32% of men. There was a greater prevalence of ADHD in the ARMS sample compared with FEP. Those with childhood ADHD, showed significantly higher rates of cannabis use and greater prevalence of neurodevelopmental delay compared with patients without ADHD. The FEP-ADHD group scored significantly higher in the positive and negative scales of Positive and Negative Syndrome Scale compared with the FEP-alone. Our 37.39% prevalence rate of childhood ADHD in FEP and ARMS was in the higher range of that reported in previous studies. This suggests the necessity of further studies to clarify the association between all of them

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Early Intervent Psychiatry. 2018;12:98.

THE PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN A COHORT OF PATIENTS WITH SCHIZOPHRENIA, AND THE IMPACT ON THEIR EXECUTIVE FUNCTIONS.

Arican I, McQuillin A, Giaroli G.

Introduction: The subgroup of patients with schizophrenia (SCZ) and an attention deficit hyperactivity disorder (ADHD) comorbidity experience a lack of recommended pharmacological therapies for their specific symptomatology. Our systematic review utilising the PRISMA statement criteria revealed that only 2 studies have measured the prevalence of adult ADHD in patients with SCZ.
Objectives: To investigate a cohort of patients with SCZ for the prevalence of childhood and adult ADHD symptoms, and measure the relationship with executive functions (EF). Methods: Impairments of EF, adult ADHD and childhood ADHD symptoms were investigated using three self-report questionnaires in 126 patients with ICD-10 diagnoses of SCZ. The severity of ADHD symptoms in relation to EF were examined using regression models.

Results: Lifetime ADHD symptoms were reported by 47% of patients with clinically diagnosed SCZ. Of these, 23% reached the cut off values in both the childhood and adult ADHD questionnaires, 11% in only the childhood and 13% in the adult ADHD questionnaire. Impairments in EF were reported by 54% of patients, and the linear regression of EF impairment scores was significant ($p < 0.001$) with both childhood ADHD and adult ADHD scores. Higher ADHD symptom scores were predictive of a history of substance abuse.
Conclusions: The study suggests that there is a higher presence of ADHD symptomatology in SCZ compared to that reported for ADHD in the general population. A greater severity of ADHD symptoms was predictive of poorer EF, highlighting the necessity of correct and early diagnosis

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Early Intervent Psychiatry. 2018;12:133.

EARLY TREATMENT FOR NON-UHR/NON-FEP MENTAL HEALTH PROBLEMS IN PATIENTS PRESENTING WITH PSYCHOSIS OR UHR.

Jòrgensen RL, Joa I, Johannnessen JO, et al.

Background: The TIPS/POP studies are ongoing Norwegian early intervention initiatives providing early access to appropriate care for individuals with first episode psychosis (FEP) and in Ultra-High risk states (UHR) by the use of multi-focal information campaigns and low threshold detection teams. In 2014 we investigated help-seeking delays and health system for 24 FEP patients who had presented to mental health care that year. Eight had previously been treated for non-FEP mental health problems in child- and adolescent care and 13 in primary health care. Only three were treatment naive. Adverse life events were common in all. Findings gave rise to the suspicion that FEP patients may be characterized by a combination of non-specific mental health care problems in childhood or adolescence such as ADHD, self-harming, depression or anxiety, for which earlier treatment has been terminated before the emergence of UHR or FEP symptoms.
Aim: To develop and pilot a study in order to investigate the prevalence of earlier treatment episodes for mental health problems not captured by FEP or UHR definitions.
Methods: Patient files of 50 consecutive referrals to TIPS/POP (FEP/UHR) will be investigated assessed according to the following: Pathways to care (help-seeking and health system delays); Earlier treatment for any psychiatric problem; Adverse life events; Possible prodromal signs in earlier treatment if the patient is FEP; Signs of psychosis in earlier treatment. PANSS and SCID are used to evaluate diagnosis and severity of psychosis.
Results: Data collection is under preparation and preliminary results will be presented

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Emot Behav Difficulties. 2018.

ERRATUM TO: HAS SCHOOLING OF ADHD STUDENTS REACHED A CROSSROADS? (EMOTIONAL AND BEHAVIOURAL DIFFICULTIES, (2018), (1-21), 10.1080/13632752.2018.1462974).

Malmqvist, J. 2018. Has schooling of ADHD students reached a crossroads?. Emotional and Behavioural Difficulties.https://doi.org/10.1080/13632752.2018.1462974 When the above article was first published online, in table 3, Teaching dimension did not cover Neuropsychiatry-based teaching and the grey shades inside the table were missed. These have now been corrected in both print and online versions. Taylor and Francis apologizes for theses errors. Tarver, J., D. Daley, and K. Sayal. 2014. ΓÇ£Attention-Deficit Hyperactivity Disorder (ADHD): An Updated Review of the Essential Facts. CHILD: Care, Health and Development 40 (6): 762-774. doi:10.1111/cch.12139

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Encephale. 2018.

CHILDREN WITH HIGH POTENTIAL AND DIFFICULTIES: CONTRIBUTIONS OF CLINICAL RESEARCH.

Tordjman S, Vaivre-Douret L, Chokron S, et al.

We have been sensitized to children with high intellectual potential (HIP) having difficulties given the number of children consulting in our outpatient medico-psychological centres for scholastic problems (possibly leading to school failure), anxiety disorders or behavioral disorders such as attention deficit/hyperactivity disorder (ADHD), and in which a high intellectual potential was discovered during psychological assessments. It is the contrast, and more precisely the paradox, between the high intellectual potential of these children and their scholastic difficulties (including school failure), and the psychic suffering expressed by some of them, which led us to question, challenge and propose therapeutic and educational care adapted to these children. It is in this context that we created in December 2005 the CNAHP (National Center for Assistance to High Potential children and adolescents) which is a public centre integrated into the hospital-university department of child and adolescent psychiatry at Rennes. It is noteworthy that not all children with HIP have difficulties, and children with school failure or behavioral problems are not always children with HIP. However, it is necessary not to minimize the problem raised by children with HIP with difficulties by ignoring its frequency or by considering that these children are intelligent enough to manage by themselves and do not need to be helped, whereas some of them can show school failure and even be de-scholarized. Indeed, based on the definition of the World Health Organization (WHO) of an intellectual Quotient (IQ) above 130 (level corresponding to a statistical threshold), the frequency of children with HIP represents 2.3% of the population of schoolchildren aged 6 to 16. The frequency is therefore not so rare. However, it remains to be determined by French epidemiological studies what is the actual frequency of children with difficulties within a population of children with HIP. The analysis of the CNAHP research data from a clinical population (children with HIP consulting for difficulties) highlights that children with HIP can show major school problems (including school failure, defined here as having or foreseeing repetition of a grade), which corresponds to 7.5% of 611 children with HIP consulting at the CNAHP) and socioemotional problems (emotional regulation disorders) in relation to their high intellectual potential. In particular, anxiety disorders were the most frequent psychiatric disorders observed in this population (40.5%) and were significantly associated with high verbal potential. This significant association requires further studies to avoid establishing a simplistic unidirectional and reductive linear cause-effect relationships. Indeed, a high verbal potential can elicit and/or reinforce anxiety-producing representations, but anxiety disorders may also lead to a defensive over investment of verbal language. The results are discussed in this article and suggest that scholastic and/or psychological difficulties encountered by some children with HIP can be related to their high intellectual potential. It is necessary to develop therapeutic and educational care adapted to these children from a better understanding, based on research results, of their possible difficulties but also cognitive abilities. Even when children with HIP have scholastic and/or psychological difficulties, some of their cognitive skills can be preserved contrary to appearances, with for example, as seen in the CNAHP results, excellent attentional capacities shown by cognitive tests contrasting with behavioral attention deficit reported by parents. These skills are important to identify as they are resources which support the therapeutic and educational project. It is probably through an articulation among professionals from national education, health and research, in alliance with the family (parents, child, and siblings), that advances will be made. In the same way that professionals have been interested in children with intellectual disabilities, it is important to be concerned by children with HIP and difficulties located at the other end of the continuum. It is a question of ethics which concerns both caregivers and teachers. It is also a societal issue that concerns all of us given that the expression of high intellectual and creative potential in children may be essential to the societal development of innovative strategies and each nation's future. Finally, the discussion can be extended to all children, independent of their potential. What we learn from children with HIP and difficulties can be applied to each child: it is important at family, school and societal levels to facilitate the expression of the potential of children, to value their skills, and to help them to remove possible inhibitions of their potential based on individualized projects. The acceptance of singularity and differences in children can contribute to tolerance and the development of creativity, in the interest of the subject and of society

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Eur Arch Paediatr Dent. 2018 Apr;19:91-97.

SLEEPINESS, OCCLUSION, DENTAL ARCH AND PALATAL DIMENSIONS IN CHILDREN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Andersson H, Sonnesen L.

AIMS: This was to compare sleepiness, occlusion, dental arch and palatal dimensions between children with attention deficit hyperactivity disorders (ADHD) and healthy children (control group).

METHODS: 15 children with ADHD (10 boys, 5 girls, mean age 10.98 years) and 36 healthy age matched children (21 boys, 15 girls, mean age 10.60 years) were included. Intra-oral three-dimensional scans of the teeth and palate were performed to evaluate the occlusion, dental arch and palatal dimensions. Sleepiness was evaluated from the questionnaires. The differences between the two groups were analysed by Fisher's exact test and general linear models adjusted for age and gender.

RESULTS: The ADHD children had a significantly narrower dental arch at the gingival level of the canines ($p < 0.05$) and a tendency to increased prevalence of posterior cross-bite compared to the controls (13.3 vs. 0.0%, $p = 0.086$). The ADHD children snored significantly more ($p < 0.05$) and slept restlessly significantly more often ($p < 0.0005$) compared to the controls. The ADHD children had a tendency to sleep fewer hours during the night ($p = 0.066$) and felt inadequately rested in the morning ($p = 0.051$) compared to the controls.

CONCLUSION: The results indicate that sleepiness and palatal width, especially the more anterior skeletal part of the palate, may be affected in children with ADHD. The results may prove valuable in the diagnosis and treatment planning of children with ADHD. Further studies are needed to investigate sleep and dental relations in children with ADHD

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Eur Child Adolesc Psychiatry. 2018 Sep;27:1105-21.

CHILDHOOD AGGRESSION AND THE CO-OCCURRENCE OF BEHAVIOURAL AND EMOTIONAL PROBLEMS: RESULTS ACROSS AGES 3-16 YEARS FROM MULTIPLE RATERS IN SIX COHORTS IN THE EU-ACTION PROJECT.

Bartels M, Hendriks A, Mauri M, et al.

Childhood aggression and its resulting consequences inflict a huge burden on affected children, their relatives, teachers, peers and society as a whole. Aggression during childhood rarely occurs in isolation and is correlated with other symptoms of childhood psychopathology. In this paper, we aim to describe and improve the understanding of the co-occurrence of aggression with other forms of childhood psychopathology. We focus on the co-occurrence of aggression and other childhood behavioural and emotional problems, including other externalising problems, attention problems and anxiety-depression. The data were brought together within the EU-ACTION (Aggression in Children: unravelling gene-environment interplay to inform Treatment and InterventiON strategies) project. We analysed the co-occurrence of aggression and other childhood behavioural and emotional problems as a function of the child's age (ages 3 through 16 years), gender, the person rating the behaviour (father, mother or self) and assessment instrument. The data came from six large population-based European cohort studies from the Netherlands (2x), the UK, Finland and Sweden (2x). Multiple assessment instruments, including the Child Behaviour Checklist (CBCL), the Strengths and Difficulties Questionnaire (SDQ) and Multidimensional Peer Nomination Inventory (MPNI), were used. There was a good representation of boys and girls in each age category, with data for 30,5

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Eur Child Adolesc Psychiatry. 2018 Sep;27:1095-104.

COMPARING THE DSM-5 CONSTRUCT OF DISRUPTIVE MOOD DYSREGULATION DISORDER AND ICD-10 MIXED DISORDER OF EMOTION AND CONDUCT IN THE UK LONGITUDINAL ASSESSMENT OF MANIC SYMPTOMS (UK-LAMS) STUDY.

Sagar-Ouriaghli I, Milavic G, Barton R, et al.

It is important to understand new diagnostic entities in classifications of psychopathology such as the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) (code F34.8) construct of Disruptive Mood Dysregulation Disorder (DMDD) and to compare it with possible equivalent disorders in other classificatory

systems such as the International Classification of Diseases-10 (ICD-10), which has a category that superficially appears similar, that is, Mixed Disorder of Emotion and Conduct (MDEC) (code F92). In this study, the United Kingdom (UK) arm (UK-LAMS) of the US National Institute of Mental Health (NIMH) supported Longitudinal Assessment of Manic Symptoms (LAMS) multi-site study was used to evaluate and retrospectively construct DMDD and MDEC diagnoses in order to compare them and understand the conditions they co-occur with, in order to improve the clinical understanding. In particular, the phenomenology of UK-LAMS participants (n = 117) was used to determine whether DMDD is a unique entity within the DSM-5. The findings showed that 24 of 68 participants with either DMDD or MDEC (35.3%) fulfilled both diagnostic criteria for DMDD and MDEC, suggesting that these entities do contain overlapping features, particularly symptoms relating to Oppositional Defiant Disorder (ODD)/Conduct Disorder (CD), Attention Deficit Hyperactivity Disorder (ADHD)/Hyperkinetic Disorder (HKD) and/or an anxiety disorder. The data also showed that most of the participants who met DMDD criteria also fulfilled the diagnostic criteria for ODD/CD, ADHD, followed by an anxiety disorder. In this context, this raises the issue whether DMDD is a unique construct or whether the symptomology for DMDD can be better explained as a specifier for ODD/CD and ADHD. Unlike DMDD, MDEC clearly specifies that the label should only be used if emotional and conduct disorders co-exist

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Eur J Med Genet. 2018 May;61:280-83.

PDD-NOS, PSYCHOTIC FEATURES AND EXECUTIVE FUNCTION DEFICITS IN A BOY WITH PROXIMAL 22Q11.2 MICRODUPLICATION: EVOLUTION OF THE PSYCHIATRIC SYMPTOM PROFILE FROM CHILDHOOD TO ADOLESCENCE.

Woestelandt L, Novo A, Philippe A, et al.

22q11.2 microduplication (22q11.2DupS) is associated with a broad spectrum of phenotypes, including normality. Psychiatric disorders are described in 13% of these patients, including Attention Deficit and Hyperactivity Disorder (ADHD), Intellectual Deficiency (ID), and Autism Spectrum Disorder (ASD), but not schizophrenia. We report changes in the psychiatric symptom profile in the course of development of a young boy with a 22q11.2DupS syndrome, from early childhood to adolescence. The boy's psychiatric presentation was characterized by features of Pervasive Developmental Disorder (PDD), with ADHD in early childhood, a single psychotic episode in mid-infancy, and executive impairment in adolescence. We discuss the importance of an in-depth assessment of cognitive functions in children with22q11.2DupS throughout their development

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Eur Child Adolesc Psychiatry. 2018;27:1433-47.

ATTENTION PROFILES IN AUTISM SPECTRUM DISORDER AND SUBTYPES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Boxhoorn S, Lopez E, Schmidt C, et al.

Attention problems are observed in attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Most neuropsychological studies that compared both disorders focused on complex executive functions (EF), but missed to contrast basic attention functions, as well as ASD- and ADHD subtypes. The present study compared EF as well as basic attention functioning of children with the combined subtype (ADHD-C), the predominantly inattentive subtype (ADHD-I), and autism spectrum disorder without ADHD (ASD-) with typically developing controls (TD). Basic attention functions and EF profiles were analysed by testing the comprehensive attention function model of van Zomeren and Brouwer using profile analysis. Additionally, neurocognitive impairments in ASD- and ADHD were regressed on dimensional measures of attention- and hyperactive-impulsive symptoms across and within groups. ADHD-C revealed a strong impairment across measures of EF compared to ASD- and TD. The ADHD-C profile furthermore showed disorder specific impairments in interference control, whereas the ASD- profile showed a disorder specific impairment in basic attention component divided attention. Attention- and hyperactive-impulsive symptom severity did not predict neurocognitive impairments across- or within groups. Study findings thus

support disorder and subtype specific attention/EF profiles, which refute the idea of a continuum of ADHD-I, ADHD-C, and ASD with increasing neurocognitive impairments

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Eur Child Adolesc Psychiatry. 2018.

BEHAVIORAL AND COGNITIVE EFFECTS OF DOCOSAHEXAENOIC ACID IN DRUG-NAÏVE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL

Crippa A, Tesei A, Sangiorgio F, et al.

This study aimed to investigate the efficacy of docosahexaenoic acid (DHA) dietary supplementation on behavior and cognition in school-aged, drug-na+»ve children with attention-deficit/hyperactivity disorder (ADHD). A total of 50 participants with ADHD aged 7 to 14 were enrolled in a 6-month randomized, placebo-controlled clinical trial and received either DHA or placebo. The primary outcome measure was the change in the ADHD rating scale IV Parent Version Investigator (ADHD-RS-IV) after 4 and 6-months. Secondary outcome measures included Conners Parent Rating Scale-revised, other behavioral rating scales including quality of life and global functioning, and computerized cognitive tasks. Baseline assessment also addressed the blood fatty acids profile. No superiority of DHA supplement to placebo was observed on ADHD-RS-IV, the a priori primary outcome. DHA supplementation showed a significant, nonetheless quite small, effect on children's psychosocial functioning, emotional problems, and focused attention. Neither major nor minor adverse events were reported throughout the trial. This study shows that 6-month DHA supplementation has no beneficial effect on the symptoms of ADHD in school-aged, drug-naïve children with an established diagnosis of ADHD. Nevertheless, the 6-ámonths treatment with supplemental DHA appears to have small positive effects on other behavioral and cognitive difficulties, which, in light of the absence of side-effects, could be reasonably followed up in future intervention studies. (https://clinicaltrials.gov/ct2/show/NCT01796262: The Effects of DHA on Attention Deficit and Hyperactivity Disorder (DADA))

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Eur Child Adolesc Psychiatry. 2018.

RELATIVE AGE AND ADHD SYMPTOMS, DIAGNOSIS AND MEDICATION: A SYSTEMATIC REVIEW.

Holland J, Sayal K.

There is a growing international literature investigating the relationship between attention-deficit/hyperactivity disorder (ADHD) and younger relative age within the school year, but results have been mixed. There are no published systematic reviews on this topic. This study aimed to systematically review the published studies on the relative age effect in ADHD. Systematic database searches of: Medline, Embase, PsycINFO, Web of Science, ERIC, Psychology and Behavioral Sciences Collection and The Cochrane Library were conducted. Studies were selected which investigated the relative age effect in ADHD in children and adolescents. Twenty papers were included in the review. Sixteen (of 20) papers reported a significantly higher proportion of relatively younger children being diagnosed with ADHD and/or receiving medication for this. Meta-analyses involving 17 of these 20 papers revealed a modest relative age effect in countries with higher prescribing rates, risk ratio = 1.27 (95% CI 1.19–1.35) for receipt of medication. The relative age effect is well demonstrated in countries with known higher prescribing rates. Amongst other countries, there is also increasing evidence for the relative age effect, however, there is high heterogeneity amongst studies. Further research is needed to understand the possible reasons under-pinning the relative age effect and to inform attempts to reduce it

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Eur Child Adolesc Psychiatry. 2018;27:1305-19.

AN INTERNATIONAL CLINICAL STUDY OF ABILITY AND DISABILITY IN ADHD USING THE WHO-ICF FRAMEWORK.

Mahdi S, Ronzano N, et al.

This is the fourth and final study designed to develop International Classification of Functioning, Disability and Health (ICF, and children and youth version, ICF-CY) core sets for attention-deficit hyperactivity disorder (ADHD). To investigate aspects of functioning and environment of individuals with ADHD as documented by the ICF-CY in clinical practice settings. An international cross-sectional multi-centre study was applied, involving nine units from eight countries: Denmark, Germany, India, Italy, Portugal, Saudi Arabia, Sweden and Taiwan. Clinicians and clinical researchers rated the functioning level of 112 children, adolescents and adults with ADHD using the extended ICF-CY checklist version 2.1a. The ratings were based on a variety of information sources, such as medical records, medical history, clinical observations, clinical questionnaires, psychometric tests and structured interviews with participants and family members. In total, 113 ICF-CY categories were identified, of which 50 were related to the activities and participation, 33 to environmental factors and 30 to body functions. The clinical study also yielded strengths related to ADHD, which included temperament and personality functions and recreation and leisure. The study findings endorse the complex nature of ADHD, as evidenced by the many functional and contextual domains impacted in ADHD. ICF-CY based tools can serve as foundation for capturing various functional profiles and environmental facilitators and barriers. The international nature of the ICF-CY makes it possible to develop user-friendly tools that can be applied globally and in multiple settings, ranging from clinical services and policy-making to education and research

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Eur Child Adolesc Psychiatry. 2018.

PARENTAL SOCIOECONOMIC POSITION AND RISK OF ADHD IN OFFSPRING: A COHORT STUDY OF 9648 INDIVIDUALS IN DENMARK 1976-2013.

Hegelund ER, Flensborg-Madsen T, Vassard D, et al.

The strength of the association between parental socioeconomic position (SEP) and risk of attention-deficit/hyperactivity disorder (ADHD) in offspring is found to vary substantially, perhaps due to the negligence of possible changes in parental life course SEP. The present study investigated the association between parental SEP in adulthood and risk of ADHD diagnosis in offspring and whether parental childhood SEP modified this association. The study population included 9648 live-born singletons followed in the Psychiatric Central Register from birth in 1976–1996 until 2013. Cox regression was used to estimate hazard ratios for ADHD diagnosis according to parental SEP in adulthood. The results showed that low parental SEP in adulthood was associated with higher risk of ADHD diagnosis in offspring, also after adjustment for possible confounders. Thus, offspring of parents with low SEP in adulthood had 4.52 (95% CI 2.81–7.26) times higher hazard of ADHD diagnosis compared with offspring of parents with high SEP in adulthood. Further, parental childhood SEP was found to modify the observed association. Thus, offspring of parents with downward social mobility from childhood to adulthood and offspring of parents with stable low SEP experienced the highest risk of ADHD diagnosis, followed by offspring of parents with upward social mobility, compared with offspring of parents with stable high SEP. The results suggest that it is important to take into account the possibility of social mobility as changes in parental life course SEP from childhood to adulthood seem to influence the risk of ADHD diagnosis in offspring

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Eur J Paediatr Neurol. 2018.

METHYLPHENIDATE USE IN MALES WITH DUCHENNE MUSCULAR DYSTROPHY AND A COMORBID ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Lionarons JM, Hellebrekers DMJ, Klinkenberg S, et al.

Attention-deficit hyperactivity disorder (ADHD) is a common comorbidity in Duchenne muscular dystrophy (DMD). Until now, treatment with methylphenidate (MPH) has never been systematically assessed and described in this population. Our aim was to evaluate the effectiveness and safety of short acting MPH for

learning problems in males with DMD and ADHD. Neuropsychological (cognition and behavior) and medical data of a sample of ten males (mean age = 8.1 years, range 6.3–9.8) with DMD and an ADHD diagnosis was retrospectively analyzed at baseline (T0; without MPH), short-term follow-up (T1; with MPH; mean interval T0-T1 = 8.3 months, range 4.3Γ Çô15.6), and long-term follow-up (T2; mean interval T1-T2 = 23.1 months, range 2.6–77.7). An initial MPH dose of 5 mg/day was given on school mornings, with an increase of 2.5–5 mg/week depending on individual tolerance and treatment response, until a sufficiently effective dose was reached (range 0.2–0.6 mg/kg/day). At T1, results demonstrated an improvement in attention (i.e. concentration, impulsivity, and distractibility) in four patients. Suboptimal effects were reported in four patients, and no effects in two patients. At T2, seven patients showed considerable improvement in attention. No major side effects were reported. Overall, our data show that short acting MPH can be clinically effective for learning problems in males with DMD and ADHD, with regular cardiac follow-up, and close monitoring of side effects and neuropsychological effects. Furthermore, this underscores the importance of the use of validated cognitive and behavioral measurement tools with adequate sensitivity to objectively evaluate the effect of MPH

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Genet Epidemiol. 2018;42:709.

JOINT GENETIC FACTORS OF BODY MASS INDEX AND ADHD COMPONENTS.

Karhunen V, Wiklund P, J+ñrvelin M-R, et al.

There is evidence for genetic overlap between body mass index (BMI) and attention-deficit/hyperactivity disorder (ADHD), however the difference in the association between two components of ADHD - hyperactivity and inattention - remains unclear. We examined the effect of BMI polygenic risk score (BMIPRS) on ADHD and its separate components in the Northern Finland Birth Cohort 1986 (N = 2916). ADHD-related questions were answered by teachers and parents at eight years and by adolescents and parents at 16 years. Based on age, respondent and ADHD component, we constructed 19 outcome variables. We generated the BMI-PRS based on external summary statistics. We used ordinal regression to examine the effect of BMI-PRS on the outcomes, adjusted for maternal education, pre-pregnancy BMI and offspring sex. We also examined BMI-PRS by sex interaction effects. We found evidence of association between BMI-PRS and ADHD-related phenotypes for 13 of the 19 outcomes examined (false discovery rate (FDR) adjusted P value <0.05). The effects were the strongest at eight years, and similar for both hyperactivity and inattention dimensions. There was some evidence for effect-modification by sex, with boys having stronger effect sizes especially for inattentionrelated outcomes. These results suggest similar effects of BMI-PRS on both ADHD components

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Handb Clin Neurol. 2018;152:99-116.

NEUROAIDS IN CHILDREN.

Wilmshurst JM, Hammond CK, Donald K, et al.

The human immunodeficiency virus-1 (HIV-1) enters the central nervous system compartment within the first few weeks of systemic HIV infection and may cause a spectrum of neurologic complications. Without combination antiretroviral therapy (cART), 50-90% of all HIV-infected infants and children develop some form of neuroAIDS. Of the estimated 2.3 million children less than 15 years of age who were living in sub-Saharan Africa at the end of 2014, only 30% were receiving cART, suggesting that there is a large burden of neuroAIDS among HIV-infected children in sub-Saharan Africa. There is complex interplay between the disease process itself, the child's immune reaction to the disease, the secondary complications, the side-effects of antiretroviral drugs, and inadequate antiretroviral drug uptake into the central nervous system. In addition there is the layering effect from the multiple socioeconomic challenges for children living in low- and middle-income countries. Adolescents may manifest with a range of neurocognitive sequelae from mild neurocognitive disorder through to severe neurocognitive impairment. Neuroimaging studies on white-matter tracts have identified dysfunction, especially in the frontostriatal networks needed for executive function. Psychiatric symptoms of depression, attention deficit hyperactivity disorder, and behavioral problems are also commonly reported in this age group. Antiretroviral drugs may cause treatment-limiting neurologic and

neuropsychiatric adverse reactions. The following chapter addresses the neurologic complications known to be, and suspected of being, associated with HIV infection in children and adolescents

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Hormones (Athens). 2018 Mar;17:25-32.

PERINATAL HYPOXIA AS A RISK FACTOR FOR PSYCHOPATHOLOGY LATER IN LIFE: THE ROLE OF DOPAMINE AND NEUROTROPHINS.

Giannopoulou I, Pagida MA, Briana DD, et al.

Brain development is influenced by various prenatal, intrapartum, and postnatal events which may interact with genotype to affect the neural and psychophysiological systems related to emotions, specific cognitive functions (e.g., attention, memory), and language abilities and thereby heighten the risk for psychopathology later in life. Fetal hypoxia (intrapartum oxygen deprivation), hypoxia-related obstetric complications, and hypoxia during the early neonatal period are major environmental risk factors shown to be associated with an increased risk for later psychopathology. Experimental models of perinatal hypoxia/ischemia (PHI) showed that fetal hypoxia-a consequence common to many birth complications in humans-results in selective long-term disturbances of the dopaminergic systems that persist in adulthood. On the other hand, neurotrophic signaling is critical for pre- and postnatal brain development due to its impact on the process of neuronal development and its reaction to perinatal stress. The aim of this review is (a) to summarize epidemiological data confirming an association of PHI with an increased risk of a range of psychiatric disorders from childhood through adolescence to adulthood, (b) to present immunohistochemical findings on human autopsy material indicating vulnerability of the dopaminergic neurons of the human neonate to PHI that could predispose infant survivors of PHI to dopamine-related neurological and/or cognitive deficits in adulthood, and

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Hum Mov Sci. 2018;62:48-57.

EFFECTS OF DUAL TASKING AND METHYLPHENIDATE ON GAIT IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Möhring W, Klupp S, Grob A.

Effects of dual tasking on motor processes such as gait have been mainly investigated with healthy adults and clinical older samples whereas studies with clinical samples of children with attention deficit hyperactivity disorder (ADHD) are rare. Similarly, even though methylphenidate (MPH) is the most often prescribed medication for children with ADHD, the influence of MPH on children's gait under single-task and dual-task situations remains poorly understood. In the current study, children diagnosed with ADHD (n = 26) came twice to the laboratory, once without and once with MPH medication. They were asked to walk over an electronic walkway without a concurrent task (motor single task) and while solving different cognitive tasks (motor-cognitive dual task). Gait variability and cognitive performance were measured. Children's performance was compared to an age- and sex-matched control sample of typically developing children (n = 26) who were also tested twice. Results indicated considerable effects of dual tasking on children's gait irrespective of group (ADHD vs. controls), with children diagnosed with ADHD showing more pronounced gait alterations in dual-task situations as compared to controls. Furthermore, MPH medication in children with ADHD enabled them to substantially decrease their stride time variability to a level that was comparable to the level of typically developing children. Overall, our findings support the notion that higher cognitive processes such as attention and executive functions influence gait and that MPH can positively affect cognitive and motor processes such as gait

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Indian Journal of Public Health Research and Development. 2018;9:592-98.

EFFECT OF PARTICIPATION IN TAEGKYEON ON PEER STATUS AND PROBLEM BEHAVIORS OF INFANTS.

Kim Y-M, Lee W-H.

This study is to investigate the influence of Taegkyeon participation on peer status and problem behavior of infants. 70 infants at age 6~7 were selected as the study subjects. 37 infants who participate in Taegkyeon class voluntarily were sampled as experimental group and the other non-participating 33 ones were sampled as control group. The Taegkyeon course was conducted twice a week for 16 weeks. The control group was asked to only go through the regular class schedule at kindergarten. The data were under the t-test, paired t-test. The results were as follows. First, there was no significant difference between experimental and control group in peer status according to Taegkyeon class participation of infants. Second, there was significant difference problem behavior according to Taegkyeon class participation. 6 years old infants showed significant difference between experimental and control group`s attention deficit and noncooperation. And 7 years old infants showed significant difference hyperactivity problem between experimental and control groups. To positively change the childrenΓÇÖs attitude, teachers guiding physical activities of children need to develop instruction methods that are appropriate and efficient given the development and characteristics of children

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Int J Clin Pharm. 2018 Apr;40:341-44.

ATTENTION DEFICIT HYPERACTIVITY DISORDER PHARMACOTHERAPY IN SLOVENIAN ADULTS: A POPULATION-BASED STUDY.

Stuhec M, Locatelli I.

Background Pharmacotherapy is the first line treatment for adult attention deficit hyperactivity disorder (ADHD) and the percentage of treated patients may indicate the quality of treatment of adult ADHD. The main aim of this study was to investigate the rates of pharmacological treatment for adult ADHD in Slovenia from 2003 to 2015.

Methods The number of prescriptions per patient was obtained for three different age groups (18-24, 25-49, 50 + age group). The national consumption rates were obtained from the national database. The only drugs that were available and were included in this study were methylphenidate (MPH) and atomoxetine (ATX).

Results Between 2003 and 2015 the rate of patients aged 18-24 who were treated with MPH increased from 0.8 per 10,000 people aged 18-24 to 8.9 per 10,000 people, while the increase in the other two age groups was less substantial (25-49, 50 + age group). The rate of patients aged 18-24 treated with ATX in 2015 was 7.3 per 10,000 people and 2.2 per 10,000 people in the 25-49 age category and 0.28 in the 50 + age group category.

Conclusion Prescription rates of ADHD medication have increased dramatically in the study period. The high proportion of ADHD patients treated with ATX can be explained by low adherence to treatment guidelines. This is the first study to compare ADHD pharmacotherapy across different adult age groups in this part of Europe, so the results could be widely relevant

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Int J Eat Disord. 2018 Mar;51:223-32.

CUE REACTIVITY, HABITUATION, AND EATING IN THE ABSENCE OF HUNGER IN CHILDREN WITH LOSS OF CONTROL EATING AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hilbert A, Kurz S, Dremmel D, et al.

OBJECTIVE: Childhood loss of control (LOC) eating and attention-deficit/hyperactivity disorder (ADHD) are highly comorbid conditions and present with disordered eating behaviors, such as overeating. This study sought to delineate shared and specific abnormalities in physiological, cognitive-motivational, and behavioral components of food-specific impulsivity in children with LOC eating and ADHD. Specifically, children's reactivity and habituation to food and eating in the absence of hunger were examined.

METHODS: Within this community-based study, four groups of 8-13-year-old children with LOC eating (n = 24), ADHD (n = 32), comorbid LOC eating/ADHD (n = 9), and matched controls (n = 34) received a standard

laboratory test meal to establish satiety and were then exposed to their favorite snack food in a cue exposure/reactivity trial, while salivation and desire to eat were repeatedly assessed. Subsequently, they were offered a variety of snack foods ad libitum.
RESULTS: Children with LOC eating, ADHD, and LOC/ADHD did not differ from controls in salivary reactivity and habituation to food cues. Children with LOC eating and ADHD showed greater cue reactivity of the desire to eat than controls, but groups did not differ in its longer-term increments. At free access, only children with LOC/ADHD consumed significantly more energy than controls. Longer-term increments of desire to eat predicted greater energy intake beyond LOC/ADHD group status.
DISCUSSION: Desire to eat among children with comorbid LOC eating and ADHD was associated with overeating in the absence of hunger, which may contribute to excess weight gain. Delineation of the specific features of childhood LOC eating versus ADHD warrants further study

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Int J Pediatr Otorhinolaryngol. 2018 Sep;112:39-44.
HYPERACUSIS IN CHILDREN: THE EDINBURGH EXPERIENCE.
Amir I, Lamerton D, Montague ML.
OBJECTIVES: This study aimed to determine the factors associated with hyperacusis in children referred to an audiology-led paediatric hyperacusis clinic in a Paediatric tertiary centre. It also aimed to identify current management strategies in paediatric hyperacusis and their outcomes.
METHODS: Retrospective cohort study conducted by case note and AuditBase((R)) review over a 5-year period (March 2010 to March 2015) in a tertiary Paediatric ENT and Audiology service.
RESULTS: 412 children were referred with hyperacusis during the 5-year period. All children were assessed and managed within a dedicated Paediatric hyperacusis clinic. Median age at referral was 7 years. 76% were boys (n=313). On average, children were sensitive to 6 identifiable sound stimuli at presentation (range 1-20). 82% complained of sensitivity to noise from household appliances and hand dryers. 60% had a background history of autistic spectrum disorder (ASD), followed by attention deficit hyperactivity disorder (ADHD) and other neurodevelopmental problems. In 91% management comprised behavioural therapy and provision of a 'sound-ball' (Wellcare((R)) Naturcare Relaxation Therapy Ball) to take home. Of these, 25% did not attend their first review appointment. A further 25% were considered to have sufficient symptom improvement to permit discharge after a single clinic review. Only 2% of children required more than 3 review sessions before achieving resolution of symptoms.
CONCLUSIONS: In our paediatric cohort, hyperacusis is more common in boys and in those children with ASD. A combined treatment approach with behavioural therapy and the provision of a sound-ball has a very high success rate in our experience

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Int Clin Psychopharmacol. 2018;33:330-33.
THE EFFECT OF METHYLPHENIDATE TREATMENT ON PSYCHOPATHIC BEHAVIOR OF PATIENTS HAVING ATTENTION-DEFICIT HYPERACTIVITY DISORDER WITH AND WITHOUT OPPOSITIONAL DEFIANT DISORDER.
Golubchik P, Levy T, Weizman A.
To evaluate the effect of 3 months of methylphenidate (MPH) treatment on psychopathic behavior in children having attention-deficit hyperactivity disorder (ADHD) with and without comorbid oppositional defiant disorder (ODD). Twenty-seven children with Diagnostic and Statistical Manual of Mental Disorders, fifth ed., ADHD (13 female/14 male; aged 13.3-¦2.2 years old) were compared to an age/sex matched ADHD/ODD group (N=27, eight female/19 male; aged 11.8-¦1.9 years). The attention-deficit hyperactivity disorder rating scale (ADHD-RS) and the California Child Q-Set (CCQ) were used in both groups before MPH treatment (0.8-1.2 mg/kg/day) and 3 months thereafter. Significant reduction in the ADHD-RS scores was detected following MPH treatment in both the ADHD/ODD group and in the ADHD group ($P<0.0011$ and $P=0.0012$, respectively). Reduction in the CCQ scores was obtained in the ADHD/ODD group ($P=0.0001$) but not in in the ADHD group ($P=0.18$). A correlation was found between the reductions in the ADHD-RS and CCQ scores following MPH treatment in the ADHD/ODD group (Spearman's $r=0.43$, $P=0.024$). MPH treatment in children

with ADHD/ODD was associated with reduction in psychopathic scores, and the reduction correlated with a corresponding improvement in their ADHD severity

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Int J Obes. 2018.

THE ROLE OF GENETIC AND ENVIRONMENTAL INFLUENCES ON THE ASSOCIATION BETWEEN CHILDHOOD ADHD SYMPTOMS AND BMI.

Do EK, Haberstick BC, Williams RB, et al .

Background/Objectives: Although childhood attention deficit hyperactivity disorder (ADHD) has been previously associated with concurrent and later obesity in adulthood, the etiology of this association remains unclear. The objective of this study is to determine the shared genetic effects of ADHD symptoms and BMI in a large sample of sibling pairs, consider how these shared effects may vary over time, and examine potential sex differences.

Subject/Methods: Sibling pair data were obtained from the National Longitudinal Study of Adolescent to Adult Health (Add Health); childhood ADHD symptoms were reported retrospectively during young adulthood, while three prospective measurements of BMI were available from young adulthood to later adulthood. Cholesky decomposition models were fit to this data using Mx and maximum-likelihood estimation. The twin and sibling sample for these analyses included: 221 monozygotic (MZ) pairs (92 male male, 139 female female), 228 dizygotic (DZ) pairs (123 male–male, 105 female female), 471 full-sibling (FS) pairs (289 male male, 182 female female), 106 male female DZ twin pairs, and 234 male–female FS pairs.

Results: The magnitude of the association between childhood ADHD symptoms and BMI changed over time and by sex. The etiological relationship between childhood ADHD symptoms and the three prospective measurements of BMI differed for males and females, such that unique or non-shared environmental influences contributed to the relationship within males and genetic factors contributed to the relationship within females. Specifically, among females, genetic influences on childhood ADHD symptoms were partially shared with those effecting BMI and increased from adolescence to later adulthood (genetic correlation = 0.20 (95% CI: 0.07-0.36) in adolescence and 0.24 (95% CI: 0.10, 0.41) in adulthood).

Conclusion: Genetic influences on ADHD symptoms in childhood are partially shared with those effecting obesity. However, future research is needed to determine why this association is limited to females

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International Journal of Play Therapy. 2018 Oct;27:187-97.

ON-TASK BEHAVIOR OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: EXAMINING TREATMENT EFFECTIVENESS OF PLAY THERAPY INTERVENTIONS.

Swank JM, Smith-Adcock S.

This study focused on examining the treatment effect associated with two 12-session interventions (child-centered play therapy and nature-based child-centered play therapy) among early elementary schoolchildren (N = 8) who had an attention-deficit/hyperactivity disorder diagnosis. Children were randomly assigned to one of the treatment groups or the waitlist group. We found that the child-centered play therapy intervention ranged from debatable (n = 1) to effective (n = 2) and the nature-based child-centered play therapy intervention ranged from debatable (n = 1) to very effective (n = 1), with one participant also scoring in the effective range for improving on-task behavior. In comparison, the waitlist group participants had a large fluctuation in scores, with the analysis revealing that noninvolvement in treatment was ineffective for improving on-task behavior

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Int J Psychiatry Clin Pract. 2018.

PREVENTIVE EFFECT OF CYPROHEPTADINE ON SLEEP AND APPETITE DISORDERS INDUCED BY METHYLPHENIDATE: AN EXPLORATORY RANDOMISED, DOUBLE-BLINDED, PLACEBO-CONTROLLED CLINICAL TRIAL.

Kadkhoda MF, Moharreri F, Mohammadpour AH, et al.

Objectives: Insomnia and loss of appetite are the most common side effects of methylphenidate in patients with attention deficit/hyperactivity disorder (ADHD). The adverse effects may limit optimal dosing and patients compliance with treatment leading to the discontinuation of treatment. This research evaluates the preventive effects of cyproheptadine on sleeping and appetite disorders induced by methylphenidate in ADHD children.
Methods: During this exploratory, randomised, double-blinded, placebo-controlled clinical trial, forty patients with ADHD diagnosis who had received methylphenidate randomly were assigned to participate in the cyproheptadine or the placebo group. Patients weight and Pittsburgh Sleep Quality Index (PSQI) score were recorded at baseline, after four, six and eight weeks of treatment. The ADHD Parent Rating Scale-V score was also defined at the beginning and the end of study for each patient.
Results: There was no significant difference between the cyproheptadine and the placebo groups regarding their weight, rate of growth and PSQI score in the monthly assessment. In addition, there was no significant difference in response to the therapy between the two groups.
Conclusions: Based on our findings, cyproheptadine does not have any considerable preventive effect on sleeping and appetite disorders induced by methylphenidate in ADHD children

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Ir J Psychol Med. 2018.

HYPERKINETIC DISORDER IN A COMMUNITY SERVICE FOR PEOPLE WITH INTELLECTUAL DISABILITY.

Patel S, Yacoub E.

Background There appears to be a higher rate of prevalence of hyperkinetic disorder in the intellectual disability (ID) population, although there is a large variability in rates in previous studies. Hyperkinetic disorder can be a challenge to diagnose in a population with ID and can present a barrier to the development of the activities of daily living in an already vulnerable population.
Objectives Our objective was to examine the point prevalence of hyperkinetic disorder in the ID population in a community ID service and also to determine the prevalence of hyperkinetic disorder based on the level of ID.MethodsA cross-sectional review of the Online Information Service 'OLIS' database was undertaken to establish the total number of patients with ID and those with comorbid hyperkinetic disorder. The overall point prevalence and prevalence based on the level of ID was calculated from the collected data.
Results The point prevalence of hyperkinetic disorder in the population with ID was similar to that found in studies in the general population at 3.1% in adults and 32.6% in children. When divided by the level of disability, the calculated point prevalence in both adults and children was highest in the population with mild ID and decreased as the level of disability increased.
Conclusion This report contributes to previous research establishing the rates of hyperkinetic disorder in an ID population and establishes the point prevalence of hyperkinetic disorder in individuals diagnosed with ID in a clinical sample

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J Addict Nurs. 2018 Apr;29:84-89.

STIMULANT USE AMONG UNDERGRADUATE NURSING STUDENTS.

Kirkpatrick ZA, Boyd CJ.

Research reveals a decade-long increase in prescription drug misuse (PDM) of stimulant medication used to treat attention deficit hyperactivity disorder, and college students in particular are at the highest risk for these behaviors. However, PDM has not been specifically studied in undergraduate nursing students, and thus, this study fills a gap in our knowledge of PDM of stimulants. This descriptive study used a cross-sectional, convenience sample of undergraduate nursing students (N = 249) attending a large midwestern university. The purpose of this study was to examine the medical use, medical misuse, nonmedical use, and diversion of attention deficit hyperactivity disorder stimulant medications as well as to compare CRAFFT

scores among these four groups of stimulant users. A 28-item, Web-based survey was sent via email to all registered undergraduate nursing students during the winter semester of 2017. Results showed that 10.4% of respondents used prescription stimulants nonmedically in the past 12 months, and over half (51.5%) of respondents screened positive on the CRAFFT, an indication of possible alcohol and drug misuse behaviors. In addition, there was a strong association between medical misuse and nonmedical use and positive CRAFFT scores. The high percentage of positive CRAFFT scores is a concern and indicates a pressing need for nursing faculty to evaluate and address substance use by nursing students

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J Altern Complement Med. 2018 Aug;24:841-49.

EFFECTS OF EQUINE-ASSISTED ACTIVITIES AND THERAPIES ON THE AFFECTIVE NETWORK OF ADOLESCENTS WITH INTERNET GAMING DISORDER.

Kang KD, Jung TW, Park IH, et al.

OBJECTIVES: Internet gaming disorder (IGD) has been suggested to be a mental health disorder. Attachment and emotional status in IGD patients are important for understanding the etiology and progression of IGD because both parameters are considered to be associated with the affective network. Equine-assisted activities and therapies (EAAT) have been reported to improve emotional status and attachment in subjects. We hypothesized that EAAT would improve attachment in IGD adolescents with insecure attachment issues and increase functional connectivity (FC) within the affective network.

DESIGN: Subjects completed a demographic questionnaire, the Korean Experiences in Close Relationships Scale Revised version (K-ECRS), the Child Depression Inventory, Young's Internet Addiction Scale, the Korean Attention-Deficit Hyperactivity Disorder Rating Scale, and resting-state functional magnetic resonance imaging at baseline at the end of EAAT.

SUBJECTS: Fifteen IGD adolescents with insecure attachment issues and 15 healthy comparison adolescents with secure attachment agreed to participate in this study.

RESULTS: After 7 days of EAAT, K-ECRS avoidance and anxiety scores improved in all adolescents. K-ECRS avoidance scores of the IGD group showed marked improvement compared with those of the healthy group. In all participants, FC from the left amygdala to the left parahippocampal gyrus, left medial frontal gyrus, and left inferior frontal gyrus, as well as from the right amygdala to the left caudate, right claustrum, and left inferior frontal gyrus increased. In IGD adolescents, FC from the left amygdala to the left frontal orbital gyrus, as well as from the right amygdala to the right corpus callosum also increased.

CONCLUSION: These findings suggested that EAAT improves attachment, which could lead to a decrease in the severity of IGD symptoms in IGD patients with insecure attachment issues. In addition, EAAT increases FC within the affective network, which was associated with attachment not only in healthy adolescents but also in adolescents with IGD

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JAMA Psychiatry. 2017;74:1093-94.

HETEROGENEITY WITHIN AND BETWEEN AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER CHALLENGE OR OPPORTUNITY?

Ameis SH.

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Jornal de Pediatria. 2018.

PARENT SNAP-IV RATING OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: ACCURACY IN A CLINICAL SAMPLE OF ADHD, VALIDITY, AND RELIABILITY IN A BRAZILIAN SAMPLE.

Costa DS, de Paula JJ, Malloy-Diniz LF, et al.

Objective: To investigate the psychometric properties of the short or multimodal treatment study version of the Swanson, Nolan, and Pelham, Version IV (SNAP-IV) scale, which measures attention-deficit/hyperactivity disorder and oppositional defiant disorder symptoms.

Methods: Participants were 765 parents of children from 4 to 16 years old (641 non-attention-deficit/hyperactivity disorder and 124 attention-deficit/hyperactivity disorder children) from Belo Horizonte, Brazil, who reported sociodemographic characteristics and answered the SNAP-IV. Parents of the clinical sample also underwent the K-SADS-PL interview.
Results: Age was significantly associated with SNAP-IV hyperactivity-impulsivity problems (r = ΓêÆ0.14), but not with inattention or oppositional defiant disorder. Sex was a significant influence on attention-deficit/hyperactivity disorder and oppositional defiant disorder severity (all p < 0.001), with boys showing higher scores in the full sample, but not within the attention-deficit/hyperactivity disorder group. Exploratory and confirmatory factor analysis supports a three-factor structure of the SNAP-IV scale. Moderate-to-strong correlations were found between SNAP-IV and K-SADS-PL measures. All SNAP-IV scales showed very high internal consistency coefficients (all above 0.91). SNAP-IV inattention scores were the most predictive of attention-deficit/hyperactivity disorder diagnosis (AUC: 0.877 for the averaging rating method and the raw sum method, and 0.874 for the symptom presence/absence method).
Conclusion: The parent SNAP-IV showed good psychometric properties in a Brazilian school and clinical sample

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J Abnorm Child Psychol. 2018 Oct;46:1395-408.

IS THE POSITIVE BIAS AN ADHD PHENOMENON? REEXAMINING THE POSITIVE BIAS AND ITS CORRELATES IN A HETEROGENEOUS SAMPLE OF CHILDREN.

Bourchtein E, Owens JS, Dawson AE, et al.

The goals of this study were to (a) evaluate the presence of the positive bias (PB) in elementary-school-aged children with and without ADHD when PB is defined at the individual level through latent profile analysis and (b) examine the extent to which several correlates (i.e., social functioning, aggression, depression, and anxiety) are associated with the PB. Participants were 233 youth (30% female; 8 to 10 years of age), 51% of whom met criteria for ADHD. During an individual evaluation, children and parents completed a battery of questionnaires to assess child competence, depression, anxiety, and aggression. Children also participated in a novel group session with same-sex unfamiliar peers (half of the group was comprised of children with ADHD) to engage in group problem-solving tasks and free play activities. After the group session, peers and staff completed ratings of each child's behavior (e.g., likeability, rule following). The best fitting LPA model for parent and self-ratings of competence revealed four profiles: High Competence/Self-Aware; Variable Competence/Self-Aware; Low Competence/Self-Aware; and Low Competence/PB, in which the PB was present across domains. Only 10% of youth showed a PB and youth with ADHD were no more likely to display the PB than their non-ADHD peers with similar levels of low competence. Lastly, the Low Competence/Self-Aware profile demonstrated higher levels of anxiety and depression than the Low Competence/PB profile; the profiles did not differ on aggression or peer or staff ratings of social/behavioral functioning. Implications for understanding the PB in children with and without ADHD are discussed

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J Abnorm Child Psychol. 2018 Oct;46:1427-37.

ADHD SYMPTOMS IN MIDDLE ADOLESCENCE PREDICT EXPOSURE TO PERSON-RELATED LIFE STRESSORS IN LATE ADOLESCENCE IN 5-HTTLPR S-ALLELE HOMOZYGOTES.

Brinksma DM, Hoekstra PJ, de Bildt A, et al.

Literature suggests that life stressors predict attention-deficit/hyperactivity disorder (ADHD) symptoms and that this relationship is moderated by the serotonin transporter polymorphism (5-HTTLPR). It is less clear whether, on reverse, ADHD symptoms may influence the risk of exposure to life stressors. Furthermore, the role of life stressors may vary across development depending on the type of life stressor. We used threewave longitudinal data of 1,306 adolescents from the general population and clinicreferred cohort of the TRacking Adolescents' Individual Lives Survey. The 5-HTTLPR genotype (SS, LS, LL), parent-reported ADHD symptoms at three time points (T1: Mage = 11.2; T2: Mage = 13.5; T3: Mage = 16.2 years), and the number of personrelated ('dependent') and environment-related ('independent') life stressors occurring between

measurements (T1-T2, T2-T3) were assessed. Using path analyses, we examined bidirectional relations between exposure to these life stressors and ADHD symptoms between the separate waves moderated by 5-HTTLPR status. Exposure to life stressors did not predict ADHD symptoms. Rather, we found that in 5-HTTLPR Sallele homozygotes, ADHD symptoms in middle adolescence (T2) predicted exposure to the number of person-related life stressors later in adolescence (T2-T3, p = 0.001). There was no relation with environment-related life stressors. Our study suggests that S-allele homozygotes with higher levels of ADHD symptoms in middle adolescence are more vulnerable to becoming exposed to person-related ('dependent') life stressors in late adolescence. Findings emphasize the need to be aware of social-emotional adversities that may occur in genetically vulnerable adolescents with ADHD symptoms in the transition into adulthood

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J Affective Disord. 2018 Oct;238:161-78.

ADVERSE DRUG EVENTS RELATED TO MOOD AND EMOTION IN PAEDIATRIC PATIENTS TREATED FOR ADHD: A META-ANALYSIS.

Pozzi M, Carnovale C, Peeters GGAM, et al.

Background: ADHD is frequently comorbid with anxiety and mood disorders, which may increase the severity of inattention and hyperactivity symptoms. Emotional symptoms (anxiety, irritability, mood lability) also affect patients without comorbidity or emerge as adverse drug events. The influence of ADHD drugs on emotional symptoms demands investigation to improve therapies.

Methods: Systematic review of trials reporting adverse events in patients pharmacologically treated for ADHD. Meta-analysis of the occurrence of irritability, anxiety, apathy, reduced talk, sadness, crying, emotional lability, biting nails, staring, perseveration, euphoria. Meta-regression analysis.

Results: Forty-five trials were meta-analysed. The most frequently reported outcomes were irritability, anxiety, sadness, and apathy. Methylphenidates, especially immediate-release formulations, were most studied; amphetamines were half as studied and were predominantly mixed amphetamine salts. Reports on atomoxetine were scant. Meta-analysis showed that methylphenidates reduced the risk of irritability, anxiety, euphoria, whereas they worsened the risk of apathy and reduced talk; amphetamines worsened the risk of emotional lability. Factors influencing risks were study year and design, patients' sex and age, drug dose and release formulation.

Limitations: Possible discrepancy between adverse events as indicated in clinical trials and as summarised herein. Confounding due to the aggregation of drugs into groups; uninvestigated sources of bias; incomplete lists of adverse events; lack of observations on self-injury.

Conclusions: Methylphenidates appeared safer than amphetamines, although younger patients and females may incur higher risks, especially with high-dose, immediate-release methylphenidates. Only atomoxetine holds a black-box warning, but amphetamines and methylphenidates also did not show a safe profile regarding mood and emotional symptoms

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J Affective Disord. 2019;243:290-96.

SUGAR CONSUMPTION AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): A BIRTH COHORT STUDY.

Del-Ponte B, Anselmi L, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is characterized by persistent symptoms of lack of attention, impulsivity and hyperactivity. The association between nutritional exposures and ADHD has been investigated and some studies have identified adverse effects from higher intake of sugar. The objective of the present study was to evaluate the association between change in sugar consumption between 6 and 11 years of age and incidence of attention-deficit/hyperactivity disorder (ADHD).

Methods: Pelotas 2004 Birth Cohort Study in Brazil. A food frequency questionnaire (FFQ) was used to estimate sugar consumption and the Development and Well-Being Assessment (DAWBA) was applied to mothers to assess the presence of ADHD.

Results: Only children without ADHD at 6 years and with complete information from FFQ and DAWBA at 6 and 11 years were included in the analyses (n = 2924). Odds ratios with 95% confidence intervals were

calculated. Incidence of ADHD between 6 and 11 years was 4.6% (3.6-5.6%) among boys and 1.8% (1.2 2.5%) among girls. Adjusted analyses showed no association between always high sucrose consumption between 6 and 11 years and incidence of ADHD, compared with individuals who always presented low consumption, both among boys (OR = 0.66; 0.21-2.04) and girls (OR = 2.71; 0.24-30.35).
Limitations: Reflect those that are inherent to use of FFQs, such as memory bias and lack of precision in quantifying the diet.
Conclusions: The results suggest that there is no association between sucrose consumption between 6 and 11 years of age and incidence of ADHD

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Journal of Behavioral Addictions. 2018;7:781-91.
RELATIONSHIP BETWEEN ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AND PROBLEM GAMBLING: A MEDIATION ANALYSIS OF INFLUENTIAL FACTORS AMONG 7,403 INDIVIDUALS FROM THE UK.
Jacob L, Haro JM, Koyanagi A.
Background and aims: Our goal was to examine the association between attention-deficit hyperactivity disorder (ADHD) symptoms and gambling problems, and to identify potential mediating factors of this association.
Methods: This study used cross-sectional, community-based data from 7,403 people aged 16 years who participated in the Adult Psychiatric Morbidity Survey 2007. ADHD symptoms were assessed using the Adult ADHD Self-Report Scale (ASRS) Screener. Problem gambling was assessed using a questionnaire based on the 10 DSM-IV diagnostic criteria for pathological gambling. Respondents were classified as having no problem, at-risk, or problem gambling. Logistic regression and mediation analyses were conducted to analyze the association between ADHD symptoms (i.e., ASRS score 14) and problem gambling and the role of several variables in this association.
Results: The prevalence of at-risk (5.3% vs. 2.4%) and problem gambling (2.4% vs. 0.6%) was higher in individuals with ADHD symptoms than in those without ADHD symptoms. ADHD symptoms were significantly associated with both at-risk (OR = 2.15; 95% CI = 1.22-3.79) and problem gambling (OR = 3.57; 95% CI = 1.53-8.31) when adjusted for age, sex, and ethnicity. Common mental disorders (CMDs; i.e., depression and anxiety disorders) (mediated percentage = 22.4%), borderline personality disorder (BPD) traits (22.1%), stressful life events (13.2%), stress at work or home (12.6%), alcohol dependence (11.8%), and impulsivity (11.2%) were significant mediators in the ADHD-gambling association.
Discussion and conclusions: Overall, ADHD symptoms were positively associated with problem gambling. CMDs, BPD traits, and stressful life events were important mediators in this relationship

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J Child Adolesc Psychopharmacol. 2018;28:494-507.
THE EFFECTS OF LONG-ACTING STIMULANT AND NONSTIMULANT MEDICATIONS IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.
Cerrillo-Urbina AJ, Garc+¡a-Hermoso A, Pardo-Guijarro MJ, et al.
Objective: The aim of this study was to assess the efficacy and safety of stimulant and nonstimulant medications in children and adolescents using as an outcome measure the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV), and to examine the effect of medications in different ADHD subtypes (i.e., inattention and hyperactivity/impulsivity).
Methods: MEDLINE, Scopus, EMBASE, EBSCO (E-journal, CINAHL and SportDiscus), PUBMED, and The Cochrane Central Register of Controlled Trials databases were searched. Randomized controlled trials (RCTs) with parallel group or placebo-controlled studies comparing the effect of medications (stimulants or nonstimulants) in children and adolescents with ADHD were included. The main outcomes were the ADHD-RS-IV total score and subtypes (inattention and hyperactivity/impulsivity). Treatment-emergent adverse events (TEAEs) and secondary outcomes such as systolic and diastolic blood pressure, and pulse rate were considered.

Results: The search strategy identified 15 RCTs, including a total of 4648 children and/or adolescents diagnosed with ADHD aged 6 to 17 years old. Overall, both stimulant and nonstimulant medications reduce the ADHD-RS-IV score with a standardized mean difference (SMD) of -0.70 (confidence interval [95% CI], -0.85 to -0.55); in subgroup analyses, the SMD was -0.83 (95% CI, -1.11 to -0.54) for stimulant medications and -0.58 (95% CI, -0.69 to -0.46) for nonstimulant medications. Similar results were observed in inattention and hyperactivity/impulsivity subtypes. The placebo group also showed a medium effect SMD of -0.68 (95% CI, -0.82 to -0.54). The most frequent TEAEs for stimulant and nonstimulant medications, respectively, were decreased appetite (28.6% and 14.2%) and somnolence (4.4% and 34.1%).
Conclusions: These results suggest that both stimulant and nonstimulant medications mitigate ADHD symptoms in children and adolescents, although subgroup analyses suggest a greater effectiveness of stimulant medications

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J Child Adolesc Psychopharmacol. 2018;28:521-29.

RELATIONSHIP BETWEEN SYMPTOMATIC AND FUNCTIONAL IMPROVEMENT AND REMISSION IN A TREATMENT RESPONSE TO STIMULANT TRIAL.

Weiss M, Childress A, Mattingly G, et al.

Objective: To evaluate the relationship between symptom and functional improvement and remission in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) enrolled in an 11-week open-label dose-optimization phase of an methylphenidate extended release (MPH-MLR) pivotal study.
Methods: Assessments included the Weiss Functional Impairment Rating Scale-Parent (WFIRS-P) and ADHD Rating Scale, Fourth Edition (ADHD-RS-IV). Definitions included the following: symptom improvement (ΓëÑ30% decrease in ADHD-RS-IV total score); symptom remission (ADHD-RS-IV total score Γëñ18); functional improvement (decrease in WFIRS-P total score 0.25 [minimally important difference]); and functional remission (WFIRS-P total score 0.65).
Results: Two hundred children completed the open-label phase. At initial assessment, functional impairment was evident across all WFIRS-P domains and similar between children and adolescents. Those who were treatment naive had more functional impairment (WFIRS-P total: 0.82 vs. 0.70, p = 0.02). Significant improvements in all WFIRS-P domains were noted at open-label end (p < 0.001), with the largest improvement in Learning. At open-label end, 94% of children and adolescents demonstrated symptom improvement, of which 57% also showed functional improvement, and 75% of children and adolescents showed symptom remission, of which 81% also showed functional remission.
Conclusions: Children and adolescents treated with MPH-MLR showed moderate-to-large improvement in functioning during 3 months of treatment, both overall and in specific domains. However, a significant number of those who would be considered symptomatic responders failed to show improvement in functioning or continue to have significant functional impairment. Treatment with MPH-MLR showed that both symptomatic and functional remission are achievable goals. Identification of children and adolescents who have been successfully treated for their symptoms, but continue to suffer functional impairment, will allow us to offer additional targeted treatment interventions over and above medication to address residual difficulties

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J Child Adolesc Psychopharmacol. 2018;28:530-36.

PSYCHOSTIMULANTS: INFLUENCE ON BODY MASS INDEX AND HEIGHT IN A PEDIATRIC POPULATION WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER?

Lentferink YE, Van De Garde EMW, Knibbe CAJ, et al.

Objectives: Attention-deficit/hyperactivity disorder (ADHD) is often treated with psychostimulants. Psychostimulants' adverse effects on body mass index standard deviation score (BMI-sds) and height in children/adolescents with ADHD have been reported. However, literature is inconsistent, and it is unclear whether the observed effects are dosage- and/or BMI-dependent. Therefore, the aim of this retrospective observational study is to evaluate the influence of psychostimulants on BMI-sds and height-sds in a pediatric

cohort with ADHD from an outpatient clinic, and to study the correlation between psychostimulant dosage and BMI-sds and height-sds change.
Method: Participants Γëñ18 years of age diagnosed with ADHD who started with psychostimulants (methylphenidate) were studied. Changes in BMI-sds and height-sds over an 18-month treatment period were assessed in subgroups according to baseline BMI-sds, gender, and age. Furthermore, correlations between BMI-sds, height-sds, and psychostimulant dose were studied.
Results: In total, 298 participants [median age 9.8 years, height-sds 0.0, BMI-sds 0.5, psychostimulant dosage 0.5 (0.2-1.4) mg/kg/day] were analyzed, with an underweight, overweight, and obesity prevalence of 5%, 21%, and 7%, respectively. After 18 months of treatment a significant decline in BMI-sds (-0.4) and height-sds (-0.2) was observed. These effects were consistent in all subgroups except for no change in BMI-sds in the underweight subgroup and no change in height-sds in the overweight subgroup. Medication dosage was weakly correlated with change in BMI-sds [r = -0.3 (-0.9 to +0.5); p < 0.01] and height-sds [r = -0.2 (-0.4 to -0.1); p = 0.01].
Conclusion: After 18 months of psychostimulant treatment, a significant decline in BMI-sds and height-sds was observed. However, the correlation with psychostimulant dosage was weak, and the decline was not observed in all subgroups. Therefore, further studies on the etiology of BMI-change are warranted, particularly with regard to the ADHD symptoms

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J Child Adolesc Psychopharmacol. 2018;28:562-70.
EFFECTS OF INTERACTION BETWEEN DRD4 METHYLATION AND PRENATAL MATERNAL STRESS ON METHYLPHENIDATE-INDUCED CHANGES IN CONTINUOUS PERFORMANCE TEST PERFORMANCE IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Kim JI, Kim J-W, Shin I, et al.
Objectives: Environmental factors may interact with genetic factors via the epigenetic process, and this interaction can contribute to inter-individual variability in the treatment response. The purpose of this study was to investigate the interaction effects between dopamine receptor D4 (DRD4) methylation and prenatal maternal stress on the methylphenidate (MPH) response of youth with attention-deficit/hyperactivity disorder (ADHD).
Methods: This study was an 8-week open-label trial of MPH that included 74 ADHD youth. We investigated the associations between MPH treatment response, which was defined as a score Γëñ2 on the Clinical Global Impressions-Improvement (CGI-I) scale, and the methylation of 28 cytosine-guanine dinucleotide (CpG) sites of DRD4. Additionally, the interaction effects between DRD4 methylation and prenatal maternal stress on changes in Continuous Performance Test (CPT) scores after MPH treatment were investigated.
Results: Although there were no significant sites that showed significant association with treatment response, there was a significant interaction effect of the methylation of CpG7 and prenatal maternal stress on changes in omission errors of the CPT following treatment (p = 0.0001).
Conclusions: The present findings indicate that the interaction between methylation of CpG7 of DRD4 and prenatal maternal stress may be predictive of the treatment response to MPH in youth with ADHD

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J Child Adolesc Psychopharmacol. 2018;28:537-46.
RELATIONSHIP BETWEEN AGGRAVATION OF SEIZURES AND METHYLPHENIDATE TREATMENT IN SUBJECTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND EPILEPSY.
Park J, Choi H-W, Yum M-S, et al.
Objectives: We aimed to investigate the effectiveness and safety of methylphenidate (MPH), and especially its influence on seizures, in subjects with attention-deficit/hyperactivity disorder (ADHD) and epilepsy through a retrospective chart review of subjects treated with MPH in a clinical setting. We also evaluated factors that could affect seizure aggravation during MPH treatment.
Methods: From April 2004 to July 2011, MPH was prescribed to 105 subjects with ADHD and epilepsy. The demographic characteristics, psychiatric and medical history, and electroencephalography (EEG) results

were reviewed. Two pediatric neurologists reviewed seizure type, epilepsy diagnosis, changes in seizure frequency, and EEG parameters during MPH treatment. Pediatric neurologists and psychiatrists determined the temporal relationship between seizure aggravation and MPH treatment.
Results: The mean age of the subjects was 14.8 -¦ 3.4 years (range: 7-24 years). Sixty-five (61.9%) of the subjects were male. The mean duration of MPH treatment was 22 months (range: 2 weeks to 89 months) and the mean dose of MPH was 0.84 mg/kg/day. MPH was effective in controlling ADHD symptoms in both the seizure aggravation and nonaggravation groups. However, 21 (20%) subjects had aggravated seizures and 32 (32.3%) subjects had worsened EEG findings. Subjects with uncontrolled seizure or anxiety disorders at baseline were more likely to show aggravated seizures. Subjects who had epileptiform discharges, anxiety disorders, or were free of antiepileptic drug use at baseline experienced EEG worsening more frequently. The median duration of MPH treatment was significantly longer in subjects who did not show seizure aggravation than in those who did ($p < 0.001$).
Conclusions: MPH treatment may be related to aggravation of seizures or significant worsening of EEG findings in subjects with ADHD and epilepsy. Thus, clinicians should closely monitor seizure aggravation after MPH administration, especially for high-risk subjects with uncontrolled seizures or anxiety disorders at baseline

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J Child Psychol Psychiatry. 2018 Oct;59:1036-43.

THE ROLE OF BIRTH WEIGHT ON THE CAUSAL PATHWAY TO CHILD AND ADOLESCENT ADSD SYMPTOMATOLOGY: A POPULATION-BASED TWIN DIFFERENCES LONGITUDINAL DESIGN .

Lim KX, Liu CY, Schoeler T, et al.

Background: Available evidence points towards lower birth weight as a risk factor for the development of attention deficit/hyperactivity disorder (ADHD) symptoms. We probed the causal nature of this putative effect of birth weight on ADHD symptoms using the twin differences design, which accounts for genetic and shared environmental confounds.
Method: In a large population-based twin sample—3,499 monozygotic (MZ) and 6,698 dizygotic (DZ) pairs—parents, teachers or twins rated the twins' ADHD symptoms at nine assessment waves (2–16 years). We implemented the twin differences design, which completely accounts for shared environmental and genetic confounding in MZ twins. We tested whether: (a) the lighter-born twins had elevated ADHD symptoms compared to the heavier-born twins, by regressing within-pair differences of ADHD symptoms on within-pair differences of birth weight among MZ twins; (b) the effect of birth weight on ADHD was moderated by gender, gestational age and low birth weight; (c) this effect changed with age at ADHD assessment using adapted latent growth curve models; and (d) results differed for inattention and hyperactivity/impulsivity.
Results: Birth weight significantly predicted ADHD symptoms from early childhood to late adolescence. The lighter-born twin had more ADHD symptoms than the heavier-born cotwin among MZ twins across assessment waves and raters. No moderation effect was detected. The magnitude of the effect of birth weight decreased significantly across time for hyperactivity/impulsivity, but the decrease failed to reach significance for inattention. Estimates for inattention were significantly larger than for hyperactivity/impulsivity at each time point, implying stronger effect of birth weight on inattention symptoms.
Conclusions: Our findings provide stringent evidence for environmental effect of lower birth weight on the causal pathway to elevated ADHD symptoms. Effect of birth weight persists across a 14-year period from childhood into late adolescence, in particular for inattention symptoms

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J Child Psychol Psychiatry. 2018 Oct;59:1044-51.

A LONGITUDINAL, WITHIN-PERSON INVESTIGATION OF THE ASSOCIATION BETWEEN THE P3 ERP COMPONENT AND EXTERNALIZING BEHAVIOR PROBLEMS IN YOUNG CHILDREN.

Petersen IT, Hoyniak CP, Bates JE, et al.

Background: Externalizing problems, including aggression and conduct problems, are thought to involve impaired attentional capacities. Previous research suggests that the P3 event-related potential (ERP)

component is an index of attentional processing, and diminished P3 amplitudes to infrequent stimuli have been shown to be associated with externalizing problems and attention-deficit/hyperactivity disorder (ADHD). However, the vast majority of this prior work has been cross-sectional and has not examined young children. The present study is the first investigation of whether within-individual changes in P3 amplitude predict changes in externalizing problems, providing a stronger test of developmental process.
Method: Participants included a community sample of children (N = 153) followed longitudinally at 30, 36, and 42 months of age. Children completed an oddball task while ERP data were recorded. Parents rated their children's aggression and ADHD symptoms.
Results: Children's within-individual changes in the P3 amplitude predicted concomitant within-child changes in their aggression such that smaller P3 amplitudes (relative to a child's own mean) were associated with more aggression symptoms. However, changes in P3 amplitudes were not significantly associated with ADHD symptoms.
Conclusions: Findings suggest that the P3 may play a role in development of aggression, but do not support the notion that the P3 plays a role in development of early ADHD symptoms

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J Child Psychol Psychiatry. 2018 Oct;59:1083-93.

MEDIATING PATHWAYS FROM CHILDHOOD ADHD TO ADOLESCENT TOBACCO AND MARIJUANA PROBLEMS: ROLES OF PEER IMPAIRMENT, INTERNALIZING, ADOLESCENT ADHD SYMPTOMS, AND GENDER.

Elkins IJ, Saunders GRB, Malone SM, et al.

Background: We examined whether increased risk for adolescent tobacco and marijuana problems associated with childhood ADHD is explained by key intermediary influences during adolescence and differs by gender.
Methods: Longitudinal structural equation models examined mediating effects on problems with both substances (or each substance separately) through age-14 peer impairment, internalizing, and adolescent ADHD symptoms in two twin samples, prospectively assessed since age 11 (N = 2,164). Whether these mediators contributed beyond mediating effects of early-adolescent substance use was also considered. Twin difference analyses further illuminated which mediators might be potentially causal.
Results: Direct effects of childhood ADHD on age-17 tobacco and marijuana problems (i.e., independent of included mediators) as well as effects of adolescent ADHD symptoms were significant only for females. By contrast, mediation by peer impairment, evident particularly for marijuana, was relatively stronger for males than females. Depression and anxiety were not prospectively associated with age-17 substance problems when earlier substance problems were considered. Consistent with causal influence of early substance use on later problems, monozygotic twins with more severe tobacco or marijuana problems at age 14 than their co-twins were also more likely to have substance problems later in adolescence.
Conclusions: Mediation through peer impairment, continued presence of ADHD symptoms, and early substance use may alter development so that childhood ADHD indirectly contributes to problems with tobacco and marijuana. Targeting gender-sensitive interventions prior to mid-adolescence, before these patterns become established, is essential.

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J Child Psychol Psychiatry. 2018 Oct;59:1094-104.

DIFFERENTIAL IMPACT OF TRAIT SLUGGISH COGNITIVE TEMPO AND ADHD INATTENTION IN EARLY CHILDHOOD ON ADOLESCENT FUNCTIONING.

Becker SP, Burns GL, Leopold DR, et al.

Background: Sluggish cognitive tempo (SCT) is distinct from attention-deficit/hyperactivity disorder inattention (ADHD-IN) and concurrently associated with a range of impairment domains. However, few longitudinal studies have examined SCT as a longitudinal predictor of adjustment. Studies to date have all used a relatively short longitudinal time span (6 months to 2 years) and only rating scale measures of adjustment. Using a prospective, multi-method design, this study examined whether SCT and ADHD-IN were differentially associated with functioning over a 10-year period between preschool and the end of ninth grade.

Methods: Latent state-trait modeling determined the trait variance (i.e. consistency across occasions) of SCT and ADHD-IN across four measurement points (preschool and the end of kindergarten, first grade, and second grade) in a large population-based longitudinal sample (N = 976). Regression analyses were used to examine trait SCT and ADHD-IN factors in early childhood as predictors of functioning at the end of ninth grade (i.e. parent ratings of psychopathology and social/academic functioning, reading and mathematics academic achievement scores, processing speed and working memory).
Results: Both SCT and ADHD-IN contained more trait variance (Ms = 65% and 61%, respectively) than occasion-specific variance (Ms = 35% and 39%) in early childhood, with trait variance increasing as children progressed from preschool through early elementary school. In regression analyses: (a) SCT significantly predicted greater withdrawal and anxiety/depression whereas ADHD-IN did not uniquely predict these internalizing domains; (b) ADHD-IN uniquely predicted more externalizing behaviors whereas SCT uniquely predicted fewer externalizing behaviors; (c) SCT uniquely predicted shyness whereas both SCT and ADHD-IN uniquely predicted global social difficulties; and (d) ADHD-IN uniquely predicted poorer math achievement and slower processing speed whereas SCT more consistently predicted poorer reading achievement.
Conclusions Findings of this study—from the longest prospective sample to date—provide the clearest evidence yet that SCT and ADHD-IN often differ when it comes to the functional outcomes they predict

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J Child Psychol Psychiatry. 2018 Oct;59:1105-13.
INVESTIGATING LATE-ONSET ADHD: A POPULATION COHORT INVESTIGATION.
Cooper M, Hammerton G, Collishaw S, et al.
Background: Adult ADHD has been assumed to be a continuation of childhood-onset ADHD. However, recent studies have identified individuals with ADHD in adulthood who have not had ADHD in childhood. Whether or not these individuals have a 'typical' neurodevelopmental profile is not clear.
Methods: We tested two explanations for the emergence of apparent late-onset ADHD symptomatology using the ALSPAC epidemiological cohort, by grouping individuals according to their scores on the Strengths and Difficulties Questionnaire (SDQ) hyperactivity subscale at ages 12 and 17 years. First, we tested whether some of those with apparent late-onset ADHD symptoms had been potentially misclassified on the basis of earlier SDQ hyperactivity scores (ages 7, 8 and 9 years) or of subthreshold symptoms at age 12 years. Second, we investigated the possibility that those with 'genuine' late-onset ADHD symptoms had a delayed manifestation of the same liability that underlies childhood-onset symptoms, by investigating whether they had a similar profile of neurodevelopmental impairments (in the domains of autistic symptomatology, language, reading, spelling, executive functioning and IQ) as those with typical childhood-onset ADHD.
Results: N = 56/75 (75%) of those with apparent late-onset ADHD had had high ADHD scores at least one point in childhood, suggesting that they may have been misclassified on the basis of their score at age 12 years. The remaining 19 individuals (25%) with genuine late-onset ADHD symptoms did not show a profile of neurodevelopmental impairment typically seen in ADHD, instead showing similar levels of autistic symptoms, language skills, executive functioning ability and IQ to those without ADHD symptoms. The only exceptions were that this group showed reading and spelling problems at age 9 years.
Conclusions: Our work suggests that this small number of individuals with genuine late-onset symptoms may not be most appropriately considered as having a typical neurodevelopmental disorder

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J Child Psychol Psychiatry. 2018 Oct;59:1114-23.
A MULTICOHORT, LONGITUDINAL STUDY OF CEREBELLAR DEVELOPMENT IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Shaw P, Ishii-Takahashi A, Park MT, et al.
Background: The cerebellum supports many cognitive functions disrupted in attention deficit hyperactivity disorder (ADHD). Prior neuroanatomic studies have been often limited by small sample sizes, inconsistent findings, and a reliance on cross-sectional data, limiting inferences about cerebellar development. Here, we conduct a multicohort study using longitudinal data, to characterize cerebellar development.

Methods: Growth trajectories of the cerebellar vermis, hemispheres and white matter were estimated using piecewise linear regression from 1,656 youth; of whom 63% had longitudinal data, totaling 2,914 scans. Four cohorts participated, all contained childhood data (age 4–12 years); two had adolescent data (12–25 years). Growth parameters were combined using random-effects metaanalysis.
Results: Diagnostic differences in growth were confined to the corpus medullare (cerebellar white matter). Here, the ADHD group showed slower growth in early childhood compared to the typically developing group (left corpus medullare z = 2.49, p = .01; right z = 2.03, p = .04). This reversed in late childhood, with faster growth in ADHD in the left corpus medullare (z = 2.06, p = .04). Findings held when gender, intelligence, comorbidity, and psychostimulant medication were considered.
Discussion: Across four independent cohorts, containing predominately longitudinal data, we found diagnostic differences in the growth of cerebellar white matter. In ADHD, slower white matter growth in early childhood was followed by faster growth in late childhood. The findings are consistent with the concept of ADHD as a disorder of the brain's structural connections, formed partly by developing corticocerebellar white matter tracts

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J Clin Exp Neuropsychol. 2018 Oct;40:841-51.

PARENT RATINGS OF WORKING MEMORY ARE UNIQUELY RELATED TO PERFORMANCE-BASED MEASURES OF SECONDARY MEMORY BUT NOT PRIMARY MEMORY.

Ralph KJ, Gibson BS, Gondoli DM.

Introduction: Existing evidence suggests that performance- and rating-based measures of working memory (WM) correlate poorly. Although some researchers have interpreted this evidence as suggesting that these measures may be assessing distinct cognitive constructs, another possibility is that rating-based measures are related to some but not all theoretically motivated performance-based measures. The current study distinguished between performance-based measures of primary memory (PM) and secondary memory (SM), and examined the relation between each of these components of WM and parent-ratings on the WM subscale of the Behavior Rating Inventory of Executive Function (BRIEF–WM). Because SM and BRIEF–WM scores have both been associated with group differences in attention-deficit/hyperactivity disorder (ADHD), it was hypothesized that SM scores would be uniquely related to parent-rated BRIEF–WM scores.
Method: Participants were a sample of 77 adolescents with and without an ADHD diagnosis, aged 11 to 15 years, from a midwestern school district. Participant scores on verbal and spatial immediate free recall tasks were used to estimate both PM and SM capacities. Partial correlation analyses were used to evaluate the extent to which estimates of PM and SM were uniquely related parent-rated BRIEF–WM scores.
Results: Both verbal and spatial SM scores were significantly related to parent-rated BRIEF–WM scores, when corresponding PM scores were controlled. Higher verbal and spatial SM scores were associated with less frequent parent-report of WM-related failures in their child's everyday life. However, neither verbal nor spatial PM scores significantly related to parent-rated BRIEF–WM scores, when corresponding SM scores were controlled.
Conclusion: The current study suggested that previously observed low correlations between performance- and rating-based measures of WM may result from use of performance-based WM measures that do not capture the unique contributions of PM and SM components of WM

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J Dev Behav Pediatr. 2018 Sep;39:531-37.

COMMON USE OF STIMULANTS AND ALPHA-2 AGONISTS TO TREAT PRESCHOOL ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A DBPNET STUDY.

Blum NJ, Shults J, Harstad E, et al.

Objective: To describe the use of stimulants and alpha-2 agonists (A2As) for the treatment of preschool-aged children with attention-deficit hyperactivity disorder (ADHD) at 2 Developmental-Behavioral Pediatrics Research Network sites.

Methods: Demographic information, diagnoses, and medications prescribed by developmental-behavioral pediatricians (DBPs) were extracted from the electronic health record for all outpatient visits from January 1, 2010, to December 31, 2011. The subset of visits for children aged 2 to 5 years who had a diagnosis of ADHD was included in this analysis. Multivariable models were constructed to identify factors associated with prescribing stimulants and A2As.
Results: Over the 2-year period, 984 children with a diagnosis of ADHD were seen at 1779 visits. Of the 984 children, 342 (34.8%) were prescribed a stimulant, and 243 (24.7%) were prescribed an A2A. Both medications were prescribed at the same visit at least once during the 2-year period for 97 children (9.9%). Alpha-2 agonists were prescribed more often at site 2 than site 1 (OR [odds ratio] = 1.62, p = 0.015). Stimulants were more likely to be prescribed for older preschool-aged children (OR = 1.66, p < 0.001), and A2As were more likely to be prescribed for younger children (OR = 0.82, p = 0.02). Both stimulants and A2As were more likely to be prescribed to children with ADHD and comorbid conditions.
Conclusion: Alpha-2 agonists are commonly used by some DBPs for preschool ADHD. Variation in the use of A2As across sites may indicate a lack of consensus on when to use these medications and suggests a need for comparative effectiveness research to better define the relative benefits and side effects of A2As and stimulants for the treatment of preschool ADHD

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J Indian Assoc Child Adolesc Ment Health. 2018;14:74-88.
PREVALENCE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN PRIMARY SCHOOL CHILDREN: A CROSS-SECTIONAL STUDY.
Suthar N, Garg N, Verma KK, et al.
Background: Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder affecting children causing significant impairment in functioning. There is a lacuna of studies on ADHD in the Indian context and especially the community sample. Keeping this in mind the present study was conducted to identify prevalence, sociodemographic variables and comorbidities of ADHD in primary school children.
Methods: Total 1000 Children of age group 6-12 years, from three different schools were included in this cross sectional study. In first stage, screening of children was done with the help of AAP (American Academy of Pediatrics) practice guidelines screening questionnaire and in the second stage, detailed diagnostic interview were conducted with the help of VADTRS (Vanderbilt ADHD diagnostic Teacher Rating Scale) and VADPRS (Vanderbilt ADHD diagnostic Parent Rating Scale).
Results: In this study the prevalence of ADHD in school going children was 5.7%, and it was found to be higher in male children (7.08%) as compare to that of females (3.80%). Prevalence was highest in the 9-10 year of age, and in children of Lower socioeconomic class (11.47%). In this study most common type of ADHD was Inattentive type and most common co morbid disorder was Depression Anxiety Disorder.
Conclusion: ADHD is a highly prevalent, so early identification and thus early intervention of this disorder is helpful to prevent long term negative consequences

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J Indian Assoc Child Adolesc Ment Health. 2018;14:125-30.
METHYLPHENIDATE INDUCED ACUTE PSYCHOSIS IN A CASE WITH MILD INTELLECTUAL DISABILITY AND ADHD.
Mahawer B, Aneja J, Nebhinani N.
Methylphenidate (MPH) is used as the first line drug for treating the attention deficit hyperactive disorder (ADHD). Therapeutic dose of MPH is known to causes psychotic symptoms in a small number of cases and these symptoms usually disappear on discontinuing MPH. Here we describe a case of 11 years old boy with diagnosis of ADHD and mild intellectual disability, who was treated with methylphenidate and later developed acute psychosis

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Journal of Kermanshah University of Medical Sciences. 2018;22.

THE EFFECTIVENESS OF RESPONSE INHIBITION COGNITIVE REHABILITATION IN IMPROVING THE QUALITY OF SLEEP AND BEHAVIORAL SYMPTOMS OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Yazdanbakhsh K, Aivazy S, Moradi A.

Background: In children with attention deficit hyperactivity disorder, defects in executive functions and sleep problems are also recognized. Currently, drug interventions and behavioral therapy are used more than any other therapist to treat this disorder. Behavioral or pharmaceutical approaches do not directly target cognitive problems and sleep disorders associated with the disorder.

Objectives: The aim of this study was to measure the effectiveness of cognitive rehabilitation of response inhibition in Improving the quality of sleep and behavioral symptom of children with attention deficit/hyperactivity disorder (ADHD).

Methods: The present study was semi-experimental design with pre-test and post-test with control group and it was done in the fall of 1396. In this study, children aged 7 to 12 years who were diagnosed with (ADHD) by psychological experts of the counseling center of Kermanshah were selected. The Conners-parent's questionnaire and the Petersburg sleep inventory by parents and the Conners-teacher form by teachers were completed. 20 people were randomly divided into two groups. The experimental group was subjected to 12 sessions of The captain's log mind power builder and the control group did not receive treatment. After the last session of treatment, both groups were re-evaluated.

Results: The findings showed that cognitive rehabilitation of response inhibition was effective in Improving the quality of sleep ($P < 0.001$) and behavioral symptoms of attention deficit/hyperactivity disorder ($P < 0.001$).

Conclusions: Therefore, it can be concluded that cognitive rehabilitation of response inhibition is effective inhibition in improving the quality of sleep and behavioral symptoms in ADHD

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Journal of Neurolinguistics. 2019;49:93-108.

DIFFERENTIAL EFFECT OF READING TRAINING ON FUNCTIONAL CONNECTIVITY IN CHILDREN WITH READING DIFFICULTIES WITH AND WITHOUT ADHD COMORBIDITY.

Horowitz-Kraus T, Hershey A, Kay B, et al.

A comorbidity of attention deficit hyperactivity disorder (ADHD) with reading difficulties (RD) is common in children. However, children with ADHD + RD have a different reading and executive functions (EF) profile than children with RD alone. We compared the effect of an EF-based intervention on neural circuits related to EF in children with RD and those with ADHD + RD. Functional connectivity MRI data from a lexical decision task suggest that the RD-alone group showed greater improvement in EF and reading tests and greater functional connectivity between networks related to both higher- and lower-level visual processing and those related to ventral attention and dorsal attention, as well as semantic processing. Children with ADHD + RD showed greater connectivity between networks related to attention and dorsal attention and those related to visual processing and EF. Results are consistent with the Cognitive Subtype hypothesis and suggest that RD and ADHD + RD, although related behaviourally, are distinct disorders with regard to network response and connectivity during reading and after an EF-based intervention

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J Psychopathol Behav Assess. 2018.

THE REVISED CHILD ANXIETY AND DEPRESSION SCALES (RCADS): PSYCHOMETRIC EVALUATION IN CHILDREN EVALUATED FOR ADHD.

Becker SP, Schindler DN, Holdaway AS, et al.

Co-occurring internalizing symptoms are common and important to assess in children with attention-deficit/hyperactivity disorder (ADHD). One frequently used child self-report measure of internalizing symptoms is the Revised Child Anxiety and Depression Scales (RCADS), yet the psychometric properties of the RCADS remain unexamined in children referred for ADHD specifically. The present study evaluated the RCADS in 117 children (ages 8–12; 66% male) evaluated for suspected ADHD at an ADHD specialty clinic

(83% met criteria for ADHD). In addition to the RCADS, children completed measures of social anxiety and depression. Parents completed the RCADS-Parent Version (RCADS-P) in addition to other measures of internalizing and externalizing symptoms. Children and parents both completed a measure of aggression. Factor structure, reliability, and convergent/discriminant validity of the RCADS were examined. Results supported the six-factor structure of the child-report RCADS (Separation Anxiety, Social Phobia, Generalized Anxiety Disorder, Panic Disorder, Obsessive Compulsive Disorder, and Major Depressive Disorder). The RCADS demonstrated adequate reliability as well as convergent and discriminant validity with other child ratings. The total anxiety score on the RCADS also demonstrated convergent and discriminant validity with parent measures, though the depression score on the RCADS did not. Findings provide preliminary psychometric support for the RCADS in children referred for ADHD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S295.

SHARED ATYPICAL FUNCTIONAL CONNECTIVITY IN CHILDREN WITH ASD AND ADHD.

Choi EJ.

Objectives: ASD and ADHD are relatively common childhood neurodevelopmental disorders (NDDs). Both have been found to be associated with alterations in resting-state functional connectivity. The present study aimed to investigate shared large-scale, whole-brain fMRI networks in children and adolescents with ASD and ADHD compared with typically developing (TD) subjects in a large single cohort using graph theoretical measures.

Methods: The current study included a total of 271 participants (ages 3.4–21.7 years, mean age 11.62 years): 216 with NDDs (151 with ASD and 65 with ADHD); and 55 TD control subjects. Subject-specific networks were constructed, and local and global network measures were obtained for each network. An analysis of covariance was used to compare children with NDDs with the TD control subjects, with age and sex as covariates followed by pairwise group comparisons (ASD vs TD, ADHD vs TD, and ASD vs ADHD) to explore overlapping functional alterations. Nonparametric permutation testing was used to determine significance ($p < 0.05$).

Results: Children with NDDs showed decreased network degree in visual (VIS), frontoparietal (FP), and default mode (DMN) networks and increased network degree and efficiency in sensory-motor (SMOT) and subcortical (SC) networks compared with TD control subjects. On following pairwise comparisons, children with ASD and ADHD exhibited very similar patterns of functional connectivity compared with TD, with decreased DMN degree and increased SC degree and efficiency. Children with ASD indicated a lower network degree in VIS and a higher network degree and efficiency in SMOT compared with TD control subjects, although no significant group differences were noted between ASD and ADHD. In addition, age was negatively correlated with SMOT degree in the entire sample group, but no other age and sex effects or interactions were found in following comparisons.

Conclusions: Children with ASD and ADHD share atypical functional connectivity in DMN and SC, although alterations in VIS and SMOT may be more ASD-specific features, indicating their hyper- or hyposensitivity to sensory stimuli. These findings expand our understanding of shared biology across NDDs and further highlight the need to explore biological heterogeneity within the NDD spectrum irrespective of diagnosis. ADHD, ASD, NIMAG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S112.

THE INTERPLAY BETWEEN SLEEP AND NEUROBEHAVIORAL FUNCTIONING IN YOUTH WITH ADHD.

Gruber R.

Objectives: ADHD manifests as a high and chronic level of inattention and/or impulsivity/hyperactivity and occurs in 3-7.5% of children. In clinical practice, sleep problems are reported in 25-50% of children and adolescents with ADHD. However, the association between ADHD and sleep disturbance remains poorly characterized. Sleep impacts neurocognition and daytime functioning, which are already disrupted in ADHD.

The objective of this presentation is to describe the associations and explain the mechanisms underlying the interplay of sleep disruption, ADHD symptoms, and neurobehavioral deficits in youth.
Methods: A series of studies used the following: 1) objective (actigraphy, polysomnography) and subjective (sleep logs and questionnaires) sleep measures; 2) computerized neurobehavioral measures [neurobehavioral functioning (NBF)]; and 3) parentsΓÇÖ or teachers reports to characterize the sleep abnormalities of children with ADHD, to explore potential causes of such abnormalities, and to measure the impact of inadequate sleep on daytime functioning.
Results: Bedtime problems in children with ADHD were associated with bedtime resistance (a behavioral problem) and sleep-onset delay associated with delayed melatonin synthesis onset (a biological problem). Children with ADHD and typically developing children differed in terms of associations between sleep patterns and daytime outcomes. Experimental sleep restriction of approximately 55 minutes over 6 nights resulted in deterioration of NBF from the subclinical to the clinical range of inattention on 4 of 6 measures in children with ADHD.
Conclusions: Sleep has a tremendous impact on the cognitive and neurobehavioral health of children, and sleep deprivation has been shown to correlate with and cause inattention, irritability, impulsivity, and emotional/behavioral dysregulation. For children with ADHD, comorbid sleep disorders may be particularly problematic because they exacerbate daytime symptoms and complicate the effective treatment of the primary diagnoses of these children. Therefore, it is important that clinicians assess and treat sleep disturbances in youth with ADHD. SLP, ADHD, COG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S316-S317.
EXPLORING GENETIC VARIATION IN ADHD QUANTITATIVE TRAITS AND EXECUTIVE FUNCTION ENDOPHENOTYPES USING RARE COPY NUMBER VARIANTS.
Crosbie J, Burton CL, Zarrei M, et al.
Objectives: This Symposium will evaluate the contribution of rare and common genetic variants to response inhibition and response variability in ADHD, 2 leading candidate endophenotypes for ADHD, in a population-based sample group.
Methods: DNA and quantitative traits were collected from 16,718 youth (ages 6-17 years) at a local science museum. We measured ADHD traits using the Strengths and Weaknesses of ADHD and Normal Behavior (SWAN) scale and response inhibition and response variability using the stop task. We genotyped unrelated Caucasians (n = 5,636) using Illumina HumanCoreExome BeadChips. Rare copy number variants (CNVs) were evaluated. CNV calls were retained if they were detected by at least 2 algorithms, were at least 10 kb in size, and had a frequency of 1%. We examined whether CNV burden, overall and within psychiatrically relevant gene sets (eg, brain expression, synaptic function), is associated with cognitive measures and ADHD. Polygenic risk scores are calculated based on quantitative endophenotypes (response inhibition and response variability discovery sample groups) to determine the relationship with ADHD traits.
Results: For the CNV analysis, 4817 (85.4%) of participants passed quality control analyses. Pathogenic or neurodevelopmental risk CNVs were observed in 97 (2%) of participants, and ADHD and response inhibition traits were elevated in individuals with CNVs. For ADHD traits, there was enrichment for large deletions, particularly in genes involved in synapse structure, neuron projection, and neurophenotypes. For response inhibition, there was enrichment for duplications, particularly in genes highly and specifically expressed in the brain. Polygenic score results are also reported and compared with results in other presentations.
Conclusions: ADHD traits and response inhibition are associated with CNVs enriched with genes highly expressed in the brain. CNVs specific to response inhibition may point to unique genetic risks in those individuals with particular neurocognitive deficits. A combined trait-based approach that explores rare and common variation can help to build cognitive and behavioral profiles associated with specific patterns of genetic risk. ADHD, COG, GS

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J Am Acad Child Adolesc Psychiatry. 2018;57:S323.

ADULT FINDINGS IN THE MULTIMODAL TREATMENT STUDY OF ADHD (MTA) FOLLOW-UP: MEDICATION AND PHYSICAL MATURATION, ICD-10 AND COMORBIDITY, SUBSTANCE USE AND DEPRESSION, AND CAR CRASHES.

Hechtman L, Sonuga-Barke E.

Objectives: This presentation will share recent adult findings from the Multimodal Treatment Study of Children with ADHD (MTA) follow-up regarding medication and physical maturation, ICD-10 and comorbidity, substance use and depression, and car crashes.

Methods: The MTA was a 7-site study of children aged 7–9.9 years with DSM-IV combined type ADHD (N = 576). They were randomly assigned to 4 treatment groups: 1) medication; 2) behavioral; 3) combined; and 4) community care for 14 months. At 24 months, the local normative comparison group (LNCG) matched for age and sex without ADHD (N = 258) was added. The MTA then became an observational follow-up with assessments in childhood (3 years), adolescence (6, 8, and 10 years), and adulthood (12, 14, and 16 years). The Symposium will report some findings from the adult follow-up.

Results: The effects of medication and maturation on growth, presented by James Swanson, PhD, shows that because girls develop earlier than boys, they may receive medication during a more critical period of development. This may have a 1 to 1.5-inch greater impact on their final growth. Thus, awareness of medication timing during maturation is important. L. Eugene Arnold, MD, reports on a subgroup of the subjects with ADHD who also met criteria for hyperkinetic disorder (HKD) by ICD-10 at baseline, which requires more stringent and pervasive symptoms and no internalizing comorbidity. In adulthood, this subgroup was very similar to the rest of the group with ADHD. Comorbid internalizing disorders seem to have a worse prognosis than initial ADHD symptom severity. Andrea Howard, PhD, explores the role of adolescent depression on adolescent and adult substance abuse and found that adolescent depression impacts adolescent substance abuse in both the group with ADHD and the LNCG but not adult substance abuse, which is more influenced by a history of ADHD. Arunima Roy, PhD, presents findings on car crashes, taking driving experience into account, and found that the adolescents and adults with a history of ADHD are at greater risk for crashes despite getting licensed at an older age. Adult ADHD persistence is associated with car crashes beyond the risk of comorbid ODD/CD and substance use.

Conclusions: These presentations point out the risk that a history of ADHD confers on adult outcome regarding adult substance abuse and car crashes. The persistence of ADHD symptoms into adulthood has an important impact on adult functioning, suggesting that treatment of these adults is required. ADHD, LONG, STIM

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J Am Acad Child Adolesc Psychiatry. 2018;57:S179.

DASOTRALINE IN CHILDREN WITH ADHD: EFFECTS ON SLEEP HABITS AS MEASURED BY THE CHILDREN'S SLEEP HABITS QUESTIONNAIRE.

Goldman RS, Hopkins SC, Koblan KS, et al.

Objectives: In a previously reported study in children with ADHD, the efficacy of dasotraline in fixed doses of 2 and 4 mg/day was examined. The aim of this secondary analysis was to evaluate the effect of dasotraline on sleep-related outcomes as measured by the Children's Sleep Habits Questionnaire (CSHQ).

Methods: Children ages 6–12 years with ADHD were randomized to 6 weeks of double-blind treatment with dasotraline (2 or 4 mg/day) or placebo. The CSHQ (assessed weekly) is a 45-item parent questionnaire that rates, on a 3-point scale, the severity/frequency of problems in the following 8 sleep-related domains: 1) bedtime resistance; 2) sleep-onset delay; 3) sleep duration; 4) sleep anxiety; 5) night awakenings; 6) parasomnias; 7) sleep-disordered breathing; and 8) daytime sleepiness.

Results: A total of 342 patients (mean age 9.1 years; 66.7% male) were randomized to dasotraline or placebo. Mean change from baseline for dasotraline (2 and 4 mg/day) versus placebo in CSHQ total sleep score was 3.2 and 2.6 versus 4.8, respectively; Last Observation Carried Forward). Mean change in CSHQ domain scores for dasotraline (2 and 4 mg/day) versus placebo were as follows: bedtime resistance: 0.5 and 0.3 vs 0.8; sleep-onset delay: 0.1 and 0.1 vs 0.3; sleep duration: 0.1 and 0.0 vs 0.3; sleep anxiety: 0.4 and 0.2 vs 0.6; night awakenings: 0.1 and +0.2 vs 0.4; parasomnias: 1.3 and 1.1 vs 1.1; sleep-disordered breathing: 0.2 and 0.2 vs 0.2; and daytime sleepiness: 0.8 and 0.8 vs 1.4, respectively. The proportion of

patients reporting insomnia (combined) as a treatment-emergent adverse event was 15.3% in the 2 mg/day dasotraline group, 21.7% in the 4 mg/day group, and 4.3% in the placebo group.
Conclusions: In this 6-week, placebo-controlled study of children with ADHD who are treated with dasotraline in fixed doses of 2 and 4 mg/day, change in sleep habits assessed by the CSFQ was comparable to placebo. Insomnia was reported more commonly as an adverse event in dasotraline versus placebo-treated patients. ADHD, PPC, SLP

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J Am Acad Child Adolesc Psychiatry. 2018;57:S165-S166.
LISDEXAMFETAMINE DIMESYLATE FOR PRESCHOOL CHILDREN WITH ADHD.
Childress AC, Kollins SH, Wu J, et al.
Objectives: We will examine the safety, tolerability, and pharmacokinetic (PK) profiles (primary) and clinical outcomes (secondary) of lisdexamfetamine dimesylate (LDX) in preschool-aged children with ADHD.
Methods: Children (age 4-5 years) with DSM-IV, Text Revision based ADHD and ADHD-Rating Scale-IV Preschool version total scores (ADHD-RS-IV-PS-TS) 28 (in boys) and 24 (in girls) were eligible. The study included 4 periods: 1) screening/washout; 2) dose optimization (6 weeks); 3) dose maintenance (2 weeks); and 4) follow-up (1 week). LDX treatment was started at 5 mg and titrated weekly (increments of 5-20 mg and then to 30 mg) until an optimized dose was attained; this optimized dose was then maintained. Assessments included treatment-emergent adverse events (TEAEs), vital sign changes, ADHD-RS-IV-PS-TS changes, and noncompartmental measures and population modeling.
Results: Of 24 enrolled participants, 19 completed the study. The most frequently reported TEAEs (>10%) were as follows: 1) decreased appetite (33.3%); 2) insomnia (25.0%; initial insomnia, middle insomnia, or insomnia); 3) upper respiratory tract infection (16.7%); 4) upper abdominal pain (12.5%); 5) affective lability (12.5%); and 6) irritability (12.5%). At the final on-treatment assessment (FoTA), mean -¦ SD changes from baseline in systolic and diastolic blood pressure and pulse were 1.1 -¦ 7.31 and 1.5 -¦ 6.93 mm Hg and 0.8 -¦ 12.75 bpm. The mean (95% CI) change from baseline ADHD-RS-IV-PS-TS at the FoTA was 26.1 (32.2, 20.0). d-Amphetamine exposure increased dose-dependently, with no apparent relationship between dose-normalized exposure and participant weight. PK modeling and simulations indicated that mean steady-state d-amphetamine exposure at 30 mg LDX was 44% higher in children ages 4-5 years than in children ages 6-10 years, suggesting a starting dose in children ages 4-5 years that could be as low as half the approved starting dose in individuals ages 6 years (ie, 15 mg).
Conclusions: In preschool-aged children with ADHD, LDX exhibited a safety profile consistent with studies in other populations and was associated with clinically meaningful improvement in ADHD symptoms. Based on these combined safety, tolerability, PK, and clinical-outcome findings, the same dosing regimen (5-30 mg) and weekly titration schedule have been carried forward for evaluation in phase 3 studies. ADHD, PSC, STIM

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J Am Acad Child Adolesc Psychiatry. 2018;57:S180.
EARLY TEMPERAMENTAL RISK FACTORS FOR ADHD-RELATED BEHAVIORS IN CHILDHOOD.
Joseph HM, McKone KMP, Molina BSG, et al.
Objectives: Early detection of risk for childhood attention problems may allow for interventions to reduce or prevent later development of ADHD and improve outcomes. This study tested the contributions of negative emotionality and poor effortful control in toddlerhood on parent- and teacher-rated ADHD-related behaviors in childhood. Additionally, parenting was tested as a moderator of the association between these extreme temperament traits and later inattention.
Methods: Participants (N = 310), all boys (54% white, 37% African American, 9% other), were drawn from a longitudinal study of child development. Mean monthly family income was $1092 (SD = $658). Negative emotionality was obtained using the Infant Characteristics Questionnaire at ages 1.5 and 2 years. Poor effortful control was observed during a delayed gratification cookie task at age 3.5 years. Supportive (vs rejecting) maternal parenting was measured via 2 observer-rated assessments, the Early Parenting Coding System and the Home Observation for Measurement of the Environment (HOME) inventory, for families and

toddlers at ages 1.5 and 2 years. We used ordinary least square (OLS) linear regression to test the effects of predictors and covariates on mother- and teacher-reported child attention at ages 5 and 6 years using the Child Behavior Checklist (CBCL) and the Teacher Report Form, respectively.
Results: Lower family income was associated with more ADHD-related behaviors by both mother ($p < 0.001$) and teacher report ($p < 0.01$). Negative emotionality was significantly associated with more mother-reported ADHD-related behaviors ($p < 0.01$). Poor effortful control significantly predicted teacher-reported attention problems ($p < 0.05$) and marginally significantly predicted mother-reported attention problems ($p = 0.050$). More supportive parenting predicted fewer attention problems, as reported by both parents ($p < 0.05$) and teachers ($p < 0.01$). However, parenting did not attenuate the relationship between either difficult temperament or self-regulation and childhood attention problems.
Conclusions: Toddlers who are fussy or have poor effortful control are at greater risk for ADHD-related behaviors in childhood. Although supportive parenting is predictive of greater childhood attention, it does not appear to be a target to decrease the association between negative emotionality or poor effortful control and childhood ADHD. INF, ADHD, LONG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S239.
EFFECTS OF ANTIDEPRESSANT TREATMENT ON CLINICAL MEASURES OF ATTENTION IN ADOLESCENTS WITH DEPRESSION.
Choi C-H, Lee J, Lee KH, et al.
Objectives: Previous studies have reported mixed findings on deficits in executive function and attention in youth with MDD. Moreover, longitudinal effects of SSRI on executive function and attention in adolescents with MDD are relatively unknown. This study aimed to investigate the changes in clinical measures of attention in youth with MDD treated with SSRI.
Methods: The study included 80 adolescents with MDD (56 girls) and 53 healthy controls (HC) subjects (30 girls) aged 12 17 years. Clinical measures of attention were assessed using ADHD Rating Scale (ADHD-RS) and Child Behavior Checklist (CBCL) attention problem scale at baseline and at weeks 8. Adolescents with MDD underwent an 8-week open-label trial of escitalopram after the baseline assessment, and those who had at least a 40% improvement in Childrens Depression Rating Scale (CDRS-R) scores from baseline to week 8 were defined as responders. We used a linear-mixed model to examine changes in clinical measures of attention over time (baseline vs week 8) in groups (responders, nonresponders, and HC subjects). Multiple comparisons were Bonferroni corrected. Statistical analysis was performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL).
Results: No baseline differences were found between the responders (n = 44, 27 girls) and nonresponders (n = 36, 29 girls) in their age, sex, IQ, CDRS-R score, and clinical measures of attention (ADHD-RS total score: 10.7 -¦ 10.3 vs 10.7 -¦ 9.6; ADHD-RS inattention subscale score: 7.7 -¦ 7.1 vs 7.9 -¦ 6.4; ADHD-RS hyperactivity-impulsivity subscale score: 3.0 -¦ 4.1 vs 2.8 -¦ 3.4; CBCL attention problem scale score: 51.4 +é-¦ 13.2 vs. 56.7 -¦ 12.5). Linear-mixed models showed significant group-by-time interaction effects in the ADHD-RS inattention subscale score ($p = 0.008$), but not in the ADHD-RS total, ADHD-RS hyperactivity-impulsivity subscale, or CBCL attention problem scale scores. Only responders showed significant improvement in the ADHD-RS inattention subscale score at week 8 (mean estimated change: +ó-2.8 -¦ 0.6, $p < 0.001$).
Conclusions: Our results suggest that treating depressive symptoms with SSRI may accompany attentional improvement in adolescents with MDD. Monitoring cognitive changes may be useful when treating adolescents with MDD. DDD, ADOL, COG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S133.

ASD AND ASSOCIATED PSYCHOPATHOLOGY: AN UPDATE ON SCREENING, DIAGNOSIS, AND MANAGEMENT.

Joshi G, Vasa RA.

Objectives: This Institute provides a practical review of diagnosis, treatment, and management of ASD and frequently co-occurring psychopathologies in children and adolescents. Clinicians will learn about common psychiatric comorbidities with ASD. Review of evidence-based psychopharmacological, educational, and behavioral interventions for youth with ASD and psychopathology will be provided. This full-day program was developed specifically for mental health providers who are providing diagnoses and ongoing treatment to psychiatrically referred populations of youth with ASD.

Methods: The following presentations relevant to diagnosis and treatment will be included: 1) Screening and Diagnostic Assessment for ASD in Psychiatrically Referred Youth, by Gagan Joshi, MD; 2) The Genetics of ASD: Relevance for Clinical Practice in the Era of Precision Medicine, by Rebecca Muhle, MD, PhD; 3) Behavioral Interventions for ASD: A Review of the Evidence and Emerging Technologies, by McLeod Gwynette, MD; 4) Assessment and Management of ADHD in Youth with ASD, by Benjamin Yerys; 5) Assessment and Management of Anxiety in Youth with ASD, by Roma A. Vasa, MD; 6) Assessment and Management of Emotional Dysregulation and Aggression in Youth with ASD, by Jeremy Veenstra-VanderWeele, MD; and 7) Management of Irritability/Aggression in ASD in the Clinical Setting, by Alice R. Mao, MD.

Results: Clinicians will learn current clinical perspectives for the diagnosis, genetic workup, treatment, and management of children and adolescents with ASD. By integrating the most evidence-based treatments for ASD, the clinician will be better equipped to help the family to develop an individualized treatment plan that will help to improve the functioning, integration, and management of challenging behaviors associated with ASD.

Conclusions: Learning current clinical perspectives on the diagnostic assessment and management of ASD and associated psychopathology will enable clinicians to institute a multimodal treatment plan that will take into account the childs profile of ASD and associated psychopathology in the context of age-related social challenges. Clinicians will be able to educate the families of children with ASD about multiple options for managing challenging behaviors for ASD. ASD, PSP, DIAG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S294-S295.

STRUCTURAL NEUROIMAGING CORRELATES OF SOCIAL ABILITIES ARE SIMILAR IN ASD AND ADHD.

Baribeau DA.

Objectives: ASD, ADHD, and OCD are often associated with difficulties recognizing and responding to social cues. It is unknown whether the brain structures that correlate with social abilities vary among neurodevelopmental illnesses.

Methods: Children (N = 312) underwent structural MRI of the brain (n = 32 control subjects, n = 44 with OCD, n = 77 with ADHD, n = 159 with ASD; mean age 11 years). Their social abilities were quantified through parent- and child-completed measures. Social brain regions were grouped into 3 networks as follows: 1) midline/lateral regions (eg, temporal parietal junction); 2) anterior/prefrontal regions (eg, orbitofrontal cortex); and 3) subcortical regions (eg, limbic system). Structural MRI correlates of social abilities were examined using multivariable regression models. The impact of common genetic variation in the oxytocin receptor (OXTR) on brain structure in ASD and ADHD was also examined.

Results: All 4 groups showed an association between cortical networks 1 and 2 and social abilities where thicker cortices were advantageous (p Γëñ 0.001). Results diverged for subcortical network 3, with multiple significant region-by-diagnosis interactions (p = 0.002 to <0.0001). Larger structures were associated with fewer social deficits in ASD and ADHD, and smaller structures were advantageous in OCD. Trends suggested a similar pattern regarding the structural effects of OXTR genotype on corticolimbic networks in ASD and ADHD.

Conclusions: Overall, biological correlates of social processing in ASD and ADHD were highly similar, challenging the diagnostic boundary between these 2 disorders. Data support a distributed and interconnected social brain that is potentially vulnerable to both injury and compensation in neurodevelopmental illnesses. ASD, ADHD, OCD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S141.

SUBSTANCE USE DISORDER AND ASSOCIATION WITH ADHD AND DISRUPTIVE DISORDERS IN A BRAZILIAN SAMPLE OF ADOLESCENT INPATIENTS.

Kaio CH, Carneiro MCB, Doria GMS.

Objectives: High rates of ADHD, ODD, and conduct disorder (CD) have been found in sample groups of adolescents with substance use disorder (SUD). Children with these mental disorders are at risk for the development of SUD in adolescence. The main aims of this study were to identify mental illness comorbidities and their associations in adolescent inpatients with SUD.

Methods: We prospectively recruited 35 male adolescent inpatients (aged 12–17 years) in treatment for SUD. Mental disorders were assessed using the Brazilian version of the Schedule for Affective Disorder and Schizophrenia for School-Aged Children Present and Lifetime version (K-SADS-PL). This study was approved by the local ethics committee.

Results: The most frequent comorbidities among adolescents found in this study were CD (57.1%), ADHD (48.6%), and ODD (40%). Frequencies were estimated using FisherΓÇÖs Exact test, and we found a strong association between disruptive disorders, ADHD, and SUD in adolescence. Overall, 70.6% of all subjects with ADHD met DSM-IV criteria for comorbid ODD, CD, or both ($p = 0.01$). Patients with ODD had comorbid diagnosis with ADHD, CD, or both ($p = 0.002$) in 78.6% of cases, and 70% of adolescents with CD had comorbidities with ADHD, ODD, or both ($p = 0.01$).

Conclusions: These results are in line with literature highlighting that ADHD, ODD, and CD are significant risk factors for the development of SUD in youth. To prevent substance abuse in adolescence, it is extremely important to identify and treat these mental illness comorbidities in childhood. Furthermore, the early diagnosis of these comorbidities in adolescents with SUD is of major importance in the pursuit to optimize their treatment. SUD, ADOL, CM

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J Am Acad Child Adolesc Psychiatry. 2018;57:S177.

PERCEPTION OF CHILDHOOD ADHD AMONG PEDIATRIC AND PSYCHIATRIC RESIDENTS.

Kallman JR, Boazak M, O'Banion D.

Objectives: While controversy has arisen regarding the diagnostic rates of ADHD, there remains evidence to suggest that it is underdiagnosed, with clear indications that many remain untreated. Previously, researchers have commented that efforts should be directed in improving education of medical residents to target this population-level problem. To evaluate resident physicians educational needs, we conducted a survey assessment of both pediatrics and psychiatry resident trainees relating to ADHD. Our aims were to conduct an exploratory assessment of resident experience, perception (including assessment of stigma), comfort, and knowledge related to the diagnosis and treatment of ADHD.

Methods: We developed a 53-item survey assessing resident demographic characteristics, experience, perception, comfort level, and knowledge related to the diagnosis and treatment of ADHD. Descriptive statistics were collected for a primary combined group analysis.

Results: We have distributed the survey and received 60 responses (psychiatry, $n = 27$; pediatrics, $n = 33$). Preliminary combined group findings demonstrate limited resident ADHD training, limited resident experience of optimistic outcomes, high rates of pessimistic beliefs related to diagnosis, treatment, and stimulant abuse, with specific high rates of pessimistic beliefs related to Caucasians and upper socioeconomic groups. Residents expressed limited comfort in the diagnosis and treatment of ADHD.

Conclusions: Our findings demonstrate that continued efforts need to be applied to increase resident didactic and clinical experience of ADHD. Notably, it appears that residents either do not experience or do

not attend to optimistic clinical outcomes relating to the treatment of ADHD. Furthermore, residents appear to have pessimistic beliefs relating to both the diagnosis and treatment of ADHD, in addition to pessimistic beliefs related to the abuse of stimulant therapy. These pessimistic biases may impact their future treatment of children with the disorder and may perpetuate the problems of underdiagnosis and undertreatment of ADHD. Thus, training should, in part, be directed toward emphasizing the overall rates of underdiagnosis and undertreatment of ADHD, as well as reducing the stigmas related to ADHD and its treatment with stimulant medications. ADHD, REST

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J Am Acad Child Adolesc Psychiatry. 2018;57:S142-S143.

DIFFUSION TENSOR IMAGING FINDINGS IN CHILDREN WITH SLUGGISH COGNITIVE TEMPO COMORBID ADHD.

Bolat GU, Baytunca B, et al.

Objectives: The construct of sluggish cognitive tempo (SCT) is characterized with daydreaming, mental confusion, staring blankly, and hypoactivity. Previous studies showed that SCT is a distinct disorder from ADHD but highly comorbid with it. Although research distinguishing SCT from ADHD on sociodemographic characteristics, comorbidity patterns, impairment, and neuropsychological functioning increased; there is a lack of studies examining biological factors in relation to SCT.

Methods: The main goal of the current study was to compare diffusion tensor imaging (DTI) findings between SCT cases comorbid with ADHD and typically developing control (TD) subjects. DTI provides an understanding of the structural connectivity of white matter. In this study, 576 patients were screened from outpatient clinic of the child and adolescent psychiatry department. Finally, 18 cases of SCT comorbid with ADHD (combined presentation), 24 SCT cases comorbid with ADHD (inattentive presentation), and 24 TD subjects were included. We applied tract-based spatial statistics to the DTI measures for obtaining fractional anisotropy (FA) and axial, radial and mean diffusity (AD, RD, MD) to explore white matter differences for the whole brain.

Results: Comparing SCT and ADHD-inattentive presentation with TD subjects, we detected increased FA in the bilateral anterior and posterior limb of internal capsule, bilateral cerebral peduncle, and the fornix ($p < 0.05$). Comparing SCT and ADHD-combined presentation with TD subjects, we did not find any differences for all measures ($p > 0.05$). Conclusions: We are not aware of any study that compared these results for SCT cases. Significant differences for the SCT cases may be preliminary evidence that they have distinct microstructure properties. ADHD is a heterogeneous disorder with various clinic presentations, impairment domains, and biological traits. In addition, heterogeneous findings support that we need more homogeneous groups to understand ADHD well. For ADHD and DTI studies, evaluating comorbidity of SCT may decrease heterogeneity of the findings. ADHD, NIMAG, NEPSYC

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J Am Acad Child Adolesc Psychiatry. 2018;57:S166.

EFFICACY AND SAFETY OF DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE (DR/ER-MPH) IN CHILDREN WITH ADHD: RESULTS FROM A PIVOTAL PHASE 3 CLASSROOM TRIAL.

Childress AC, Cutler AJ, Marraffino A, et al.

Objectives: Evening-dosed HLD200 is a delayed-release and extended-release methylphenidate (DR/ER-MPH) designed to delay initial drug release by 8-10 hours to provide onset of treatment effect upon awakening and lasting into the evening. Herein, we present the efficacy and safety of DR/ER-MPH from a pivotal, multicenter, phase 3, placebo (PBO)-controlled laboratory classroom study that enrolled 125 children (age 6-12 years) with ADHD (ClinicalTrial NCT02493777). Methods: During a 6-week open-label (OL) phase, once daily DR/ER-MPH was titrated to an optimal dose (20, 40, 60, 80, or 100 mg/day) and dosing time (8:00 PM -¦ 1.5 hours) based on improvements on ADHD Rating Scale IV, Before School Functioning Questionnaire, and ConnersΓÇÖ Global Index Parent. Participants were then randomized 1:1 to double-blind (DB) optimized DR/ER-MPH or PBO for 1 week. The primary endpoint was the model-adjusted average of postdose Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale-combined score (SKAMP CS) over a 12-hour laboratory classroom day (8:00 AM to 8:00 PM). Key and/or other secondary measures included

the Parent Rating of Evening and Morning Behavior-Revised, Morning (PREMB-R AM) and Evening (PREMB-R PM) subscales, and Permanent Product Measure of Performance-Attempted (PERMP-A) and -Correct (PERMP-C). Safety endpoints included treatment-emergent adverse events (TEAEs), with direct questioning for sleep disturbances. Results: After dose optimization (mean optimized dose = 66 mg; most common prescribed dosing time = 8:00 PM), 1 week of DR/ER-MPH treatment significantly improved outcomes over a 12-hour classroom day versus PBO: SKAMP CS ($p < 0.001$); PERMP-A ($p = 0.006$); and PERMP-C ($p = 0.009$). DR/ER-MPH also significantly improved functional impairment versus PBO in the early morning (PREMB-R AM: $p < 0.001$) and late afternoon/evening (PREMB-R PM: $p = 0.003$). No serious TEAEs or TEAEs leading to discontinuation were reported following dose optimization. Most common TEAE (10%) in both groups was diastolic blood pressure increase. Sleep-related TEAEs (DR/ER-MPH: 7.7%; PBO: 9.3%) were mild/moderate in severity. Conclusions: DR/ER-MPH was well tolerated and demonstrated significant improvements in ADHD-related symptoms and functional impairment from the early morning until evening versus PBO in children with ADHD. ADHD, RCT, STIM

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J Am Acad Child Adolesc Psychiatry. 2018;57:S299-S300.

IMPACT OF SLEEP DURATION ON ATTENTIONAL AND BEHAVIORAL FUNCTIONING IN ADOLESCENTS WITH ADHD.

Becker SP.

Objectives: There is ongoing interest in the interplay between sleep problems and ADHD. This study used an experimental sleep restriction/extension protocol to examine whether sleep duration is causally linked to attention and behavioral functioning in adolescents diagnosed with ADHD.

Methods: A total of 69 adolescents with ADHD (ages 14–17 years; 75% male) were enrolled in a 3-week summer sleep manipulation protocol using a cross-over experimental design. The protocol included a phase stabilization week, followed in counterbalanced order by a sleep restriction week and a sleep extension week. Sleep was monitored with actigraphy and daily sleep diaries. At the end of each week, parents and adolescents completed measures of attention and behavior.

Results: Approximately 70% of the sample group was adherent to the sleep protocol and obtained 1.5 more hours of actigraphy-measured sleep during the extension condition than the restriction condition. Compared with the restricted sleep week, parents reported fewer inattentive and oppositional symptoms during the extended sleep week, with findings consistent across daily diary and end-of-week measures. Both parents and adolescents reported fewer sluggish cognitive tempo (SCT) attentional symptoms, as well as less difficulty waking in the morning and daytime sleepiness, during the extended sleep week compared with the restricted sleep week. Effects were not found for parent-reported hyperactivity-impulsivity or adolescent-reported ADHD symptoms.

Conclusions: This study provides the first evidence that sleep duration causally contributes to inattentive and oppositional behaviors in adolescents with ADHD. Among adolescents with ADHD, insufficient sleep may exacerbate attentional functioning and daytime impairments. This study cannot answer lingering questions about whether ADHD is caused by sleep difficulties but can underscore the close interrelations of sleep and daytime functioning. ADHD, ADOL, SLP

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J Am Acad Child Adolesc Psychiatry. 2018;57:S174.

QUANTITATIVE ELECTROENCEPHALOGRAPHY IN CHILDREN AND ADOLESCENTS WITH ADHD.

Duric NS, et al.

Objectives: This project presents a progress beyond the state-of-the-art that can be used for a large patient group. Brain wave analysis appears to be the diagnostic tool of the future for mental health. This project is a clinical study and will help to clarify the underlying neurophysiologic changes in ADHD children and adolescents related to diagnosis and treatment, presented in the quantitative electroencephalography (qEEG).

Methods: The project is designed as a randomized controlled trial (RCT). A sample group size of 120 children and adolescents of both genders in the age group up to 18 years (ages 7–18 years) referred to the Child and

Adolescent Clinic Trust Fonna, Haugesund in Norway and diagnosed with ADHD according to DSM-5 criteria in a 3-year period are included in the project. All qEEGs are recorded on MITSAR 19 channels using 10-20 international electrode placement 1. The quantitative data obtained using WinEEG software are compared with an HBImed normative database.
Results: We observed decreasing Power(uV-å2) values for the patients in all domains, although they increase for the normal population up to an age of 11–12 years, after which they decrease again, although there are differences from the normal population mean for theta frequency and the age of children. For ADHD children under age 11 years, the theta frontal frequency mean was larger [ages 7-8 years: median (min-max) = 13.73 (6.31-23.05); ages 9-10 years: 8.34 (6.73-19.27)] than the normal population mean (ages 7-8 years: mean = 3.94; ages 9-10 years: mean = 5.2). The other theta frequency measures (central, global) show a similar tendency. The theta/beta ratio for older ADHD children (ages 11-16 years) was for all frequencies lower than normal control subjects [eg, theta/beta ratio global, ages 15-16 years: ADHD 1.64 (0.79, 3.79) vs control 2.4], whereas beta frequency discriminated poorly. For older children, we did not observe differences.
Conclusions: Selected domains of qEEG (theta frequency, theta/beta ratio) measurements are promising to discriminate between ADHD and healthy children and adolescents. More research with individual data for normal control subjects and a better resolution in age are necessary to perform further discrimination analysis. ADHD, DIAG, R

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J Am Acad Child Adolesc Psychiatry. 2018;57:S282.
SAMPLE CHARACTERISTICS, TBR%, AND VITAMIN D STATUS FOR THE ICAN RCT OF NEUROFEEDBACK FOR ADHD.
deBeus R, Lightstone H, Roley-Roberts ME, et al.
Objectives: This Symposium will explain how the International Collaboration ADHD Neurofeedback (ICAN) study addressed flaws in previous RCTs of neurofeedback (NF, EEG biofeedback) for ADHD; describe characteristics of sample group; determine the proportion of well-diagnosed ADHD, with a high EEG theta-beta ratio (TBR); and determine prevalence of vitamin D insufficiency in ADHD at 2 latitudes.
Methods: The sample group size (N = 140), in contrast to previous trials, was adequate to detect a medium effect. Diagnoses were established categorically by structured interview (DSM-IV criteria) and dimensionally by parent- and teacher-rated symptoms. The medical history, physical exam, and vitamin D level ruled out physical causes of ADHD symptoms. Age was restricted to 7–10 years for developmental homogeneity of TBR. High TBR, a biomarker of a possible treatment responder, was required for randomization. A double-blind trial was achieved by using a sham of equal duration, intensity, frequency, and likelihood of reinforcements; a prerecorded de-artifacted EEG of active NF with the childΓÇÖs muscle artifacts was superimposed so it looked like their own. A standardized but personalized treatment protocol was monitored by an expert. Ecologically valid teacher and parent ratings were the primary outcome.
Results: Of 285 screens who met categorical and dimensional criteria for ADHD, 226 (79%) had TBRs 4.5 by the Thought Technology ADHD Suite, suggesting suitability of TBR downtraining. Of 172 with blood tests not taking a vitamin D supplement, 64 (37%) had insufficient vitamin D (<30 ng/ml): 42/82 (51%) at the Ohio site and 22/90 (23%) at the North Carolina site. Five were frankly deficient (<20 ng/ml). Average levels were 30.8 -¦ 8.1 ng/ml in Columbus, Ohio and 35.1 -¦ 9.9 in Asheville, North Carolina. Of those randomized, 79% were male, 68% were white non-Hispanic/Latino, 12% were African American, and 10% were Hispanic/Latino. The mean age was 8.7 years. Baseline Conners 3 inattention scores averaged 2.1 -¦ 0.5 by parent rating and 2.0 -¦ 0.6 by teacher rating. In addition, 49% had comorbidity: 33% with ODD, 20% with an internalizing disorder.
Conclusions: There is a high proportion of high TBRs and vitamin D insufficiency in children aged 7-10 years with categorically and dimensionally diagnosed ADHD, with vitamin D insufficiency doubled by a 400-mile northward shift. ADHD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S39-S40.

GENETIC STUDIES RELEVANT TO THE TREATMENT OF ADHD.

Elia J.

Objectives: Using a case-based report, this presentation will review the usefulness and limits of clinically relevant genotyping data and pharmacotherapy. The clinical case will highlight the drug response, drug-drug interactions, and adverse events as they relate to genetic variants and the clinical relevance for various ethnicities.

Methods: A case-based approach will be used to frame each presentation in this Clinical Perspectives. In this case, an African American male aged 12 years with ADHD and anxiety, who was treated with atomoxetine for 4 months, was having difficulty sleeping. Diphenhydramine was added with subsequent development of dizziness, headaches, irritability, and QTc prolongation. This case provides context for the discussion of the following: 1) drug metabolism and P450 genetic isozyme variants; 2) K-channel ion genetic variants and cardiac risks; 3) ethnicity and genetic variant risks; and 4) drug-drug interactions.

Results: In this case, D26-genotyping data that indicated poor metabolism was useful. Because only 2% of African Americans (vs 3–10% of whites) are slow metabolizers, the risk of using only clinical information may be minimized in this population. In addition, the lack of knowledge regarding K-ion channel genetic variants (higher in African Americans) may have further minimized the risk of a serious event. The addition of another drug, diphenhydramine, which was possibly considered to be safe given the low D26 inhibition, would have been assessed differently with the availability of genotyping data.

Conclusions: There are opportunities for direct clinical application of genetic testing related to pharmacotherapy. The clinical case presented here provides a context for understanding the limitations of clinical data and the potential for minimizing serious risks with genotyping data. GS, RF, ADHD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S174-S175.

TEMPERAMENT AND CHARACTER PROFILES ASSOCIATED WITH INTERNALIZING AND EXTERNALIZING PROBLEMS IN CHILDREN WITH ADHD.

Kim DH, Kwack YS.

Objectives: Children with ADHD can manifest with various externalizing and internalizing disorders, and the effects on the level of development and function vary depending on the pattern of the comorbid psychopathology. There have been studies on the relationship between emotional and behavioral problems and temperament in children with ADHD. Although the temperament and character profile affect the manifestation of psychopathology in children, few studies on the temperament of children with ADHD, who have comorbid internalizing and externalizing problems, have been conducted. This study aimed to identify temperament and character profiles associated with internalizing and externalizing problems in children with ADHD.

Methods: Children with ADHD (N = 114, mean age = 8.51-¦1.87 years) were selected. They were diagnosed by K-SADS-Present and Lifetime Version and evaluated using the Advanced Test of Attention and Korean Wechsler Intelligence Scale for Children–Fourth Edition. Their parents completed the ADHD Rating Scale, Korean-Child Behavioral Checklist, and Junior Temperament and Character Inventory. The temperament and character profiles of the children with no problems (N = 48, NO group), only internalizing problems (N = 11, INT group), only externalizing problems (N = 26, EXT group), and comorbidity of internalizing and externalizing problems (N = 28, COM group) were examined.

Results: The COM group had more severe ADHD symptoms and significantly higher level of novelty-seeking behavior ($p < 0.001$), harm avoidance ($p < 0.001$), and self-transcendence ($p < 0.040$), as well as lower self-directedness ($p = 0.005$) and cooperativeness ($p < 0.001$) than the NO group. Linear regression analysis revealed that harm avoidance ($p < 0.001$) was correlated with their level of internalizing problems, regardless of severity of ADHD symptoms. In addition, novelty seeking ($p < 0.001$) and sex (male, $p = 0.034$) were associated with the level of externalizing problems.

Conclusions: Differences were observed in the temperament and character profiles of children with ADHD according to their comorbid psychopathology. Results suggested that temperament and character profiles may affect the comorbid psychopathology in children with ADHD, regardless of ADHD symptom severity. TEMP, ADHD, PSP

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J Am Acad Child Adolesc Psychiatry. 2018;57:S326-S327.

PREVALENCE AND CO-OCCURRENCE OF PARENT-REPORTED MENTAL, BEHAVIORAL, AND DEVELOPMENTAL DISORDER DIAGNOSES IN US CHILDREN: NATIONAL SURVEY OF CHILDREN'S HEALTH, 2016.

Holbrook J, Bitsko RH, Danielson M, et al.

Objectives: The objective of this Symposium is to characterize the prevalence of the parent-reported diagnosis and co-occurrence patterns of mental, behavioral, and developmental disorders (MBDDs) in a national sample group of US children.

Methods: Our analytic sample group from the 2016 National Survey of ChildrenΓÇÖs Health included children (aged 2–17 years; N = 46,100). We examined lifetime diagnoses and the current presence of MBDDs. Parents answered survey questions on whether a health care provider had ever told them that their child had ADHD, anxiety problems, ASD, behavioral or conduct problems, depression, developmental delay (DD), intellectual disability (ID), a learning disability, a speech or other language disorder (SLD), substance abuse (children aged 6+ years only), or Tourette's disorder (TD). We used SUDAAN 11.0.1 to account for the complex sampling design. Results reflect weighted estimates generalizable to noninstitutionalized children in the United States.

Results: In 2016, one-fourth (16.3 million) of children aged 2–17 years in the United States had been diagnosed with an MBDD, and one-fifth (13.3 million) currently had an MBDD. The most commonly diagnosed conditions were ADHD (9.4% [95% CI 8.8–9.9]), behavioral or conduct problems (8.9% [8.4–9.5]), SLD (8.0% [7.4–8.5%]), and anxiety problems (7.9% [7.4–8.5%]). For most MBDDs, more than half of children who had one condition also had at least 2 co-occurring conditions and more than one-fourth had at least 4 co-occurring conditions. Of children diagnosed with depression, 74.5% also had anxiety. ADHD co-occurred in approximately half of children with TD, depression, ASD, behavioral or conduct problems, substance abuse, or a learning disability. Approximately half of children with an SLD (47.3%) had been diagnosed with DD. These results reflect lifetime diagnoses of MBDDs. Relative prevalence patterns and co-occurrence patterns were similar for children who currently had MBDDs.

Conclusions: MBDDs represent a set of conditions commonly diagnosed in the United States. Most children with an MBDD have another co-occurring MBDD, and many children have several co-occurring MBDDs. Treatment for children with co-occurring MBDDs may require coordinated care from multiple health care providers. CM, EPI, ADHD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S283.

OUTCOMES OF DOUBLE-BLIND RCT OF NEUROFEEDBACK FOR ADHD.

Arnold LE, Kerson C, Monastra V, et al.

Objectives: This Symposium will determine whether neurofeedback (NF) has a specific benefit for ADHD beyond a nonspecific benefit, such as the placebo response and the benefit of 30+ sessions with coaching and encouragement to focus on a screen. Unblinded RCTs have shown encouraging results, but small blinded, flawed RCTs have not. Despite wide variation in the quality of NF, it has the potential to be an alternative or adjunct to medication with a more enduring effect.

Methods: Children aged 7–10 years (N = 140) at 2 sites were randomly assigned in a 3:2 ratio to 38 sessions of active NF (3 times a week) using the Monastra-Lubar method to down-train the theta-beta ratio (TBR) versus sham NF of equal duration, frequency, and intensity. Active and sham NF were programmed into a central server by an unblinded off-site investigator, who never met the family, using de-artifacted recordings of active NF for sham on which the real-time artifacts of the child were superimposed. The primary outcome

(comparison of active vs sham on parent- and teacher-rated inattentive symptoms) is analyzed by a linear-mixed model, with repeated measures and both site and site X treatment interaction being entered.
Results: The planned sample group was randomized by screening 290 children. Adherence to treatment was good, with 7 dropouts (5%). There were 8 adverse events definitely related to treatment (eye pain, irritability, oppositionality, crying, self-injury), 5 probably related (headache, oppositionality, depression, crying), and 43 possibly related (both treatment arms summed). End-of-treatment blind guesses to the treatment assignment were correct 36% of the time by children, 42% by trainers (therapists), and 35% by parents, none of which was greater than expected by chance. The primary outcome (improvement in parent- and teacher-rated ADHD symptoms with active NF compared with sham NF) will be presented.
Conclusions: The primary clinical results of this NIMH-funded 2-site double-blind RCT of NF will be presented. Blinding was excellent, and treatment adherence was good. A few nonserious adverse events attributable to treatment were found. ADHD, TREAT, CAM

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J Am Acad Child Adolesc Psychiatry. 2018;57:S281-S282.

WHAT IS THE EVIDENCE FOR NEUROFEEDBACK FOR ADHD?

Arnold LE, Jensen PS.

Objectives: This Symposium will provide a review and critique of the evidence base for neurofeedback [EEG biofeedback (NF)] as treatment for ADHD and unveil preliminary results of a NIMH-funded double-blind 2-site RCT designed to address the flaws of previous studies.
Methods: Joel Nigg, PhD, presents a meta-analysis with random-effects models and critiques flaws of published RCTs. Roger deBeus, PhD, reports baseline findings, and L. Eugene Arnold, MD, reports on the preliminary outcomes from the new NIMH-funded 2-site RCT, which randomized 140 children aged 7–10 years with combined or inattentive ADHD 3:2 to 38 sessions of NF or a refined sham that allowed therapists to be blind to the study. The primary outcome is parent- and teacher-rated inattentive symptoms. Analysis is by mixed-effects models. Peter Jensen, MD, discusses the methods.
Results: Published trials have problems with selection and inadequate sample group size, suboptimal treatment protocols, lack of blinding, lack of convincing placebo sham of equal duration and intensity, poor sample group retention, failure to record safety data, failure to measure the learning curve, and suboptimal statistical approaches. Significant effects were found on ADHD symptoms rated by most proximal (least blinded) assessors, but not with probable blinded ratings, or in trials with active/sham controls. Of the 285 screens in the NIMH-funded RCT who met categorical and dimensional criteria for ADHD, 226 (79%) had theta-beta ratios 4.5 by the ADHD Suite, suggesting suitability of TBR downtraining. Of 172 with blood tests, 64 (37%) had insufficient vitamin D (< 30 ng/ml): 42/82 (51%) at the Ohio site and 22/90 (23%) at the North Carolina site. Five were frankly deficient (<20 ng/ml). Dr. Arnold reports outcomes of that study in which there were 8 adverse events as a result of treatment and 5 probably because of treatment. Correct posttreatment guesses with regard to treatment assignment were 36% by children, 42% by therapists, and 35% by parents.
Conclusions: Although encouraging RCTs for NF in ADHD have been published, the results are in question because of flaws and countervailing failed trials, with small sample groups. There appear to be minor safety issues, which were previously ignored. Definitive studies with well-blinded sham conditions are needed. The results of the largest, most rigorous study to date, designed to address the flaws of previous studies, are presented and integrated into an updated meta-analysis. ADHD, RCT, TREAT

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J Am Acad Child Adolesc Psychiatry. 2018;57:S324.

ADULT OUTCOMES OF ICD-10 HYPERKINETIC DISORDER IN THE MTA AND EFFECT OF COMORBIDITY.

Arnold LE, Roy A, Taylor E, et al.

Objectives: This presentation shows how to track adult outcomes of children diagnosed with hyperkinetic disorder (HKD) by ICD-10 criteria and examine how they differ from adult outcomes of ADHD classified by DSM-5. Only 145 of 579 children in the Multimodal Treatment Study of ADHD (MTA), with combined type of DSM-IV-classified ADHD, met criteria for ICD-10 HKD at baseline (ages 7–9 years), because major

internalizing comorbidities excluded 147 cases and more stringent symptom count/pervasiveness requirements excluded 200. The 145 HKD had greater initial symptom severity and a significantly better 14-month medication response than the rest. The purpose of this study was to examine adult outcomes of children in the MTA with and without HKD at baseline.
Methods: Multi-informant assessments were conducted for 16 years. We used the 12/14/16-year assessments in young adulthood (ages 19–26 years).
Results: Attrition was greater for HKD than the rest of the MTA sample group. The postattrition 109 with baseline HKD had no greater adult persistence of ADHD symptoms/impairment than 358 without HKD, but they had more stimulant use, more job losses, fewer car crashes, and lower emotional lability. However, 26 excluded for internalizing comorbidity, but otherwise meeting HKD criteria, had significantly greater persistence of ADHD symptoms than either HKD + externalizing comorbidity or other participants in the non–HKD group.
Conclusions: Despite greater initial symptom severity, HKD had no worse 16-year young adult outcome than other ADHD, except more job losses were balanced by fewer crashes and less emotional lability. HKD is a more pure subgroup of ADHD with greater initial symptom severity and pervasiveness, better response to medication, and as good adult prognosis as non–HKD ADHD. Comorbid internalizing disorder seems to have worse prognosis than initial severity and/or pervasiveness of ADHD symptoms. ADHD, DEV, NSS

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J Am Acad Child Adolesc Psychiatry. 2018;57:S172.

A MULTICENTER, RANDOMIZED, ACTIVE-CONTROL REGISTRATION TRIAL OF SOFTWARE TREATMENT FOR ACTIVELY REDUCING SEVERITY OF ADHD (STARS-ADHD) TO ASSESS THE EFFICACY AND SAFETY OF A NOVEL, HOME-BASED, DIGITAL TREATMENT FOR PEDIATRIC ADHD.

Kollins SH, Bower J, Findling RL, et al.

Objectives: AKL-T01 is a home-based, video game-like digital treatment in development for inattention and cognitive dysfunction in pediatric patients with ADHD. We assessed the efficacy and safety of AKL-T01 in a randomized, active-control trial [STARS-ADHD (Software Treatment for Actively Reducing Severity of ADHD); NCT02674633].
Methods: Eligible patients aged 8–12 years with confirmed ADHD diagnoses and Test of Variables of Attention (TOVA) Attention Performance Index (API) scores 1.8, not currently taking stimulant medication or willing to discontinue medication before the trial, were recruited (20 sites). Treatment comprised approximately 25 minutes per day, 5 days per week for 4 weeks. Outcomes were measured at baseline and postintervention. TOVA API was the primary outcome; secondary outcomes were measurements by the Impairment Rating Scale, ADHD-Rating Scale (RS)-IV, Clinical Global Impressions–Improvement (CGI-I), Cambridge Neuropsychological Test Automated Battery–Spatial Working Memory, and Behavior Rating Inventory of Executive Function. Safety, tolerability, and compliance were also assessed. Patients, parents, and investigators were blinded.
Results: Patients were randomized to AKL-T01 (n = 180; mean age = 9.7 years) or active control (n = 168; mean age = 9.6 years). AKL-T01 showed statistically significant improvement in TOVA API (nonparametric tests; within-group $p < 0.0001$); active control showed no improvement ($p = 0.7$); the between-group difference was statistically significant ($p = 0.006$). Statistically significant improvements in all secondary outcomes were observed within ($p < 0.01$) but not between groups. The subgroup of patients who discontinued stimulant medication and received AKL-T01 (n = 65) showed statistically significant improvements in ADHD-RS-IV inattentive subscale and total scores (n = 31) and CGI-I (n = 32) versus active control (n = 33) ($p < 0.04$ for all). Treatment-related adverse events (AEs) occurred (mostly mild frustration) in 6% of AKL-T01 patients and 1% of active control patients; no serious AEs occurred in either group.
Conclusions: This study further demonstrates the efficacy and safety of AKL-T01 in improving objectively measured inattention in pediatric patients with ADHD. Patients who recently discontinued medication may show a more robust response. AKL-T01 may offer a novel digital treatment option for ADHD. Patients with comorbid ADHD warrant further study. ADHD, COG, RCT

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J Am Acad Child Adolesc Psychiatry. 2018;57:S293-S294.

ASD AND ADHD: OVERLAPPING SYMPTOMS AND SHARED BIOLOGY.

Anagnostou E, Veenstra-VanderWeele J.

Objectives: The goal of this session is to synthesize new research evidence supporting clinical and biological overlap between ASD and ADHD.

Methods: The Province of Ontario Neurodevelopmental Disorders (POND) Network study has recruited more than 2000 children and youth with neurodevelopmental disorders (783 with ADHD, 882 with ASD, 240 with OCD, as well as 209 typically developing control subjects). The results of 4 POND studies will be presented. The first study examined the intersecting behavioral phenotype of 622 participants with ASD or ADHD through principal component analysis of symptom surveys. The second study used diffusion tensor imaging (DTI) to examine and compare the brain white matter structure of 200 participants with ASD, ADHD, and OCD or control subjects. The third study examined the association between gray matter structure and social abilities in 312 children with ASD, ADHD, and OCD or control subjects. In the fourth study, large-scale, whole-brain fMRI networks were examined in 271 children and adolescents, comparing those with ASD and ADHD with typically developing subjects using graph theoretical measures.

Results: Profile analysis showed that inattentive and hyperactive/impulsive factor scores do not differ between ASD and ADHD. In the DTI study, fractional anisotropy was lower in the groups with ASD and ADHD compared with the group with OCD and the control group, but it was not different in children with ADHD compared with ASD or children with OCD compared with control subjects. In the structural MRI study examining gray matter, larger cortical thickness measurements in the frontal and temporal-parietal regions were associated with fewer social deficits across all 4 groups (ASD, ADHD, OCD, control subjects). However, for subcortical brain regions, larger structures were associated with fewer social deficits in groups with ASD and ADHD, and smaller structures were advantageous in those with OCD. In the fMRI study, children with ASD or ADHD showed decreased network degree in the default mode network and increased network degree and efficiency in the subcortical network compared with control subjects. No significant group differences were noted between ASD and ADHD.

Conclusions: Overall, data support striking similarities in the both the phenotype and the biology of ASD and ADHD. Clinical and diagnostic implications will be discussed. ASD, ADHD, NIMAG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S175.

SKILLS A PSYCHOEDUCATIONAL GROUP PROGRAM FOR ADOLESCENTS WITH ADHD.

Meyer J, Ramklint M, et al.

Objectives: ADHD is characterized by symptoms of inattention and/or hyperactivity/impulsiveness, resulting in impaired functioning in important domains of life. Psychoeducation has been suggested as the first-line treatment for ADHD, whereby information and support are provided to the patient with the aim to increase understanding and coping strategies. However, most psychoeducational programs are designed for adult populations or parents, and there is a lack of programs directed toward children. The rationale of this study was to describe and evaluate a newly developed psychoeducational group-based treatment, SKILLS, for adolescents with ADHD.

Methods: Participants comprised adolescents (N = 56; mean age = 16.94 years; SD = 0.95, 64.9% females), with a clinical diagnosis of ADHD, recruited within a larger RCT. The diagnosis was confirmed using Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). The treatment consists of three 2-hour sessions and includes information on ADHD symptomatology and emotion regulation, strengths and challenges associated with the disorder, sleep, food and stress management, problem solving, and strategies for handling daily life routines. An evaluation form was filled in by participants after the treatment and Wilcoxon-signed rank tests were used to compare pre- and postratings (self- and parental reports) on functional impairment as measured with the Sheehan Disability Scale (SDS).

Results: A majority of the participants (84.8%) rated that their knowledge about ADHD had increased, that they could better control problems related to their ADHD (71.1%), and that they would recommend the treatment to others (90.9%). Parents, but not adolescents, rated a reduction of functional impairments with the SDS after the treatment ($Z = 2.31$; $p = 0.021$).

Conclusions: SKILLS was appreciated by the participating adolescents and their parents rated a reduction of functional impairments. Group-based psychoeducational treatments may be included in the regular services within clinics as a first-line treatment for children and adolescents, possibly in connection with parental educational groups. For the future, symptom reduction and increased adaptive behaviors after treatment need to be assessed in larger populations. ADHD, TREAT, ADOL

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J Am Acad Child Adolesc Psychiatry. 2018;57:S252.

COMPARATIVE STUDY ON THE PERCEPTION OF THE NEIGHBORHOOD ENVIRONMENT AND EXPERIENCE WHEN PARTICIPATING IN OUT-OF-SCHOOL ACTIVITIES BETWEEN TYPICAL STUDENTS AND PATIENTS WITH ADHD.

Lee J, Choi B-S, Kim J, et al.

Objectives: The exact cause of ADHD is not known, but it is known that both genetic and environmental factors are involved. Sociodemographic factors, such as low social income, mental illnesses in parents, and place of upbringing, have been correlated with ADHD. The purpose of this study is to investigate the differences between the group with ADHD and the general student group in terms of the perception of the residential environment and periodic activities outside the classroom.

Methods: The patient group consisted of 62 outpatients or inpatients at the Department of Pediatric Psychiatry, Pusan National University Yangsan Hospital, and 49 patients diagnosed with ADHD were selected. For the control group, 3727 youths in elementary schools, middle schools, and high schools of the metropolitan city of Busan were asked to fill out questionnaires. Of the 1717 respondents who responded to the questionnaires, 245 were selected for patient-controlled studies. Perception of the residential environment was evaluated with the following expressions: My neighborhood is dirty and littered; There are many dark and secluded places in my neighborhood; My neighborhood is full of people who are drunk at night; I often see flocks of teens in my neighborhood; and There are times when I feel afraid that someone in my neighborhood may attack me. Regular activities asked about include religion, leisure, club, and volunteer activities. The differences between the patient group and control group were compared using the Chi-squared test (+í2 test). All analyses were conducted using SPSS software, version 24 (IBM SPSS Institute), and $p < 0.05$ was considered statistically significant.

Results: There was a significant difference between the patient group and the control group in areas for which students responded, My neighborhood is dirty and littered ($p < 0.05$). There was also a significant difference between the patient group and the control group in terms of having more than one club activity per month ($p < 0.05$)

Conclusions: It was found that patients with ADHD are more aware of perceived negative aspects of the area in which they reside, thus reflecting their anxiety. In addition, it was also found that the patient group did not partake in as many social activities as the control group. SAC, ADHD, R

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J Am Acad Child Adolesc Psychiatry. 2018;57:S174.

ADHD AND SUICIDAL IDEATION AMONG CHILDREN AND ADOLESCENTS: THE MEDIATING ROLE OF DEPRESSION AND IRRITABILITY.

Levy T, Kronenberg S, Schachar R.

Objectives: Previous studies indicate that ADHD increases the risk for suicidal ideation (SI) and acts but provides little insight into the reason for this association. This study examined whether depression, irritability, and anxiety symptoms, which often accompany ADHD, mediate between ADHD and suicidality.

Methods: Participants comprised 1451 people, ages 7–17 years (mean = 9.23), from a psychiatric outpatient clinic. Parent reports (PR-S) and teacher reports (TR-S) on ADHD, depression, irritability, generalized anxiety, and suicidal ideation or acts within the past 6 months were measured using the Ontario Child Health Study (OCHS) inventory. Psychosocial Adversity Index (PAI) summed the risk factors as financial problems, single parent, and low parental education. Logistic regression was used to assess the association of symptom severity and risk for SI. The multiple mediator model was used based on the parent report and the teacher report separately, adjusting for age, gender, and PAI.

Results: Parents reported a higher proportion of suicidality compared with the teachers (10.4 and 2.5%, respectively, McNemar: p < 0.001; CohenΓÇÖs K = 0.18, p < 0.001). PAI was associated with PR-S (OR = 1.35 [95% CI 1.10–1.64]), but not TR-S. ADHD symptoms were associated with PR-S (OR = 1.11 [95% CI 1.08–1.14]) and TR-S (OR = 1.09 [95% CI 1.04–1.14]). Calculated separately for the parent report and the teacher report (values detailed, respectively), ADHD symptoms were associated with depression (B = 0.21; B = 0.15, p < 0.001 for both), anxiety (B = 0.13; B = 0.07, p < 0.001 for both), and irritability (B = 0.16; B = 0.16, p < 0.001 for both) symptoms. In addition, depression (B = 0.26; B = 0.28, p < 0.001 for both) and irritability (B = 0.17, P < 0.001; B = 0.19, p < 0.01 for both), but not ADHD and anxiety symptoms, were associated with PR-S and TR-S [¤ç2 (7, N = 1461) = 204.13; ¤ç2 (7, N = 1368) = 61.27, p < 0.001 for both]. Both parent report- and teacher report-based models indicated that depression (60 and 55% of total association, respectively) and irritability (35 and 48% of total association, respectively), but not anxiety symptoms, mediated the association between ADHD and suicidality.
Conclusions: ADHD serves as a risk factor for suicidal ideation and acts. Depression symptoms only partially mediate between ADHD and suicidality. This study is the first to suggest that irritability symptoms may mediate between ADHD and suicidality. S, IMD, ADHD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S168.

PREDICTORS FOR PHARMACOLOGICAL AND PSYCHOTHERAPEUTIC TREATMENT IN CHILDREN NEWLY DIAGNOSED WITH ADHD.

Koelch M, Fegert JM, Kollhorst B, et al.

Objectives: The goal of this study is to investigate predictors for use of medication and psychotherapy within 5 years after a first ADHD diagnosis in Germany.
Methods: This cohort study was based on the German Pharmacoepidemiological Research Database and included 12,250 treatment-na+»ve children aged 5–12 years with an incident ADHD diagnosis in 2010 and a minimum follow-up of 5 years. Children were categorized into treatment groups based upon dispensations of ADHD drugs and billed codes for psychotherapy within 5 years after the first ADHD diagnosis. Multivariable logistic regression was used to estimate associations between children's characteristics at the first diagnosis and the chosen treatment approach.
Results: Within 5 years after the incident ADHD diagnosis, 37% of the children received medication; 11% received only psychotherapy; and 52% received no treatment. Of those receiving medication, 27% had additional psychotherapy. Boys [adjusted OR (aOR) = 1.41 [95% CI = 1.28–1.55]], children with an ADHD diagnosis with hyperactivity (5.64 [4.94–6.44]), and those with comorbid conduct disorders (1.35 [1.21–1.51]) were more likely to receive medication than no treatment. Male sex (aOR = 1.18 [95% CI = 1.02–1.35]) and comorbid neurotic and somatoform (1.38 [1.12–1.70]), conduct (1.45 [1.23–1.71]), and emotional disorders (1.60 [1.33–1.92]) were associated with only psychotherapy. Comorbid depression (aOR = 1.41 [95% CI = 1.13–1.77]), neurotic and somatoform (1.31 [1.02–1.68]), conduct (1.52 [1.29–1.78]), and emotional disorders (1.48 [1.21–1.81]) increased the odds of receiving both treatments than medication only. In contrast, higher age (aOR = 0.73 [95% CI = 0.59–0.90]) and mental retardation (0.48 [0.28–0.83]) decreased the odds. Children who were initially diagnosed by a nonspecialist were more likely to receive no treatment than medication, whereas diagnosis by a psychotherapist increased the odds of receiving medication, only psychotherapy, or both.
Conclusions: This study is the first to show patterns of 2 main ADHD treatment approaches in newly diagnosed children and to identify several patient characteristics as predictors. ADHD, PPC, EPI

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J Am Acad Child Adolesc Psychiatry. 2018;57:S287.

A Controlled Trial of Active Versus Sham Trigeminal Nerve Stimulation (TNS) in Children With ADHD.

McGough JJ.

Objectives: Trigeminal nerve stimulation (TNS), a minimal-risk noninvasive method of neuromodulation, is effective for depression and epilepsy and is associated with increased activation in the anterior cingulate gyrus on positron emission tomography imaging. A prior open-label investigation suggested potential benefits of TNS in treating ADHD. This double-blind, sham-controlled trial is the first blinded controlled study of TNS in youth and the first to examine the efficacy of TNS as a form of treatment for ADHD.

Methods: Children aged 8–12 years, with full-scale IQ > 85 and K-SADS-diagnosed ADHD, were randomized to 4 weeks of nightly treatment with active or sham TNS. Active versus sham treatments were identical except that no stimulation was administered with sham. Assessments were weekly clinician ADHD-Rating Scales (ADHD-RS) and Clinical Global Impressions–Severity (CGI–S) and CGI-Improvement (CGI-I) scales, and Conners Parent-Teacher Ratings. Dimensional outcomes were fitted via a mixed-effects model with group +ù time interaction to test for differential effects of active treatment using a piece-wise linear time trend.

Results: The total number of children in the study was 62 (N = 62). ADHD-RS total scores showed significant group +ù time effects (Fdf1/df2 = 8.12 1/228, p = 0.005), with Cohen's d estimate at visit 4 = 0.5, suggesting a medium-sized effect. CGI-I favored active treatment (Chi-square = 9.12, df = 1, p = 0.003). There were no clinically meaningful side effects or adverse events in either condition.

Conclusions: Although limited by a sample size and short duration, results demonstrated the potential efficacy of TNS in ADHD and provide further evidence that TNS is safe and has minimal risk. Future research is needed to assess the durability of treatment response and impact on brain development with sustained use (Clinicaltrials.gov: NCT02155608). ADHD, NM, RCT

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J Am Acad Child Adolesc Psychiatry. 2018;57:S300.

A Network Analysis of Change in ADHD Symptom Structure Between Childhood and Adolescence.

Martel MM, Goh P.

Objectives: The current study examines associations among individual ADHD symptoms in middle childhood and adolescence using cross-sectional and longitudinal samples of typically developing individuals and individuals with ADHD.

Methods: Two cross-sectional samples of 548 children aged 6 to 12 years and 357 adolescents aged 13 to 17 years were used. Both sample groups were community-recruited and included approximately equal numbers of typically developing individuals and individuals with ADHD. Parent and teacher symptom ratings on the ADHD Rating Scale were obtained on all participants, and a diagnostic team arrived at clinical diagnoses following a comprehensive review of ratings and a clinical interview.

Results: Network analysis indicated that ADHD symptom structure became more differentiated between childhood and adolescence. During childhood, 2 symptom clusters of inattention, hyperactivity, and impulsivity were best supported. However, in adolescence, 3 clusters of inattention, hyperactivity, and impulsivity were best supported. In adolescence, impulsivity symptoms were more central, appearing in the middle of the cluster. Furthermore, there was a verbal impulsivity triad with the following symptoms tightly linked as follows: 1) often talks excessively; 2) often unable to play or engage in leisure activities quietly; and 3) often interrupts or intrudes. It is noteworthy that network comparison tests indicated no significant differences in the overall strength of connectivity of nodes within networks or network structure between typically developing individuals and individuals with ADHD in either sample group (all p > 0.15). Across both age ranges, 2 symptoms 1) often easily distracted; and 2) difficulty sustaining attention–appeared as central or core symptoms.

Conclusions: Results suggest that the structure of ADHD appears to become more differentiated across development, with impulsivity being particularly important among typically developing adolescents and adolescents with ADHD. ADHD, ADOL, DIAG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S209.

IMPACT OF LANGUAGE DISORDER ON PRESCRIBING PATTERNS AND HEALTHCARE UTILIZATION AMONG LOW-INCOME CHILDREN WITH ADHD.

Lohr WD, Feygin YB, Le JF, et al.

Objectives: This presentation will determine the prevalence of language disorders (LDs) in low-income children with ADHD and its impact on these children's rate of health care utilization.

Methods: Using Kentucky Medicaid records from 2012 through 2016, we developed a detailed demographic, behavioral, clinical, and diagnostic dataset for all children <18 years of age. Presence of LDs was defined by ICD codes for the following: language disorder (F80.9); speech sound disorder (F80.0); childhood-onset fluency disorder (stuttering) (F80.81); social (pragmatic) communication disorder (F80.89); and unspecified communication disorder (F80.9). ADHD was defined by F90.0, F90.1, and F90.2. We performed a descriptive analysis and tested for differences in health care utilization between those with and without an LD using the Chi-squared and Wilcoxon methods.

Results: A total of 8923 children were diagnosed with both ADHD and an LD over the study period (10.4% of total number with ADHD). Diagnoses of ADHD and LD were significantly less common in older children ($p < 0.001$), nonwhites ($p < 0.001$), females ($p < 0.001$), and those living in a nonmetro region ($p < 0.001$). Compared with children with ADHD and no LD (N = 77,033), those with both ADHD and LD were significantly more likely to visit an emergency department (ED) (60.9 vs 55.6%, $p < 0.001$); receive psychosocial therapy (58.7 vs 51.5%, $p < 0.001$); receive an antipsychotic medication (22.7 vs 18.7%, $p < 0.001$); receive a psychotropic medication (83.9 vs 81.7%, $p < 0.001$); and have additional mental illness diagnoses (2.3 vs 1.11, $p < 0.001$). The children with both ADHD and LD received a higher average number of prescriptions for both stimulants (20.01 vs 15.76, $p < 0.001$) and antipsychotic medications (4.95 vs 3.09, $p < 0.001$).

Conclusions: Low-income children with ADHD with a comorbid LD represent a neurodevelopmental burden to the health care system. These children have more mental illness comorbidity, go to the ED more often, and are more likely to receive antipsychotic medications than children with only ADHD. Given concerns that LDs are underrecognized, providers should screen all children with ADHD for LDs and advocate for additional support and treatment. COMD, ADHD, RF

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J Am Acad Child Adolesc Psychiatry. 2018;57:S144.

NEURAL MECHANISMS OF IRRITABILITY IN CHILDREN WITH ADHD.

Ishii-Takahashi A, Faria AV, Mangalmurti A, et al.

Objectives: Emotional dysregulation, manifesting as irritability, is frequently observed in children with ADHD. It can have greater impact on childrenɔs well-being and self-esteem than symptoms that are used to diagnose ADHD. Based on the literature, we hypothesized that irritability within the context of ADHD would be underpinned by anomalous connectivity, indexed by resting-state functional connectivity (RSFC) between the amygdala and lateral/ventromedial prefrontal regions.

Methods: Children [N = 302; 105 with ADHD, 197 unaffected, mean age 10.9 years (SD = 2.4)]. Irritability was measured through items extracted from parent completed questionnaires (Behavior Rating Inventory of Executive Function, Affective Reactivity Index, and Child Behavior Checklist). Resting-state functional MRI was obtained on a 3T scanner and underwent quality control (removing 27% of original data). To define RSFC, the brain was parcellated using MRICloud, and pairwise correlations in the regional time series were calculated. We focused on connectivity between bilateral amygdala and cortical areas (regions of interest defined using the JHU atlas [MRICloud: Pediatric8-16yo_283labels_M2_v9B]. A linear mixed-effects analysis was assessed to test for associations between irritability and RSFC using age, gender, IQ, and ADHD symptoms as covariates.

Results: Irritability was negatively associated with the RSFC between left amygdala and the right pre-/postcentral, superior parietal gyrus ($t < 3.4$, $p < 0.0006$) and between right amygdala and right superior frontal gyrus ($t < 3.4$, $p < 0.0008$). These associations survived Bonferroni adjustment for multiple testing.

Conclusions: Irritability was associated with decreased connectivity between the amygdalae and lateral prefrontal/superior parietal cortical regions-both key components of the cognitive control network. These findings survived adjustments for core ADHD symptoms and for multiple testing. Future work will integrate data on structural connectivity. ADHD, NIMAG, IMD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S294.

DISTINCT AND SHARED WHITE MATTER DISRUPTION AND DIMENSIONAL BRAIN-BEHAVIOR RELATIONSHIPS IN CHILDREN WITH ASD, ADHD, AND OCD COMPARED TO CHILDREN WITHOUT MENTAL HEALTH DIAGNOSES.

Ameis SH.

Objectives: Children with different neurodevelopmental disorders (NDDs), including ADHD, ASD, and OCD, feature significant overlap in genetic vulnerability, clinical presentation of symptoms, and findings from brain-imaging studies examining a single disorder compared with control subjects, although few studies have examined whether brain alterations are distinct or nondistinct across different NDDs. We will present recently published data comparing white matter circuits in children with different NDDs and control subjects and examine brain-behavior relationships across NDDs using dimensional measures.

Methods: Diffusion imaging and behavioral measures were acquired in 200 children and adolescents (n = 31 with ADHD; n = 36 with OCD; n = 71 with ASD; n = 62 control subjects; mean age range: 10.3–12.6 years). Multigroup comparison of white matter indices across the brain using a voxelwise approach was conducted, followed by pairwise comparisons between diagnostic groups. Relationships of fractional anisotropy with dimensional measures of inattention, social deficits, obsessive-compulsive symptoms, and general adaptive functioning were conducted across the sample group with NDD. All reported results are significant at a p value of <0.05, fully corrected for multiple comparisons across space using familywise error.

Results: Lower fractional anisotropy was found in each group with NDD, compared with control subjects, within the splenium of the corpus callosum. On pairwise comparison, fractional anisotropy was lower in the groups with ASD and ADHD compared with the group with OCD and the control group but was not different in children with ADHD compared with ASD or children with OCD compared with control subjects. Finally, a positive relationship between fractional anisotropy and general adaptive functioning across NDDs was shown.

Conclusions: Although our study indicates the presence of disruption in the corpus callosum as a shared feature of ASD, ADHD, and OCD, fractional anisotropy alterations may be more widespread and severe in ASD and ADHD than in OCD. Higher fractional anisotropy across major white matter tracts appears to be related to better adaptive function across NDDs. ASD, IMAGS, ADHD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S48.

EXERCISE CAN REDUCE SYMPTOMS OF AGGRESSION AND IMPROVE FUNCTIONING IN CHILDREN WITH ADHD.

Lohr WD.

Objectives: This Clinical Perspectives will review the evidence evaluating exercise in reducing aggression and improving symptomology in children with ADHD. The role of exercise in reducing aggressive behavior in research groups and its role in reducing consequences of bullying will also be reviewed.

Methods: The material for this Clinical Perspectives results from an evidence-based literature review and clinical practices.

Results: Physical activity benefits many areas of cognition and executive function in youth. In children with ADHD, exercise can lead to reduction in levels of hyperactivity and improved self-regulation. Although the amount of exercise needed to provide effect is being evaluated, some have found that exercise may have a long-lasting benefit in those with ADHD. In addition, exercise provides a protective effect from the consequences of peer bullying. Physical activity has been associated with reduced aggression in research subjects, and access to space conducive to physical activity may be a factor in the association between green space and wellness.

Conclusions: Exercise is felt to be safe, economical, and useful as an intervention for child populations afflicted with mental illness. The role of physical activity in improving levels of function in children with ADHD should be understood by child psychiatrists and other involved stakeholders. ADHD, AGG, PRE

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J Am Acad Child Adolesc Psychiatry. 2018;57:S145.

THE EFFECTS OF CATECHOL-O-METHYLTRANSFERASE (COMT) POLYMORPHISM ON CORTICAL THICKNESS AND SURFACE AREA ABNORMALITIES IN CHILDREN WITH ADHD.

Mizuno Y, Jung M, Fujisawa TX, et al.

Objectives: The catechol-O-methyltransferase (COMT) gene is associated with frontal cortex development and the pathophysiology of ADHD. However, how the COMT gene impacts brain structure and behavior in ADHD remains unknown. In the present study, we identify the effect of COMT on cortical thickness and surface area in children with ADHD and children with typical development (TD) by use of a machine-learning approach.

Methods: Thirty-nine children with ADHD and 34 age- and IQ-matched children with TD were studied on cortical thickness and surface area characteristics using structural MRI. COMT V158M genotype data were also obtained from children with ADHD and TD.

Results: We found that cortical thickness and surface area differences were predominantly observed in the frontal cortex. Furthermore, a path analysis revealed that a COMT genotype affected abnormal development of the frontal cortex in terms of both cortical thickness and surface area and was associated with working memory changes in children with ADHD.

Conclusions: Our study confirms that the role of COMT in ADHD is not restricted to the development of behavior but also may affect the cortical thickness and surface area. Thus, our findings may help to improve the understanding of the neuroanatomic basis for the relationship between the COMT genotype and ADHD pathogenesis. ADHD, NIMAG, ND

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J Am Acad Child Adolesc Psychiatry. 2018;57:S208-S209.

PREDICTORS OF ACADEMIC OVERACHIEVEMENT, NORMAL ACHIEVEMENT, AND LEARNING DISABILITY IN ADHD, ASD, AND GENERAL POPULATION SAMPLES.

Mayes S, Waschbusch D, Calhoun S, et al.

Objectives: Little is known about characteristics of overachievers, children whose achievement significantly exceeds their IQ.

Methods: By use of multinomial logistic regression, predictors of overachievement (achievement 1 SD above IQ), normal achievement, and learning disability (LD; achievement 1 SD below IQ) were analyzed in 1543 children (739 ADHD, 285 ASD, and 519 general population), ages 6 16 years, who were administered Wechsler reading and math tests. Dependent variables were as follows: 1) diagnoses; 2) demographics; 3) Wechsler IQ; 4) multiple neurocognitive scores; and 4) mother and teacher Pediatric Behavior Scale ratings.

Results: Achievement predictors were diagnosis (ASD greatest overachievement, ADHD greatest LD), IQ (lowest in overachievers and highest in LD), and some neurocognitive scores, primarily working memory (highest in overachievers and lowest in LD). Age, sex, race, parent occupation, and parent and teacher psychopathology and personality ratings did not contribute more to predicting achievement.

Conclusions: Psychopathology (ODD, conduct problems, anxiety, and depression), personality traits (motivation and self-confidence), peer relationships, and demographics are important in life, but our results showed that they were not primary determinants of overachievement. This suggests the following: 1) the absence of psychological problems does not contribute to overachievement, and the presence of psychological problems does not contribute to underachievement; and 2) overachievement does not protect a child from psychological problems, and underachievement does not cause the psychological problems we measured. This is profoundly significant, given the prevailing assumptions to the contrary and old theories put forth in the literature. Findings that overachievers score high on tests sensitive to neurological impairment and that overachievement is far more common in ASD than in ADHD suggest that neurobiology plays a

significant role. This is supported by our finding that IQ, diagnosis, and some neurocognitive scores contributed significantly to predicting overachievement and that none of the psychological and demographic variables did. Research has already established that LD is a neurobiological disorder with a strong genetic component. Our findings suggest that neurobiology may also underlie overachievement. SAC, LD, EPI

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J Am Acad Child Adolesc Psychiatry. 2018;57:S172.

EFFICACY AND LONG-TERM CLINICAL OUTCOME OF COMORBID PTSD AND ADHD AFTER REMINDER FOCUSED POSITIVE PSYCHIATRY INTERVENTION.

Ahmadi N, Molla M, Kase M, et al.

Objectives: Recent studies revealed that positive psychiatry (PP) can decrease psychopathology and increase well-being in youth. This study investigates the long-term clinical outcome of reminder-focused positive psychiatry (RFPP) in adolescents with comorbid ADHD and PTSD.

Methods: Eleven adolescents (ages: 11 -¦ 3 years, age range: 10–15 years; 50% female), after obtaining informed consent/assent, randomized to group RFPP (n = 5) or group CBT (n = 6). Eight participants (RFPP, n = 4; CBT, n = 4) completed twice-weekly intervention for the 6-week trial. Vascular function, C-reactive protein (CRP), homocysteine, and neuropsychiatric measures [ie, SNAP (Special Needs and Autism Project) questionnaire; PERMA (positive emotion, relationships, meaning, and accomplishments); Gratitude Questionnaire; Posttraumatic Growth Inventory; Connor–Davidson Resilience Scale; and Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA)] were measured. Subjects were followed for 12 months. The group RFPP interventions included posttraumatic growth, resilience, gratitude, optimism, self-compassion, growth-mindset, and connectedness.

Results: A significant decrease in homocysteine and CRP and an increase in vascular function in both groups, especially the RFPP group, were noted ($p < 0.05$). At the 12-month follow-up evaluation, no psychiatric hospitalization or suicidal ideation in either group was reported. A continuation of the significant improvement in CAPS-CA and SNAP in both groups was noted, which was more robust in the RFPP group ($p < 0.05$). Similarly, a continuation of the significant increase in PERMA, gratitude, resilience, and posttraumatic growth inventory scores was noted in the RFPP group but not in the CBT group ($p < 0.05$). A direct relationship between the increase in PERMA, gratitude, resilience, posttraumatic growth inventory and a decrease in CAPS-CA and SNAP was noted ($p < 0.05$). The most-robust improvement was in positive connectedness, resilience, and gratitude ($p < 0.05$).

Conclusions: The current findings reveal that RFPP is associated with long-term favorable effects in improving PTSD and ADHD symptoms, as well as in increasing well-being and vascular function in adolescents with comorbid ADHD and PTSD. This highlights the importance of the dual role of RFPP in addressing vulnerable symptoms and in enhancing well-being in youth with ADHD and PTSD. ADHD, PTSD, P

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J Am Acad Child Adolesc Psychiatry. 2018;57:S175.

A ROBOT-ASSISTED KINEMATIC MEASUREMENT FOR CHILDREN WITH ADHD (RAKMA): FOCUSED ON MOVEMENT SPEED.

Min A, Kim K, Lee G, et al.

Objectives: In this study, we checked the possibility of whether Robot-Assisted Kinematic Measurement–ADHD (RAKMA) for children with ADHD is useful as a diagnostic tool by objectively measuring the activity amount.

Methods: The participants evaluated in this study were 42 children diagnosed with ADHD and 55 normal children within the age range of 5 to 12 years. For the evaluation of the children, first came a 30-minute interview and observation by a child psychiatrist, followed by an evaluation of the group with ADHD and the general population group based on DSM-5 criteria. We examined behavioral levels using RAKMA to conduct an evaluation and comparative analysis of the results from the Child Behavior Checklist (CBCL) and the Korean ADHD Diagnostic Scale (K-ADHDDS). The independent t-test and correlation analysis were

performed to determine the differences between groups of clinical variables of the robot evaluation, which included the existing ADHD diagnostic evaluation. The collected data were analyzed using the SPSS (version 20.0).
Results: There were significant mean differences between the ADHD group and the control group in their CBCL score in attention problem, ADHD, and the K-ADHDDS score. Movement speeds in level 1 were 6.02 m/sec (SD = 3.25 m/sec) in the group with ADHD and 6.06 m/sec (SD = 3.30 m/sec) in the general population group. The difference was not significant (p = 0.015). In contrast, movement speeds in level 2 were 4.38 m/sec (SD = 2.07) and 5.60 m/sec (SD = 2.01), and the difference was significant (p = 0.014). Movement speeds in level 3 were 4.81 m/sec (SD = 4.55) and 7.32 m/sec (SD = 5.18), and the difference was significant (p = 0.014). The control group moved faster as the RAKMA level progressed, and the ADHD group moved slower.
Conclusions: Children with ADHD were getting slower, and children without ADHD were getting faster as the level progressed. The RAKMA can be used to overcome limitations of previous questionnaires by producing objective kinematic information on the childrenΓÇÖs activities to determine the diagnosis. ADHD, DIAG, ND

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ASSESSMENT AND MANAGEMENT OF WEIGHT LOSS WITH CNS STIMULANTS AND ITS IMPACT ON GROWTH IN CHILDREN WITH ADHD: AN ADAPTIVE INTERVENTION STUDY .

Waxmonsky JG.

Objectives: The goal of this session is to examine the comparative efficacy of interventions to promote weight recovery and their impact on growth in children taking CNS stimulants for ADHD.
Methods: The study provided 30 months of treatment with extended-release CNS stimulants and behavioral therapy to 230 medication-na+»ve children with ADHD. Initially, participants were randomized to receive medication (med) and low-dose behavioral therapy or intensive behavior therapy without medication to examine the impact of stimulant use on growth. Children in the medicine arm were prescribed osmotic release oral system (OROS) methylphenidate 7 days per week. Children were seen at the following time points: 1) every 2 weeks until the dose was stabilized; 2) monthly for 3 months; and 3) at least every 3 months. Weight and height were measured at each visit using standardized procedures. After 6 months, any child with a BMI deficit of 0.5 z units was randomized to 1 of 3 weight recovery treatments (WRTs) as follows: 1) monthly weight checks [monitoring arm (MON)]; 2) caloric supplementation (CS) with 150 kcal of nightly supplement; or 3) drug holiday (DH) when the med was limited to school days only. Families of children receiving CS and MON were advised to give the med 7 days a week. Monthly WRT visits, with a collection of 24-hour calorie logs, occurred until the BMI (z units) was normalized.
Results: Children taking the med had significantly less weight (0.60 z units, p < 0.0001) and height (ΓêÆ0.11 z units, p < 0.001) gain over the first 6 months versus those not taking the med. Differences increased to 2 cm and 2.5 kg over the study. Participants (n = 71) taking the med were assigned to WRT (43% med users), with a mean WRT duration of 16.4 months. Adherence to CS and DH was high. All 3 groups significantly increased their rate of weight gain in WRT from the pre-WRT period (+ö2.8 kg/year, p < 0.001), with no between-group differences based on WRT random assignment. When analyzed per protocol, DH and CS gained more weight than MON during WRT (+ö1.6–1.9 kg/year, p < 0.05). On medicated days, calories increased in MON and CS but not DH. Changes in calories and milligrams of methylphenidate exposure were associated with changes in weight and height. There were no differences in pre- to post-WRT height velocity either by the intention-to-treat population or per protocol for any WRT group.
Conclusions: The use of CNS stimulants suppressed weight and height. Calorie supplements, drug holidays, and monthly weight checks increased weight gain. However, these interventions did not significantly increase growth velocity. ADHD, STIM, MAE

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J Am Acad Child Adolesc Psychiatry. 2018;57:S119.

PHARMACOLOGICAL STRATEGIES IN ADHD.

Wilens T.

Objectives: Increasingly complex cases of children with ADHD are presenting to child and adolescent psychiatrists, requiring practitioners to learn new strategies for sequencing treatment, managing refractory core-ADHD symptoms, and treating comorbidity(ies).

Methods: A systematic review of the literature from historic, recently completed, and ongoing trials was reviewed to elucidate data on stimulant and nonstimulant treatments for ADHD. The limited data on sequential treatment is punctuated by anecdotal and open reports.

Results: The literature combined with the clinical experience indicate that alterations in the use of traditional stimulants in existing and novel release forms atomoxetine, alpha agonists, the use of alternative agents, and combinations of medications can enhance a patient's ADHD response. Strategies exist for the management of common comorbid conditions. Specific nonstimulant responses may be influenced by prior stimulant exposure.

Conclusions: Pharmacological strategies will be reported for those who: 1) have not responded to traditional agents; and 2) present with comorbidity(ies). Both empirically derived data and illustrative cases will be used in the presentation. ADHD, STIM, PPC

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NEW RESEARCH ON THE ASSESSMENT AND MANAGEMENT OF THE ADVERSE EVENTS WITH CENTRAL NERVOUS SYSTEM STIMULANTS FOR THE TREATMENT OF ADHD IN CHILDREN.

Waxmonsky JG, Wilens T.

Objectives: The goal of this session is to present new findings for assessing and managing adverse events associated with CNS stimulants in the treatment of pediatric ADHD. CNS stimulants have a large evidence base for improving symptoms of ADHD; however, tolerability has not been as well studied, leaving clinicians with less guidance on how to assess and manage adverse events.

Methods: This Symposium will present new data on ways to assess and manage common adverse events of CNS stimulants in children with ADHD. Presentations will summarize new trial data addressing stimulants impact on sleep, mood, cardiovascular parameters, weight gain, and growth, with a focus on how these findings translate to clinical practice.

Results: In a 30-month trial of 230 treatment-na+»ve youth with ADHD, CNS stimulants were associated with reductions in weight gain and growth. Increasing monitoring of weight, caloric supplements, and drug holidays all significantly improved weight but did not significantly impact growth. In a crossover trial of osmotic release oral system (OROS) methylphenidate and atomoxetine in 230 youth with ADHD, rates of parent-reported sleep problems were 21%, with higher rates in the stimulant arm. Although children took more time to fall asleep in the stimulant arm, they exhibited greater weekend sleep duration. The impact of CNS stimulants on cardiovascular parameters was assessed over 30 months in 167 medically healthy, treatment-na+»ve children with ADHD. Mean elevations in blood pressure and pulse were minor and similar across stimulant formulations and class. BMI moderated results, with larger elevations seen in youth with the lowest BMIs. In a trial of 260 patients with ADHD and high levels of aggression, participants underwent open flexible optimization of their CNS stimulant. Between 17% and 25% experienced some degree of adverse emotional effects that often resolved with change in agent or dose. Another 15% had their aggression and irritability abate, whereas only a few children experienced intolerable emotional effects at any dose.

Conclusions: Systematic assessment of adverse events improves tolerability of CNS stimulants. Most children taking CNS stimulants will not experience problematic changes in pulse or blood pressure. There are efficacious methods for reducing irritability and aggression and for promoting sleep and weight gain in youth taking CNS stimulants. ADHD, PPC, MAE

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J Am Acad Child Adolesc Psychiatry. 2018;57:S125-S126.

WHAT'S NEW IN SUBSTANCE USE DISORDERS AND ADHD IN ADOLESCENTS AND ADULTS?

Wilens T.

Objectives: The goal of this session is to review articles chosen by the Lifelong Learning Committee that address current concepts and understanding in the following areas: 1) diagnosis of ADHD in adults; 2) longer-term course of ADHD and its relationship to treatment; 3) facilitating youth who have had special education into adulthood; and 4) novel substances of misuse in adolescents.

Methods: This presentation reviews articles from the following perspectives: 1) importance/context; 2) participants; 3) hypotheses, study design, and findings; 4) implications for clinical practice; and 5) limitations and recommendations for future practice and research.

Results: The studies report the following: 1) approximately 50% of children with ADHD will persist with the disorder into adulthood with noted predictors of remission those with remitted ADHD fared better than those with persistent ADHD and new-onset adult ADHD cases are appearing more in the literature; 2) treatment of ADHD seems to reduce the ultimate risk for substance use disorders; and 3) new natural and synthetic substances of abuse are being used by adolescents some compounds for which little is known; and 4) children and adolescents with special educational accommodations pose special challenges when transitioning into adulthood.

Conclusions: Many children with ADHD continue to have persistent ADHD into adulthood, with particular challenges posed when there are special educational requirements. The diagnosis of adult-onset ADHD appears to be complex and may reflect varying degrees of cognitive changes, comorbidity, or effects of substances as opposed to truly new-onset cases. Treatment of ADHD seems to reduce the overall risk for substance use disorders. New and potent substances of abuse pose serious health risks to adolescents. ADHD, SUD, OTH

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ADHD TREATMENTS FOR CHILDREN: PARENT PERSPECTIVES.

Vitulano LA, Saunders DC, Kober H, et al.

Objectives: ADHD occurs in 11% of children. Although there is a plethora of available treatments for ADHD, little is known about how parents of children with ADHD perceive available treatments. The purpose of this surveyΓÇöand exploratory analysis is to address this gap.

Methods: Parental impressions of available ADHD treatments were collected through an anonymous 14-item survey. Parents were recruited through Amazon Mechanical Turk (MTurk). All procedures were approved by the Yale Institutional Review Board.

Results: Six hundred parents of children with ADHD completed the survey; 568 responses were validated and included in the analyses. Parents tried an average of 4.49 interventions (SD = 2.63). The most common treatments that parents had tried were as follows: 1) the child meeting with a therapist (65.5%); 2) the parent meeting with a therapist (49.5%); 3) parent training (41.2%); 4) skills training for the child (35.2%); 5) vitamins (28.5%); 6) diet modifications (26.8%); and 7) medication (25.5%). The most important parent-rated factors in treatment selection, in descending order, were as follows: 1) trust or comfort with the provider; 2) research support for treatment efficacy; 3) the child liking the intervention; and 4) a doctor's recommendation. Strategies that participants rated as most helpful in their parenting practices were the use of a reward system (66.7%) and praise (58.6%). The most common strategies that parents reported that they wanted to incorporate into their parenting included exercise (68.1%), healthy eating habits (63.9%), and outdoor activity (53.0%). Parents also reported wanting children to learn emotional coping skills (70.4%), study habits (57.9%), mood and temper management (52.5%), and time management (49.6%). Parent-reported barriers to treatment included cost, convenience, and availability.

Conclusions: The findings show that parents most commonly try child and parent therapy but also more than 4 interventions. Trust in the provider, research support, and the child's preference are the most important factors in treatment selection. Parents find reward systems and praise to be the most helpful parenting strategies, but they also desire to incorporate other parenting strategies. However, parents encounter significant treatment barriers, and many parents wish that other treatments were available. ADHD, TREAT

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ON-CAMPUS SUPPORT, ACCOMMODATIONS, AND MENTORSHIP FOR LEARNING DISABLED AND ADHD STUDENTS.

Soutra M.

Objectives: Many college students with ADHD and specific learning disabilities (SLDs) leave for school with fewer supports than they had in high school and are less likely to seek out supports. Although more than 90% of those individuals use accommodations in high school, only 17% use them in college; many no longer identify as having SLD/ADHD. Nonetheless, self-awareness, self-advocacy, and connection to a supportive community are essential to successful outcomes in college. Mentoring programs of K–12 school-age children with SLD/ADHD are helping college students with SLD/ADHD access services in college and to self-advocate.

Methods: Discussion of the Eye To Eye mentorship model. This program trains college students who have SLD/ADHD so that they can serve as mentors for local children with SLD/ADHD. A review of the 18-week art-based curriculum that serves as the basis of the mentoring model will be provided. Preliminary efforts to assess outcomes will be reviewed along with case examples that highlight the benefits of developing a personal advocacy plan.

Results: Previous research found that mentoring programs designed to teach character traits to students with SLD/ADHD led to the following: 1) increased social competence; 2) increased homework completion; and 3) more satisfying school experiences. Involvement predicts success via improved self-awareness, perseverance, and reliance on social support systems. Pilot data and clinical experience show that college students with SLD/ADHD are more actively engaged in self-advocacy following involvement in the Eye To Eye mentorship program. Through promoting self-awareness and self-advocacy, these college students develop their own self-advocacy skills.

Conclusions: The Eye To Eye mentorship program and arts-based curriculum offer an intervention to K–12 students through college mentors who have SLD and ADHD. The program has benefited the mentors by increasing their self-advocacy skills, enhancing self-awareness, leading to enhanced willingness to identify on campus as a student with SLD/ADHD, and by increasing the likelihood of registering at the campus accessibility office and seeking accommodations. Research findings have shown that homework completion and attitudes toward school improved following a mentoring program for students with SLD and ADHD. COLST, ADHD, LD

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LOSING SLEEP OVER ADHD AND STIMULANTS?

Stein MA.

Objectives: The goal of this session is to increase the understanding of the effects of ADHD medications on sleep in youth with ADHD by reviewing previous studies and a recent comparative effectiveness study [Methylphenidate-Atomoxetine Crossover (MACRO) Study].

Methods: We will first review literature on the sleep effects of ADHD treatment and discuss the impact of methodological issues, such as subject ascertainment, titration, dose, length of trial, and ways that sleep is measured on findings. We will then describe the effects on sleep from the MACRO Study, a 2-site, double-blind crossover, comparator trial of methylphenidate (MPH) and atomoxetine (ATX), using a flexible dosing titration in 230 children and adolescents.

Results: In the MACRO study, global sleep problems assessed with a previously validated scale occurred in 21% of the participants. The most common sleep problems reported at baseline were as follows: 1) takes

>30 minutes to fall asleep (23.9%); 2) grinds teeth (19.3%); 3) snores (16.4%); 4) too much energy to sleep (13.4%); 5) talks in sleep (11.7%); and 6) excessive movements in sleep (10.5%). When comparing the effects of MPH (mean dose = 51.3 mg; SD = 17.8) at the end of ATX treatment (mean dose = 1.3 mg; SD = 0.5), there were significant increases in insomnia symptom scores on MPH compared with ATX (p = 0.01). When receiving MPH, 23.4% displayed nightly insomnia at end-of-treatment evaluation compared with 11.9% when receiving ATX. Weekend sleep duration was greater on MPH compared with ATX.
Conclusions: All ADHD medications can affect sleep. Stimulants increase sleep-onset latency and decrease total sleep duration. Effects are dose and time dependent, and younger and smaller children are at increased risk of insomnia. Although some children may have more challenges with sleep onset while on MPH than on ATX, once asleep they may sleep for greater total duration on weekends when there are less external constraints on wake times. This study highlights the importance of examining weekend sleep separately and raises questions about the characteristics of weekend catch-up sleep among youth with ADHD. A clinical implication is that if the child is hard to wake up on school days or sleeps longer on weekends, they may be showing signs of not getting enough sleep. Intermediate-duration stimulants or ATX are considered for combination treatment in cases in which sleep onset or duration is of concern. ADHD, STIM, SLP

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PREVALENCE OF BULLYING IN TYPICALLY DEVELOPING CHILDREN AND CHILDREN WITH ASD AND/OR ADHD.

Roberts TM, Roberts A-M, Hinton L, et al.

Objectives: Some studies have shown that children with ADHD and/or ASD are more likely than other children to experience bullying. However, one study found that bullying in children with ASD may be moderated by comorbid ADHD. Because of these varied results, I decided to measure the level of bullying experienced among typically developing children versus children with ASD and/or ADHD.
Methods: Subjects with clinical diagnoses of ASD and/or ADHD (n = 44) were obtained through the University of California Davis (UCD) Behavioral Health Clinic and MIND Institute Clinic. Typically developing subjects (N = 692) were obtained at a local middle school. The subjects were separated into a clinically verified diagnosis group, typically developing group, and self-reported diagnosis group. The Victimization Scale and the Adolescent Peer Relations Instrument (APRI) were completed anonymously by all subjects. Statistical analysis is as follows: bullying behaviors were left-skewed, with many values at the minimum, rescaled by subtracting the minimum score so that a value of 0 corresponded to no bullying. Because of overdispersion, negative binomial regression models used to estimate differences between diagnosis groups, whole accounting for age. All models included the following fixed terms: group [clinical, self-reported, typically developing, age (in years)].
Results: Estimated difference between clinical and typically developing groups on the Victimization Scale, APRI victimization behaviors scale, and APRI aggressive behaviors scale, respectively (with SE within parentheses), are as follows: 0.12 (0.26); 0.16 (0.22); and Γêǽ0.57 (0.25); p < 0.05. Estimated difference between self-reported and typically developing groups on the respective scales listed above are as follows: 0.27 (0.22); 0.32 (0.19), p < 0.10; 0.48 (0.21), p < 0.05.
Conclusions: Children with a clinically verified diagnosis of ASD and/or ADHD are less likely to be aggressors, and children that self-report a diagnosis of ASD and/or ADHD are more likely to be aggressors than typically developing children. I can venture to hypothesize that those children receiving care at UCD and the MIND Institute may have better access to interventions, in general, such as social skills groups that would be protective, but further studies are required to explore this thought. ADHD, ASD, BLY

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THE BURDEN OF ADHD IN CHILDREN AND ADOLESCENTS AS PERCEIVED BY CAREGIVERS AND THE DIAGNOSED INDIVIDUAL.

Robertson B, Farahbakhshian S, Andreini M, et al.

Objectives: Children/adolescents with ADHD face significant disease burden. We compared disease burden perceptions in children/adolescents with ADHD and caregivers of children/adolescents with ADHD.

Methods: An online survey was conducted with children/adolescents (ages 6–17 years; n = 174) with ADHD currently treated with stimulants and with caregivers (n = 300). ADHD burden on daily activities was rated on a 5-point scale (1, no effect; 5, significantly hurts ability), with high burden defined as ratings of 4 or 5. Between-group comparisons used 2-sample t tests (continuous variables) or Chi-square tests (categorical variables).

Results: High ADHD burden on daily activities was reported by 51% of children/adolescents and 43% of caregivers. Significantly greater percentages of children/adolescents versus caregivers reported high ADHD burden during the school year (60 vs 45%, $p < 0.05$) and the school week (58 vs 47%, $p < 0.05$). Across the day, a significantly greater percentage of children/adolescents versus caregivers reported high ADHD burden during the later part of the school day (51 vs 36%, $p < 0.05$). A significantly greater percentage of children/adolescents versus caregivers reported that their ADHD medication started to wear off during the later part of the school day (32 vs 21%, $p < 0.05$), and a significantly lower percentage reported that their ADHD medication started to wear off at dinner (17 vs 26%, $p < 0.05$). Furthermore, significantly greater percentages of children/adolescents taking long-acting (LA) stimulants reported high ADHD burden during the later part of the school day (49 vs 30%, $p < 0.05$) and during after-school activities/afternoon homework (55 vs 39%, $p < 0.05$) compared with the caregivers of children/adolescents taking LA stimulants.

Conclusions: Despite stimulant medication use, children/adolescents with ADHD and caregivers reported high ADHD burden. Greater percentages of children/adolescents than caregivers perceived ADHD burden to be high, with differences in perceived burden being especially pronounced in children/adolescents taking LA stimulants. These findings suggest that caregivers may underestimate ADHD burden and support the need for improved ADHD management. ADHD, ADOL, IMP

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J Am Acad Child Adolesc Psychiatry. 2018;57:S134.

ASSESSMENT AND MANAGEMENT OF ADHD IN YOUTH WITH ASD.

Yerys B.

Objectives: The DSM-5 is the first diagnostic manual to allow clinicians to make concurrent diagnoses of ASD and ADHD. ADHD is now one of the most common comorbidities for youth with ASD. Diagnosis of ADHD is complicated by parents and teachers who do not know whether the observed behaviors are truly related to ADHD symptoms of inattention and hyperactivity/impulsivity or whether they are related to the social demands of a situation. These measurement issues can interfere with accurate diagnosis and treatment of these behaviors and may be a key contributor to the relatively poorer long-term prognosis of youth with diagnoses of ASD and ADHD. The objectives of this session are as follows: 1) to review recent literature on phenomenology, psychological factors and functional outcomes, and pathophysiology of ADHD in ASD; and 2) to review treatment data for symptom management in youth with ASD with and without intellectual disability.

Methods: Data on phenomenology, risk, pathophysiology, and treatment will be obtained from a PubMed and PsycINFO search of published studies within the last 18 months, as well as a recent secondary analysis study on 414 youth with ASD.

Results: Approximately half of youth with ASD without intellectual disability meet a DSM-5 categorical definition of ADHD, and more exhibit significant symptoms of ADHD. Preliminary data suggest that cognitive and adaptive behaviors are more impaired as ADHD symptoms increase and that ADHD is associated with physiological abnormalities. A lower percentage of youth with ASD and ADHD responds to pharmacological treatments, and there is a higher rate of significant side effects. No evidence-based behavioral treatments for ADHD have been evaluated in ASD.

Conclusions: Youth with concurrent ASD and ADHD diagnoses represent a high-risk segment of the ASD population, even for those with average or better IQ. A number of challenges remain in both the diagnosis

and treatment of ADHD in ASD, and further research is needed to improve measurement of ADHD, the phenotype, treatment success, and long-term prognosis. Until more data are available, clinicians are advised to use careful clinical interviewing paired with current ADHD instruments for diagnosis and to apply common behavioral treatment modifications for children with ASD when targeting ADHD with behavioral approaches. ADHD, OTH, CM

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INFLUENCE OF DEPRESSION AND SCHOOL ON QUALITY OF LIFE IN PATIENTS WITH ADHD IN SOUTH KOREA: COMPARISON BETWEEN PATIENTS□ÇÖ AND PARENTS□ÇÖ VIEWS.

Park B-E, Ock S-M, Lee J-S.

Objectives: The purpose of this study was to investigate the effects of various factors related to ADHD on the quality of life (QOL) of those who have ADHD. We compared separately the patientsΓÇÖ and parentsΓÇÖ points of view on the QOL of ADHD and the differences between them. Methods: PatientsΓÇÖ self-reported quality of life was measured by PedsQL (Pediatric Quality of Life Inventory) 4.0 self-report; depression was measured by CDI (Children's Depression Inventory), and anxiety was measured by RCMAS (Revised ChildrenΓÇÖs Manifest Anxiety Scale). QOL of the patient was measured by PedsQL 4.0 parent-proxy report; ADHD symptoms were measured by Conner's parent-rating scale. A total of 66 patients with ADHD (age 10.68 -¦ 2.61 years, 55 boys) and their parents completed the survey. The paired T-test, Pearson correlation analysis, and multiple regression analysis were used.

Results: Mean score of PedsQL self-report in school (42.54 -¦ 40.22) was very low compared with those with somatic symptom (83.27 -¦ 15.26), emotional (76.92 -¦ 20.51), and social (75.92 -¦ 23.01) disorders. There was a significant difference in the QOL in school between PedsQL self-report (42.54 -¦ 40.22) and parent report (65.00 -¦ 14.03; $p < 0.01$). However, the overall mean score of PedsQL self-report was 78.39, which was significantly higher than PedsQL parent-proxy report mean score of 68.66 ($p < 0.001$). The total score of PedsQL self-report was correlated with CDI and RCMAS (Pearson coefficient = ΓêÆ0.601, ΓêÆ0.556). The total score of PedsQL parent-proxy report was correlated with the CPRS total score (Pearson coefficient = ΓêÆ0.431). Multiple regression analysis showed that PedsQL self-report and PedsQL parent-proxy report were significantly predicted by CDI (+¦ coefficient = ΓêÆ1.147, standardized +¦ coefficient = ΓêÆ0.603) and Comprehensive Psychopathological Rating Scale (+¦ coefficient = ΓêÆ0.398, standardized +¦ coefficient = ΓêÆ0.417), respectively.

Conclusions: Our study showed that quality of life in school was very low by self-report in patients with ADHD in South Korea. There is a clear difference between what patients and their parents think about their quality of life in school. In addition, our results show that the accompanying depression greatly affects the quality of life for patients with ADHD. It seems to be important to treat the associated depressive symptoms to improve the quality of life in ADHD. ADHD, DDD, SAC

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J Am Acad Child Adolesc Psychiatry. 2018;57:S299.

ADOLESCENT ADHD IN PEDIATRIC PRIMARY CARE: CLINICAL CHARACTERISTICS AND STIMULANT DIVERSION RISK.

Molina BSG, Pedersen SL, Kipp HL, et al.

Objectives: Most stimulant treatment for pediatric ADHD is prescribed in primary care, yet little is known about the clinical characteristics and diversion risk of this population. This study addresses this knowledge gap by describing the baseline sample group of adolescents participating in a cluster-randomized trial of provider training in clinical practice strategies to prevent stimulant diversion.

Methods: Patients were ages 13–18 years (mean age = 15 years, 78% male, 89% white) and prescribed stimulants for ADHD at 1 of 7 pediatric practices. Patients and parents completed questionnaires on clinical histories and diversion risk factors. Cohort 1 included 174 patients and provided initial results; data from cohort 2 (n = 173 to date; data collection to close in 2/18) will be added before presentation.

Results: By parent report, most patients (68%) were first diagnosed with ADHD in elementary school. More than half were diagnosed by a pediatrician (61%). The mean age of first ADHD medication and the first years

of ADHD medication were 9 (SD = 2.77) and 6 years (SD = 2.82), respectively. Few ever stopped medication for >6 months (most common reasons: side effects, summer holidays, experimenting). It is surprising that only 62.2% reported >5 DSM-5 symptoms of inattention and/or impulsivity-hyperactivity when not medicated (parent report). The average grade in school is and most (78%) plan to graduate from college; serious conduct problems (17%, according to parent report) were comparable to tertiary clinic-referred sample groups; and lifetime substance use (31% alcohol, 15% marijuana) was comparable to national rates. Tobacco use (23%) was high. A third of teenagers (35%) reported depression or anxiety. Only 8% were approached to divert their stimulant medication (one diverted); intentions to divert were generally low (only 13% reported something other than ΓÇ£I definitely will not). The age of first diagnosis was unrelated to most variables except those related to treatment (eg, years medicated).
Conclusions: Most teenagers treated for ADHD in pediatric primary care predominantly had onset in childhood. However, monitoring for continued medication need may be important given the apparent perception by some parents and teenagers that nonmedicated symptoms have a subthreshold. At mean age 15 years, diversion is infrequent and may present an opportunity for prevention. ADHD, ADOL, STIM

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DOES PARENTAL TRAINING IN CHILDREN WITH ADHD OFFER BETTER OUTCOMES IN RESPECT TO TREATMENT AND PARENTAL STRESS?

Warren L.

Objectives: Behavioral parental training (BPT) and stimulant medication are evidenced-based treatments for children with ADHD. Although effectiveness of BPT as a stand-alone therapy has been demonstrated, there remains variability in the degree in which BPT effects enhancement with stimulant medication (routine clinical care) and the degree of improvement in ADHD symptoms. The types of BPT explored include the New Forest Parenting Package (NFPP), which is a home-based intervention, and Helping the Noncompliant Child (HNC), which is an established clinic-based intervention. The aim of this study was to evaluate the effectiveness of BPT in routine clinical care (RCC), ADHD symptoms, types of BPT, and parental stress.
Methods: A systematic review was conducted identifying all relevant studies from 2007 to 2017, with comparative data on BPT plus RCC children with ADHD compared with children receiving RCC. The primary outcome was effectiveness of BPT in RCC in children and adolescents (ages 3–12 years). Secondary outcomes included improvement of ADHD symptoms, types of BPT, and parental stress. Statistical analysis was done using random-effects meta-analysis to compare the mean value of the 2 groups (Comprehensive Meta-Analysis Version 3.3.070 software; Biostat Inc., Englewood, NJ).
Results: Four studies were quantitatively assessed and included for meta-analysis, which comprised 4 randomized, controlled studies. Among the 4 studies, 231 children received BPT plus RCC, and 198 children received RCC. BPT plus RCC was not associated with greater medication enhancement (0.184 -¦ 0.103; p = 0.07) compared with RCC. There was no improvement of ADHD symptoms in the BPT plus RCC group and RCC group (0.178 -¦ 0.146; p = 0.22) or a significant difference in the types of BPT (0.138 -¦ 0.132; p = 0.29) when comparing 2 of the 4 studies. There was a significant improvement in parental stress in the BPT plus RCC group (0.644 -¦ 0.103; p < 0.0001) compared with the RCC group.
Conclusions: BPT as an adjunct with RCC did not enhance the effectiveness of stimulant medication or improve ADHD symptoms compared with RCC. There was no comparative therapeutic difference when using NFPP, which is a home-based intervention, compared with use of HNC, which is an established clinic-based intervention. BPT plus RCC was found to be efficacious in reducing parental stress compared with RCC. ADOL, ADHD, PAT

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J Am Acad Child Adolesc Psychiatry. 2018;57:S22.

SLEEP PROBLEMS COMORBID WITH ADHD: RATIONAL APPROACH TO TREATMENT.

Owens J.

Objectives: This Clinical Perspectives will as follows: 1) provide an update on the most common sleep disorders comorbid with ADHD in children and adolescents, including behavioral insomnia, delayed sleep-wake phase disorder, sleep-disordered breathing and restless legs syndrome/periodic limb movement disorder; 2) review empirically supported behavioral treatments for ADHD-related insomnia; and 3) present an outline to assist the child mental health professional in developing a practical and rational approach to both the selection of ADHD medication regimens and the use of sedative hypnotic drugs in patients with ADHD or at risk for insomnia.

Methods: This presentation will draw upon a comprehensive literature review, lecture and discussion, and case presentations.

Results: Sleep disorders, such as obstructive sleep apnea and restless legs syndrome, are common comorbidities in children with ADHD. These may either exacerbate ADHD symptoms or in some cases be the primary cause of ADHD symptoms. Other sleep disorders, such as delayed sleep-wake phase disorder and insomnia, also appear to be significantly more common in these children and may be more intrinsic to ADHD. Thus, the child mental health professional needs to have an approach to evaluating the relative contribution of sleep problems to the daytime manifestations of ADHD. Although many behavioral interventions for insomnia are common across different mental illnesses, there is an emerging literature supporting unique approaches in children with ADHD. Finally, the role of ADHD medications, including stimulants and nonstimulants and specifics such as dosage and timing, are important to consider in evaluating emerging sleep problems in these children. In addition, the appropriate use of sedative hypnotic drugs should be based as much as possible on existing empirical evidence and clinical experience.

Conclusions: The current status of knowledge regarding comorbid sleep disorders in ADHD and the selection of both behavioral and pharmacological interventions will be discussed in detail during the presentation. ADHD, SLP, TREAT

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J Am Acad Child Adolesc Psychiatry. 2018;57:S307.

NOVEL APPROACHES IN ADHD CLINICAL TRIALS: IMPLICATIONS FOR STUDIES OF CURRENTLY AVAILABLE AND EMERGING TREATMENTS.

Newcorn JH, Wilens T.

Objectives: We will present novel and clinically relevant measures and designs for clinical trials with existing and emerging ADHD treatments and provide a rationale for understanding therapeutic effects and how to implement treatments in the real world.

Methods: Four studies are presented, each of which uses a different innovative method. 1) Steve Faraone, PhD, describes the value of the sequential parallel comparison design to detect a small but significant signal in a multisite trial of a medical food in adults with ADHD; 2) Tim Wigal, PhD, demonstrates the benefit of using an individualized measure of impairment in a clinical trial (the Target Impairment Scale) to ground the assessment of symptoms before and after treatment in a phase 2 study with mazindol controlled release (CR); 3) Mark Stein, PhD, used a sequential multiple assignment randomized trial (SMART) designed to answer questions about the sequencing of behavior therapy and maternal stimulant treatment in parent–child dyads with ADHD; and 4) Jeffrey Newcorn, MD, conducted a large, randomized cross-over trial of osmotic-release oral system-methylphenidate (MPH) and atomoxetine (ATX) to provide data on sequencing treatments.

Results: 1) The SPCD design was valuable in detecting a signal in favor of the medical food; the significant separation between drug and placebo was greatest during phase 2 among the placebo nonresponders. Had this design not been used, the positive effect of the performance-enhancing drug (PED) would have been missed. 2) The Target Impairment Scale used in the mazindol CR trial likely contributed to the robust response in favor of mazindol CR and provided an important functional reference for the magnitude of symptomatic improvement. 3) In the SMART design trial, parents who received medication + behavioral treatment showed the highest levels of positive parenting and the lowest levels of negative parenting at 16 weeks, highlighting the importance of multimodal treatment. 4) The MPH-ATX cross-over study showed the

expected findings in favor of MPH, but there were a relatively large number of families who preferred to be treated with ATX after treatment with both drugs, and ATX performed considerably better when given first.
Conclusions: Novel measures and clinical trial designs can provide important information regarding existing treatments and highlight the potential for bridging the gap between efficacy studies and clinical utility for both existing and investigational treatments. ADHD, PPC, IMP

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J Am Acad Child Adolesc Psychiatry. 2018;57:S316.

POLYGENIC SCORE AND SUBCORTICAL BRAIN STRUCTURES: PARSING THE GENETIC CONTRIBUTION TO ADHD BRAIN FINDINGS.

Nikolas MA, Momany A, Mooney M, et al.

Objectives: This presentation will evaluate subcortical structures associated with ADHD for their relationship to common genetic risk in ADHD.
Methods: A total of 587 youth (ages 7–13 years) completed a multistage, multi-informant diagnostic assessment process and underwent MRI with a 3T Siemens scanner to measure cortical and subcortical brain volumes that were evaluated using published methods. Salivary DNA was obtained, and 603,132 single nucleotide polymorphisms (SNPs) were assayed using the Illumina PsychChip. Genotype imputation was performed using the 1000 Genomes phase 3 reference panel. A polygenic risk score was derived based on the Psychiatric Genetics Consortium data (20,183 ADHD, 35,191 control subjects; a second score used 19,099 cases, 34,194 control subjects of Northern European ancestry only), by retaining linkage disequilibrium (LD)-clumped SNPs with $p < 0.5$ ($N = 193,692$; for the European-only score, $n = 139,934$) and then multiplying the number of risk alleles by the log odds association in the discovery dataset and averaging over all SNPs. A total of 324 unrelated Caucasian youth (209 ADHD, 115 control subjects), who passed MRI quality controls, were retained for analyses. Because the subcortical volumes were highly intercorrelated, a latent variable model was created to index the development of subcortical structure and circuitry for the path model analysis after initial data description.
Results: MANCOVA indicated significant differences in subcortical volumes among ADHD and non–ADHD youth ($p = 0.002$, $= 0.076$) when controlling for age, sex, and movement in the scanner. Follow-up univariate analyses indicated significantly smaller volumes for ADHD youth in the cerebellum ($p = 0.001$), putamen ($p = 0.003$), pallidum ($p = 0.026$), and hippocampus ($p = 0.021$). Significant indirect effects of subcortical volumes emerged for the latent subcortical volume variable ($+¦ = 0.12$, $p = 0.015$), such that higher polygenic risk was associated with reduced subcortical volume in these regions ($+¦ = –0.40$, $p < 0.01$). Smaller subcortical volumes in turn statistically predicted ADHD hyperactive symptoms ($+¦ = –0.29$, $p = 0.003$), resulting in a reliable mediation effect.
Conclusions: These data are believed to be the first demonstration using molecular data that structural volume variation in subcortical brain regions partially explains polygenic association with ADHD symptom severity. ADHD, NIMAG, GS

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J Am Acad Child Adolesc Psychiatry. 2018;57:S225-S226.

ROLE OF S-ADENOSYL METHIONINE, ZINC, AND MAGNESIUM IN MANAGEMENT OF PEDIATRIC DEPRESSION AND ADHD.

Zeshan M, Ali AA, Deister D, et al.

Objectives: The main objective of our literature review is to summarize the available evidence on the individual nutrient role of SAMe (S-adenosyl methionine), Mg (magnesium), and Zn (Zinc) in pediatric depression and ADHD to educate health care providers on possible mechanisms of action and their possible side effects.
Methods: Literature was searched using the MeSH (medical subject headings) terms child*, adolesc*, youth, S-adenosyl methionine, zinc, magnesium, depression, and ADHD for articles indexed in PubMed and Google Scholar. Our search was not limited by a year cutoff considering the paucity of articles, but it was limited to children and adolescents. References in reviews and systematic reviews generated by the search

strategy were also reviewed for additional literature. Study methods, sample group size, interventions, and outcomes were tabulated.
Results: A total of 90 articles were reviewed, 34 were shortlisted based on inclusion criteria consisting of observational studies, controlled and uncontrolled trials, and case series. Although well studied in adults, data supporting the use of SAMe in pediatric depression are limited to a case series of 3 children, its role in ADHD has not been examined. Poor dietary Mg intake is associated with depression, whereas Mg prophylaxis in children with a migraine has shown some improvement in depressive symptoms. The role of Mg in ADHD was mixed with some studies reporting an associated deficiency, whereas others suggest an excess. Mg supplementation in deficiency showed improvement in ADHD symptoms. Evidence showed an association of Zn deficiency with depression. One double-blind RCT demonstrated improvement in depressive symptoms in patients with comorbid anorexia nervosa with Zn supplementation. Blood serum levels of Zn were reduced in children with ADHD compared with control subjects. Variations of oral Zn supplementation have shown symptom improvement and lowers optimal stimulant dosing. Gastrointestinal symptoms were common to all 3 nutrients.
Conclusions: SAMe, Zn, and Mg may have a role in pathogenesis and treatment in pediatric depression and ADHD. Current data, although emerging, are still equivocally limited only to nutrient deficient states and, at best, adjunctive to psychotropic and stimulant agents. High quality, randomized studies are needed to further our understanding of their role in treatment and side effects. DDD, EDUC, ADHD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S308.
STIMULANTS OR NONSTIMULANTS FOR ADHD: WHAT CAN RESULTS FROM A HEAD-TO-HEAD COMPARATOR CROSSOVER STUDY TEACH US ABOUT TREATMENT ALGORITHMS?
Newcorn JH.
Objectives: Current treatment algorithms recommend stimulants as the first medication option for youth with ADHD, unless there are mitigating circumstances in which case they would switch to a different stimulant or nonstimulant if treatment is unsuccessful. However, few studies have examined the comparative efficacy of stimulant and nonstimulant medications as a function of treatment order, which is essential for algorithm development.
Methods: We compared methylphenidate (MPH) and atomoxetine (ATX) in a randomized, double-blind, cross-over study (3–6 weeks of each medication, separated by a 2-week placebo washout). Multiple group-latent growth curve models were used to estimate the effects of the drug (ATX vs MPH) on block 1 and block 2 changes in ADHD symptoms and symptom severity. Response rates were calculated by drug and block. Latent transition analyses examined the effect of order on responder status. Preference was determined under blinded conditions through a combination of direct contact and chart review.
Results: A total of 232 children, ages 7–17 years (mean = 10.41; SD = 2.72) were randomized, and 199 completed both treatments. Mean doses were 54 (18.02) mg for MPH and 1.35 (0.47) mg/kg for ATX. Overall, MPH was associated with a better symptomatic response (d = ΓêÆ0.17 in block 1; ΓêÆ0.34 in block 2) and was preferred by more families; however, there was considerable individual variability. Response to MPH was approximately equivalent whether given first or second, whereas ATX was relatively better in the first block. After the trial, although blind to condition, approximately 50% of families chose to continue treatment with MPH, approximately 35% chose ATX, and approximately 15% chose neither MPH nor ATX. ORs for the prediction of medication used after the trial favored the medication used first, but this was more dramatic for ATX (OR = 8.68 for block 1 excellent responders). Path analyses show that MPH nonresponders in block 1 almost never became excellent responders to ATX.
Conclusions: Response to both medications was good to excellent, with an overall larger effect for MPH, which was consistent with findings from previous studies. Responder profiles and treatment preference also supported the interpretation that MPH was superior to ATX. However, the large number of families who preferred ATX and the fact that ATX did substantially better when given first have important implications for the sequencing of treatments and algorithm development. ADHD, PPC, TREAT

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J Am Acad Child Adolesc Psychiatry. 2018;57:S315-S316.

COMMON RISK VARIANTS IN MOLECULAR GENETIC DATA AND COGNITIVE AND EMOTION ENDOPHENOTYPES IN ADHD: THE POWER OF LATENT VARIABLE MODELS.

Nigg J, Gustafsson H, Karalunas S, et al.

Objectives: This presentation will evaluate competing theories of neurocognitive endophenotypes for ADHD using common genetic variation indexed by genomewide data in a case control design.

Methods: A total of 514 unrelated youth (aged 7–13 years) of homogenous European ancestry (n = 337 ADHD; n = 177 non–ADHD) completed an extensive research diagnostic evaluation and a neuropsychological and cognitive research battery; parents rated temperament dimensions. Salivary DNA was obtained, and 603,132 single nucleotide polymorphisms (SNPs) were assayed using the Illumina PsychChip. Genotype imputation was performed using the 1000 Genomes phase 3 reference panel. A polygenic risk score was derived based upon the Psychiatric Genetics Consortium data (20,183 ADHD, 35,191 control subjects; 19,099 case subjects, 34,194 control subjects of Northern European ancestry), by retaining linkage disequilibrium (LD)-clumped SNPs with $p < 0.5$, multiplying the number of risk alleles by the log odds association in the consortium dataset, and averaging over all SNPs. Structural equation modeling was used to create reliable latent variables for neurocognitive constructs following evidence that this enhances the genetic signal.

Results: The polygenic risk score for ADHD was related to multiple cognitive endophenotypes, including working memory ($p < 0.001$) and arousal/alertness ($p < 0.001$) after appropriate correction for multiple testing. Response inhibition did not relate to the polygenic score. The statistical path model represents a theorized causal process. Results show that working memory and arousal/alertness statistically mediate the association between the polygenetic risk score and the ADHD symptoms (both indirect path $p < 0.01$; 25–40% of the genetic effect explained). Analysis used temperament measures to assess emotional regulation as another endophenotype related to concerns about irritability as a feature of ADHD. That result demonstrates partially independent contributions of the polygenic score to ADHD via working memory and negative emotionality (related to irritability).

Conclusions: Molecular genetic data examining common genetic variation in a polygenic score framework can differentiate hypothesized cognitive endophenotypes for ADHD, suggesting which ones are most likely to participate mechanistically in genetic aspects of ADHD etiology. ADHD, NIMAG, GS

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J Am Acad Child Adolesc Psychiatry. 2018;57:S308.

A PILOT SMART TARGETING MULTIPLEX ADHD FAMILIES: LESSONS LEARNED.

Stein MA, Chronis-Tuscano AM.

Objectives: ADHD is common in parents of children with ADHD, and little is known about how to select, sequence, or combine treatments in multiplex families in which both a child and a parent have ADHD. We will illustrate how a sequential multiple assessment randomized trial (SMART) design can be used to answer questions about sequencing treatment and to aid in clinical decision making, using an example of an unrestricted pilot, SMART.

Methods: Over a 3-year period, 35 dyads consisting of a child aged 3–8 years with ADHD symptoms not yet treated with stimulant medications and a mother with ADHD were first randomized to receive 8 weeks of behavioral parent training (BPT) or individually titrated maternal stimulant medication (MSM). After reevaluation, dyads were then rerandomized to receive combination treatment or augmented first-line treatments.

Results: Recruitment was challenging, but once enrolled, both BPT and MSM were acceptable and adherence was strong. Medication was well tolerated (17/18 responded to lisdexamfetamine, average dose 42.5 mg, one switched to methylphenidate extended release). At 8 weeks, mothers receiving BPT displayed improvements in Conners Adult ADHD and CGI–Severity Rating Scales compared with BPT ($p < 0.01$). BPT was associated with improvements in observed and ratings of positive and negative parenting ($p < 0.05$). At 16 weeks, parents who received MSM + BPT showed the highest levels of positive parenting and the lowest levels of negative parenting, and their children were more likely to be rated in the normal range on the Impairment Rating Scale in terms of family interactions and overall impairment when they received combined

treatments. Nonetheless, the majority of children remained in the clinical range on ADHD symptom measures following study treatments.
Conclusions: Targeting maternal ADHD first in multiplex families with ADHD children may be more effective if implemented in younger children, and they may require longer and multimodal interventions. Fully powered SMART trials and adaptive intervention trials show considerable promise for informing treatment algorithms that can aid in real-world clinical decision making. ADHD, PAT, STIM

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J Am Acad Child Adolesc Psychiatry. 2018;57:S169.
EFFECT OF DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE (DR/ER-MPH) ON ALL-DAY AND EARLY MORNING ADHD-RELATED SYMPTOMS: ANALYSIS OF ADHD-RATING SCALE-IV AND ADHD-AM-RATING SCALE ITEMS FROM A PHASE 3 TRIAL.
Pliszka SR, Arnold VK, Marraffino A, et al.
Objectives: In a phase 3 trial of children with attention-deficit/hyperactivity disorder (ADHD), treatment with evening-dosed HLD200, a delayed-release and extended-release methylphenidate (DR/ER-MPH), significantly reduced symptoms versus placebo (PBO), as assessed by the ADHD Rating Scale-IV (ADHD-RS-IV), throughout the day and during the early morning. This post hoc analysis evaluated the effect of DR/ER-MPH versus PBO on ADHD-RS-IV inattentive (IA) and hyperactivity/impulsivity (HI) subscales, as well as individual items, rated throughout the day and during the early morning.
Methods: Data were analyzed from a pivotal, randomized, double-blind, PBO-controlled, phase 3 trial of DR/ER-MPH in children (ages 6–12 years) with ADHD (Clinical Trial NCT02520388). Investigators assessed ADHD symptoms by rating 18 items on the ADHD-RS-IV (from 0 = none to 3 = severe). Ratings on the ADHD-RS-IV from 6:00 AM to 9:00 AM (ADHD-AM-RS) were obtained to assess early morning symptoms. After 3 weeks, treatment differences on each item and subscale were evaluated by 2-sided, unpaired t-tests without correction for multiplicity.
Results: The intent-to-treat population included 161 participants. At baseline, mean item scores were comparable between DR/ER-MPH and PBO (ADHD-RS-IV: 2.40 vs 2.42; ADHD-AM-RS: 2.24 vs 2.22). Mean subscale scores were also similar between groups at baseline (ADHD-RS-IV IA: 22.89 vs 22.94; ADHD-RS-IV HI: 20.22 vs. 20.55; ADHD-AM-RS IA: 22.25 vs. 21.83; ADHD-AM-RS HI: 18.06 vs. 18.19). After 3 weeks, both IA and HI subscale scores were significantly reduced with DR/ER-MPH (mean dose: 68.1 mg) versus PBO (ADHD-RS-IV IA: 12.64 vs 16.43, $p = 0.004$; ADHD-RS-IV HI: 11.15 vs 14.73, $p = 0.009$; ADHD-AM-RS IA: 9.38 vs 14.61, $p < 0.001$; ADHD-AM-RS HI: 6.87 vs 10.99, $p = 0.002$). Likewise, individual items were significantly reduced with DR/ER-MPH versus PBO for 15 ADHD-RS-IV and 16 ADHD-AM-RS items. Change score distributions for each item will be presented. No serious TEAEs were reported, and TEAEs were consistent with MPH.
Conclusions: In this post hoc evaluation, DR/ER-MPH treatment resulted in significant improvements on both subscales and across most items on the ADHD-RS-IV and ADHD-AM-RS versus PBO in children with ADHD, showing consistent improvement in symptoms all day and early morning. These findings warrant further study. ADHD, STIM, RCT

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J Am Acad Child Adolesc Psychiatry. 2018;57:S187.
CAN BLOOD CELL MEMBRANE POTENTIAL RATIO (MPR ÄÓ) HELP IN THE ASSESSMENT AND TREATMENT OF ADHD?
Stepanova EA, Young A, Kaplin D, et al.
Objectives: ADHD is diagnosed based on history, clinical interview, and rating scales, which are subjective measures, thereby sometimes making an accurate diagnosis challenging. In a previously conducted pilot study, the whole blood cells membrane potential ratio (MPR) showed promise in identifying individuals with ADHD from others, as well as serving as a biomarker for effective pharmacological treatment. Thus, we hypothesized that the MPR values of blood cells would differ between control subjects and individuals with ADHD, and that pharmacotherapy for ADHD would affect MPR values among youth with ADHD. In this study,

we identified the MPR values of individuals with and without ADHD and assessed the change in the MPR after taking medications for ADHD to test its sensitivity to treatment.
Methods: Forty-four youths (24 individuals with ADHD and 20 individuals with mental illness and healthy control subjects) aged 6–17 years were screened for ADHD and comorbid disorders using the Mini-International Neuropsychiatric Interview (MINI) 7 and the ADHD Rating Scale (ADHD-RS). MPR values were measured on assessment. Patients with ADHD were reassessed at least 1 month after receiving a therapeutic dose of a medication. Analyses included the following: 1) logistic regression to determine the association between MPR values and ADHD diagnosis; 2) calculation of MPR test specificity and sensitivity to help evaluate MPR as a diagnostic tool for ADHD; and 3) paired sample t-tests examining whether mean MPR values significantly differ by whether or not an individual with ADHD is taking medication.
Results: MPR values of youth with ADHD (who were not taking medication for ADHD) did not significantly differ from those of youth in the control group. Overall, the MPR test characterized 54.5% youth correctly; sensitivity was 79.2%, whereas specificity was 25.0%. After excluding an outlier, the paired sample t tests showed that, among youth with ADHD, MPR values were significantly lower when they were taking medication for ADHD compared with when they were not ($p = 0.047$).
Conclusions: Although this study does not support the use of the MPR in the diagnosis of ADHD in youth, a larger study could provide information regarding why preliminary studies with this method initially showed promise as a diagnostic tool. Because the MPR values may change when an individual with ADHD is receiving treatment, further studies need to examine the implications of this preliminary finding. ADHD, DIAG, R

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J Am Acad Child Adolesc Psychiatry. 2018;57:S268.

EFFICACY OF STIMULANT MEDICATIONS FOR PATIENTS WITH DISRUPTIVE BEHAVIOR DISORDERS: A PROSPECTIVE COHORT STUDY.

Parsley IC, Zhang Z, Kratochvil CJ, et al.

Objectives: The extent to which stimulant medications impact the core symptoms of disruptive behavioral disorders (DBD) other than symptoms of ADHD is of scientific debate. Most previous studies have either not clearly provided defined outcomes or have only evaluated DBD in the context of an existing comorbid ADHD diagnosis. The goal of the current study was to determine whether patients (especially younger individuals ages 6 10 years) on stimulants have significantly better Child Behavior Checklist (CBCL) scores on questions related to conduct disorder (CD), ODD, and irritability after behavioral modification program intervention compared with those who have not received stimulant medications.
Methods: Fifty-two participants diagnosed with a DBD, aged 6 10 years, completed the study. Each patient underwent a behavioral modification program for which pre- and postintervention CBCL symptom scores for ADHD, ODD, CD, and irritability were collected. ANCOVA analysis was performed to compare outcome differences between those on stimulant medications and those not.
Results: Paired t-tests showed a statistically significant improvement in CBCL outcomes between pre- and postintervention scores. Further ANCOVA analysis, however, showed no clear improvement in CBCL scores in the stimulant group compared with the nonstimulant. In fact, CBCL scores related to CD were marginally significant in being worse among those receiving stimulants compared with those who were not.
Conclusions: This prospective cohort study provides evidence that stimulant medications may not in fact be beneficial for the core symptoms of DBD outside of ADHD, especially for younger populations. Future study is therefore warranted to evaluate the efficacy of stimulant medications in the treatment of core symptoms of DBD in young children. DBD, STIM, IMD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S318.

INTRACORTICAL FACILITATION AS AN ELECTROPHYSIOLOGICAL SIGNATURE FOR ADHD IN YOUTH WITH ASD.

Pedapati E.

Objectives: The neurological correlates distinguishing youth with ASD and youth with ASD and co-occurring ADHD (ASD+ADHD) is poorly understood, despite evidence that ASD+ADHD youth have higher rates of hospitalization, psychopharmacology, and behavioral concerns than youth with ASD alone. There remains debate if co-occurrence of ADHD in ASD represents a continuum of a phenotype within ASD or a distinct co-occurring condition. Currently, no objective methodology for the diagnosis of ASD+ADHD is available.
Methods: Paired-pulse transcranial magnetic stimulation (TMS) data and relevant behavioral measures were performed based on age- and gender-matched sample groups of those with ASD and ASD+ADHD. These data are baseline measures from recently completed randomized placebo-controlled, single-dose methylphenidate study in youth with ADHD+ASD.
Results: Twenty-four adolescents with ASD+ADHD and 15 adolescents with ASD only (matched by age, gender, IQ, and social functioning) were included in this analysis. No group differences were found in social functioning as measured by the Social Responsiveness Scale. As expected, Conners-3 Scale-Inattention (CPRS-IA), Conners-3 Scale-Hyperactivity (CPRS-H), and Conners-3 Scale-Executive Functioning (CPRS-EF) scores were significantly higher for the group with ASD+ADHD relative to the group with ASD. Paired-pulse TMS measures demonstrated that the group with ASD had significantly enhanced intracortical facilitation (ICF) (mean = 1.26, SD = 0.28, n = 15) compared with subjects with ASD+ADHD (mean = 1.01, SD = 0.22, n = 24; t = 2.6, df = 37, p = 0.01). ICF was significantly inversely correlated with CPRS-EF (r = 0.350; p = 0.029), CPRS-IA (r = Γêǽ0.394; p = 0.013) but not CPRS-H (r = Γêǽ0.083; p = 0.61).
Conclusions: These data demonstrate that ICF, a rapidly obtained paired-pulse TMS measure, remains intact in youth with ASD but is diminished in youth with ASD and co-occurring ADHD. ICF is also associated with clinical variables representing the severity of inattention and executive function in ADHD. A previous study found impaired ICF in youth with ADHD that increased after methylphenidate treatment. Taken together, this may be evidence that ADHD has a distinct electrophysiological signature in typically developing youth or youth with ASD. ICF may represent an emerging biomarker to study the physiology of ADHD in ASD, which may align with disease prognosis or respond to treatment. ASD, ADHD, NM

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J Am Acad Child Adolesc Psychiatry. 2018;57:S323.

MEDICATION AND MATURATION IN GIRLS AND BOYS WITH ADHD IN THE MTA.

Swanson JM, Hanc T, Trampush J, et al.

Objectives: This presentation will show how to assess maturation and medication use on growth using mathematical modeling of height in 112 girls and 437 boys matched for age at entry (8.4 years) into the Multimodal Treatment Study of Children with ADHD (MTA).
Methods: Based on measures of height, milestones of growth (age, height, and height velocity at the takeoff and peak points of the adolescent growth spurt, adolescent gain, and mature adult stature) were estimated using a computer program, Auxological Analysis of Longitudinal Measurements of Human Stature (AUXAL). Patterns of extended medication use (negligible, inconsistent, consistent) estimated by parent report indicated a sex difference in stages of development: 76% of girls but only 12% of boys used medication in the 14-month randomized trial after the takeoff of the adolescent growth spurt. By age 6 years (for girls) and age 8 years (for boys) after baseline, participants were in the adolescent growth spurt. By age 10 years after baseline, most cases were at least 2 years beyond the age at peak.
Results: The self-selected negligible and consistent subgroups differed on childhood growth for girls and boys (lower height at takeoff by approximately 2 cm) but differed only for girls on adolescent growth (decreased adolescent gain by approximately 3 cm).

Conclusions: Girls and boys entered the MTA matched for age but mismatched for maturation. The use of medication suppressed adolescent growth in girls but not in boys, suggesting that the overall height suppression effect differs based on the following: 1) when treatment is initiated with respect to physical maturation; or 2) the mechanism underlying growth (growth hormone-mediated childhood or sex hormone-mediated adolescence growth). LONG, ADHD, MAE

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J Am Acad Child Adolesc Psychiatry. 2018;57:S246.

SELF- VERSUS COLLATERAL INFORMANT-REPORTED SYMPTOMS OF ADHD, ANGER-IRRITABILITY, AND IMPAIRMENT IN ADULTHOOD IN A LONGITUDINALLY FOLLOWED SAMPLE OF CHILDREN WITH ADHD.

Molina BSG, Jones NP, Versace A, et al.

Objectives: This presentation will compare self- and collateral informant-reported symptoms of ADHD, anger/irritability (an ODD item subset), and associated impairment for older adults followed longitudinally since childhood. Children with ADHD underreport their symptoms and impairment, and this tendency continues into the early 20s. The systematic study of this tendency into later adulthood is underresearched, including lack of information regarding anger/irritability underreporting and associations with pertinent characteristics.

Methods: Using a sample group of children research-diagnosed with ADHD in childhood (n = 99) and interviewed in their 30s (mean age = 33.4 years, SD = 3.5) from the Pittsburgh ADHD Longitudinal Study, the current study compared self-reported and collateral (91% parents; 9% romantic partner) informant-reported symptoms of ADHD, anger/irritability, and impairment based on standardized rating scales. Adults whose mean scores were lower than the informant report were compared across a range of demographic, personality, and task-measured variables.

Results: Self-reported scores of inattention, anger/irritability, and overall impairment were significantly lower than collateral-reported scores (p = 0.01 0.000). Self-reported impulsivity/hyperactivity was not significantly different from the collateral informant-reported score. Compared with final symptom and impairment scores calculated from both reports (using the evidence-based either-rule, taking the higher report at the item level), 49 77% of probands self-reported lower scores for ADHD symptoms overall, inattention, hyperactivity-impulsivity, anger/irritability, and impairment. Less education, male gender, higher scores on some facets of impulsive personality (eg, negative urgency), and higher/worse scores on contrasting measures of symptoms/impairment, were associated with underreporting.

Conclusions: Collateral reports of ADHD symptoms continue to be important for assessing symptomatology and impairment in the fourth decade of life. Relying only on self-report could lead to underestimating symptom severity and impairment by one half to three-fourths of a standard deviation. The current study supports the continued need for improved methods of measuring ADHD symptoms across the lifespan. ADHD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S164-S165.

EFFICACY MEASURES IN AN OPEN-LABEL DOSE-OPTIMIZATION STUDY OF AN AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION IN CHILDREN WITH ADHD.

Cutler AJ, Pardo A, King TR, et al.

Objectives: We will report on the additional efficacy of open-label (OL) amphetamine extended-release oral suspension (AMPH EROS) for the treatment of children with ADHD. AMPH EROS has a 1-hour onset of effect and 13-hour duration of action and was approved by the US FDA for the treatment of ADHD in children ages 6–17 years based on a double-blind, placebo-controlled efficacy and safety study. A significant treatment difference in change from the predose SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) Rating Scale-combined score was observed at the primary endpoint of 4 hours postdose (p < 0.0001) and at each postdose time point (1, 2, 4, 6, 8, 10, 12, and 13 hours). Data reported here are from the 5-week, OL dose optimization phase. These additional efficacy data support the primary endpoint.

Methods: Males and females ages 6–12 years with ADHD enrolled and began OL treatment with 2.5 or 5 mg per day of AMPH EROS titrated in 2.5–10 mg per day increments to the optimal dose or maximum 20

mg per day. Doses could be decreased for tolerability. Subjects took a morning dose of AMPH EROS for 5 weeks. The efficacy outcomes during the OL phase were as follows: 1) ADHD-Rating Scale (ADHD-RS); 2) Clinical Global Impression of Severity (CGI-S); 3) CGI-of Improvement (CGI-I); and 4) Conners Parent Rating Scale (CPRS). All subjects were assessed for safety.
Results: For the intention-to-treat (ITT) population (N = 99), treatment with AMPH EROS was associated with a mean improvement (decrease) in ADHD-RS-IV score (baseline to end of the OL phase; week 6) of 28.2 (-¦9.03) (baseline score = 41.3 -¦ 7.95). A total of 90.9% of subjects had a change from baseline to OL week 6 of 50% in the ADHD-RS-IV total score and were defined as responders. The CGI-S scores decreased continuously from a baseline mean of 4.8 to a mean of 2.0 at OL week 6. The percentage of subjects classified as moderately ill or greater decreased from 97% at baseline to 1% at OL week 6. The percentage of subjects with a CGI-I classification of either minimally, much, or very much improved increased from 54.5% at OL week 2 to 100% at OL week 6. CPRS for most categories decreased continuously from baseline to OL week 6. The mean changes from baseline to OL week 6 on the CPRS inattention T score subscale were 25.3 (-¦14.38) and ΓêÆ24.4 (-¦13.87). Adverse events (>5%) reported during dose optimization were decreased appetite, insomnia, affective lability, upper abdominal pain, mood swings, and headache.
Conclusions: AMPH EROS was effective in reducing symptoms of ADHD in this OL dose optimization. The adverse effect profile of AMPH EROS was consistent with that of other amphetamine products. ADHD, STIM

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J Am Acad Child Adolesc Psychiatry. 2018;57:S172-S173.

PHARMACOGENETIC PREDICTORS OF METHYLPHENIDATE RESPONSE IN CHILDREN AND ADOLESCENTS WITH ADHD.

Vallejo-Valdivielso M, D+¡ez-Su+írez A, deCastro-Manglano P, et al.

Objectives: This presentation will evaluate the association of single nucleotide polymorphisms (SNPs) across 4 dopamine (DA)-related genes (COMT, DAT1, MAOA, and MAOB) and of one brain-derived neurotrophic factor (BDNF) with methylphenidate (MPH) response in a sample group of children with ADHD.
Methods: We analyzed 7 SNPs in 4 DA-related candidate genes (COMTs rs4680 and rs6269, DAT1s rs27072 and rs2652511, MAOA rs3027399, MAOB rs1799836), and BDNF rs6265 in a sample group of 108 youth with ADHD. We recorded clinical characteristics, comorbidities, prenatal and perinatal risk factors, and neuropsychological testing results [WISC-IV (Wechsler Intelligence Scale for Children, Fourth Edition), CPT-II (Conners Continuous Performance Task-II), Stroop] as potential variables that may affect MPH response. Complete clinical response was defined as 30% reduction from baseline of total ADHD-RS-IV (ADHD Rating Scale-IV) total score and CGI-S (Clinical Global Impression–Severity) final score of 1 or 2. Analyses of the effects of different variables and genotypes on treatment response were performed using correlations and multiple/logistic regressions.
Results: Mean (SD) age of patients was 11.4 (3.3) years of age (79% male, 51.7% without comorbidity); 37.6% had a complete and 35.80% had a partial response to a mean MPH dose of 1.2 mg/kg/day. We did not find significant group differences in MPH dose between responders and nonresponders (t-test, $p > 0.1$; ANOVA, $p > 0.1$). Higher baseline ADHD-RS-IV total score (B = ΓêÆ0.020, $p = 0.021$), presence of comorbidities [oppositional-defiant symptoms (B = ΓêÆ0.054, $p = 0.017$) and alcohol (B = ΓêÆ0.78, $p = 0.032$) and cannabis use (B = ΓêÆ1.304, $p = 0.008$)], lower total IQ (B = 0.21, $p = 0.032$), and low commission errors in CPT-II (B = ΓêÆ0.13, $p = 0.049$) were significantly associated with poor MPH response (partial or no response). Moreover, the presence of DAT1 rs2652511 was significantly higher in complete responders ($p < 0.05$). When all of the variables are taken into account, the models explain between 5.1 and 6.9% (Cox-Snell R2 = 0.051; Nagelkerke R2 = 0.069) of the response to MPH.
Conclusions: This study suggests that DAT1 rs2652511, the absence of comorbidities, and less impairment at some neuropsychological performance, may predict a positive response to MPH. Other genetic or nongenetic factors may be involved in the variability of response to MPH, because our model only explains approximately 5% of the response to MPH. ADHD, GS, PPC

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J Am Acad Child Adolesc Psychiatry. 2018;57:S230.

CHARACTERIZING ATTENTION DEFICIT IN CHILDREN WITH ASD.

Trelles P, Wilkinson E, Kolevzon A.

Objectives: The overall objective of this study was to characterize attention deficits in patients with ASD with and without ADHD and to examine its impact on ASD symptomatology, adaptive functioning, and cognitive performance. The focus is placed on enhancing patient care by characterizing attention measures of specific ADHD outcomes in individuals with ASD that can be translated to clinical practice.

Methods: Twenty-five children with ASD were included in this study. Children met DSM-5 ASD criteria based on consensus diagnosis. Standardized measures of cognitive and adaptive functioning were obtained. Participants were evaluated for ADHD by an expert clinician. Caregivers completed the Swanson Nolan and Pelham Questionnaire (SNAP), Child Behavior Checklist (CBCL), and the Aberrant Behavior Checklist (ABC). Finally, all children completed the Attention Network Test (ANT) and a gap-overlap eye-tracking paradigm with social and nonsocial cues. A typically developing (TD) group was included for comparison for the ANT and eye-tracking measures.

Results: Forty-eight percent of participants with ASD met diagnostic criteria for ADHD. There was no statistical difference in baseline demographic factors, cognitive profiles, and Autism Diagnostic Observation Schedule severity scores. Children with comorbid ADHD performed worse on the Vineland Adaptive Behavior Scale, Second Edition (VABS-II) ($p = 0.03$). None of the SNAP, CBCL or ABC tests captured symptoms of ADHD as evaluated by an expert clinician. Nonetheless, statistical differences in subscales, suggestive of hyperactivity and/or impulsivity, were noted for all measures (all $p < 0.01$). The ANT found statistical differences for the orienting ($F = 9.82$, $p = 0.001$) network between the TD group and the group with ASD, but no difference within groups. TD control subjects showed greater response times ($p = 0.02$) to disengage from social stimuli (ie, faces) in the eye-tracking measures.

Conclusions: Our results indicate that commonly used clinical assessment instruments proved deficient when assessing for ADHD in children with ASD, suggesting the need to refine available tools to more accurately identify ADHD in children with ASD in clinical settings. Objective measures of attention, such as the ANT and eye-tracking, did not capture differences in attention for children with ASD with and without ADHD in this study. ADHD, ASD, DIAG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S244.

FOLLOW-UP OF THE PRESCHOOL ADHD TREATMENT STUDY: RELATIONSHIPS BETWEEN SLEEP PROBLEMS AND ADHD.

Yershova K, Paykina N, Austin J.

Objectives: Children with ADHD have significant sleep problems resulting in cognitive and behavioral impairment, but the findings on greater association of specific sleep problems with the inattention (IN) or hyperactivity/impulsivity (HI) and their effects on academic difficulties are inconsistent. The study examines ADHD and sleep problems in school-aged children who are first diagnosed and treated in the Preschool ADHD Treatment Study (PATS).

Methods: Children ($n = 192$; mean age = 7.5 years; 74% boys) of the original 204 preschoolers who completed PATS were assessed at ages 1, 2, and 4 years (mean ages = 7.5, 8.4, and 10.4 years) in an observational follow-up study. Severity of sleep problems (SPS) was calculated as a sum of daytime tiredness (TRD), sleep leg movement (LM), breathing problems (eg, apnea; BTH), and the overall sleep quality (SQ). Generalized linear model (GLM) with an autoregressive correlation structure was used to test effects of age, sex, and sleep problems on the clinician-reported IN/HI, parent and teacher IN/HI t-scores (Conners), internalizing (INT) and externalizing (EXT) t-scores (Child Behavior Checklist–Teacher Report Form), and standardized reading and math scores (Wechsler Individual Achievement Test). A binary variable of nighttime awakenings (2+/night; AW) was retained in several models.

Results: Twenty-three percent of children had a bedtime later than 9:30 pm, but bedtime alone did not predict severity of ADHD or other symptoms ($p > 0.30$). TRD, LM, and AW, but not BTH, individually predicted several outcomes. SPS and SQ predicted clinician- ($p < 0.03$) and parent-reported ($p < 0.001$), but not teacher-reported, IN and HI and EXT and INT disorders. None of the sleep problems predicted reading and

math. In the models of parent-reported (but not clinician-reported) ADHD and INT disorders, girls had more severe ADHD ($p < 0.05$) than boys.
Conclusions: No one sleep problem predicted across all outcomes, whereas the composite SPS was a consistent predictor, suggesting that sleep problems are significant when they contribute to the overall sleep efficiency and may not be strong independent indicators of disrupted sleep in children with severe ADHD. The parent SQ was the most robust item predictor and may have been driving the overall SPS significance. No effects of sleep problems on teacher-rated symptoms may be due to medication effects during school. Consistent with prior PATS reports, girls had more severe ADHD in terms of t-scores but fewer absolute counts of ADHD relative to boys. ADHD, SAC, SLP

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J Am Acad Child Adolesc Psychiatry. 2018;57:S146.
ASYMMETRIC WHITE MATTER MICROSTRUCTURE IN CHILDREN WITH ADHD.
Wu Z-M, Yang L, Cao Q-J, et al.
Objectives: Diffusion tensor imaging (DTI) studies have demonstrated altered brain white matter microstructure in children with ADHD. Multiple studies have demonstrated lateralized white matter alterations in participants with ADHD. The aim of the current study was to explore the asymmetry of white matter integrity in ADHD.
Methods: In a cohort of children (aged 8–15 years) with ADHD (n = 83) and healthy control subjects (n = 122), we used tract-based spatial statistics on DTI data to build skeletonized fractional anisotropy (FA) images. An International Consortium for Brain Mapping (ICBM)-DTI-81 white-matter labels atlas was then applied to the skeletonized images, and the mean FA in 40 bilateral regions of interest (ROIs) was obtained. The lateralization index (LI) was calculated. To reduce the number of tests, first-level 2-sample t tests were performed, and only those ROIs with significant case-control differences were fed to the second-level multiple regression, with age, gender, scanning protocol, IQ, and head motion parameter as covariates.
Results: External capsule and posterior thalamic radiation (PTR) showed significant case-control difference on first-level tests (both $p < 0.05$). However, only the difference on PTR remained statistically significant after controlling for the previously mentioned covariates in the second-level multiple regression (mean LI in ADHD 0.0096; in control 0.0044, $p = 0.0143$).
Conclusions: Children with ADHD showed more left-lateralized white matter integrity in PTR than healthy control subjects. White-matter pathway asymmetry was linked to the development of brain function, and the different leftward asymmetry that we saw in ADHD and control subjects might contribute to the impaired cognitive function in children with ADHD. ADHD, ND, NIMAG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S324-S325.
CAR CRASHES IN DRIVERS WITH CHILDHOOD AND ADULT ADHD: RESULTS FROM THE MTA.
Roy A, Epstein J, Garner A, et al.
Objectives: ADHD is associated with a risk for car accidents (crashes), but factors that influence this association are not well delineated. The Multimodal Treatment Study of Children with ADHD (MTA), with frequent symptom reassessments over a critical age range after careful childhood diagnosis, provides a unique opportunity to examine the risk of car crashes involving drivers previously diagnosed with ADHD. Here we determine the association of crashes by adults with childhood ADHD, adjusting for driving exposure, comorbid ODD/conduct disorder (CD), and substance use. We also examine the risk for crashes by adult ADHD symptom persistence compared with childhood-limited ADHD or no ADHD.
Methods: Participants with childhood ADHD (n = 453) and without (n=241; local normative comparison group, LNCG) were assessed for driving licensure age and crashes. The total number of crashes by adulthood per month of driving experience since licensure (car crashes) was regressed on baseline ADHD status, adjusting for sex and age at follow-up. In subsequent steps, we added additionally adjusted for childhood comorbid ODD/CD status and substance use between adolescence and adulthood. We repeated all analyses using adult ADHD symptom status (persistent vs desistant vs LNCG) as the grouping variable.

Results: The ADHD group had a higher age at licensure than the LNCG. Participants in the group with ADHD were also less likely to be licensed compared with the LNCG. Childhood ADHD was associated with a higher number of car crashes only when accounting for driving exposure since licensure. We found no association between childhood ADHD and car crashes after adjusting for baseline ODD/CD in the whole sample group. However, adult ADHD symptom persistence was associated with car crash risk irrespective of comorbid ODD/CD status or substance use.
Conclusions: Adolescents and young adults with a childhood diagnosis of ADHD are at a greater risk for car crashes, despite getting licensed at an older age. Driving exposure is especially important to consider when assessing car crash risk in ADHD. Furthermore, adult ADHD persistence is associated with crashes beyond the risk contributed by comorbid ODD/CD and substance use. ADHD, ADOL, DBD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S298-S299.
CONTEMPORARY ISSUES IN DIAGNOSING AND TREATING ADOLESCENT ADHD: STIMULANT DIVERSION, LATE-ONSET SYMPTOMS, SLEEP PROBLEMS, AND TEENAGE IMPULSIVITY.
Sibley MH, Nigg J.
Objectives: The DSM-5 criteria for ADHD include an onset criterion of age 12 years; however, individuals may present for a first-time ADHD diagnosis in adolescence. This Symposium will present empirical data that informs clinical dilemmas in the diagnosis and treatment of adolescent ADHD.
Methods: Brooke Molina, PhD, will present on clinical characteristics of adolescents receiving pharmacological treatment for ADHD in primary care. Margaret Sibley, PhD, will compare cases of ADHD with adolescent-onset with cases of childhood-onset ADHD and normative control subjects. Stephen Becker, PhD, will present data from an experimental sleep manipulation protocol that investigates the impact of adolescent sleep on ADHD symptom severity. Michelle Martel, PhD, will present a network analysis of ADHD symptoms in adolescence. Joel Nigg, PhD, will link the presentation findings to discuss their clinical implications.
Results: Most adolescents who receive medication in primary care have childhood-onset ADHD that has been steadily medicated since late childhood. Risk for diversion was relatively low in the middle adolescent sample group. Approximately 1 in 3 teenagers identified by high school teachers as possessing elevated ADHD symptoms at school did not have a childhood history of ADHD. Their late-onset symptoms were associated with the female gender, slightly lower IQs, less severe executive deficits (compared with childhood cases of ADHD), and slower processing speed. Late-onset cases also spent more time on electronics and had more involved parents with higher academic expectations. Reduced sleep duration appears to exacerbate inattention and oppositional symptoms in teenagers with ADHD. Impulsivity appears to be a central feature in adolescent ADHD, compared with childhood ADHD, and is central in teenagers without ADHD.
Conclusions: Although approximately one-third of teacher-identified high school students with ADHD symptoms have no childhood history of ADHD, these cases may be unlikely to seek treatment in primary care. First-time adolescent ADHD diagnoses should be met with scrutiny until additional work can be done to refine our understanding of late-onset ADHD symptoms. Careful assessment of sleep, the nature of impulsive behaviors, parent scaffolding, and screen time may augment the clinical assessment of adolescents with ADHD. ADHD, ADOL, DIAG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S146.
VOLUMETRIC BRAIN ABNORMALITIES IN ADOLESCENTS WITH CONDUCT DISORDER WITH AND WITHOUT ADHD.
Seleem M, El-Shafey R, Shahin L, et al.
Objectives: Conduct disorder (CD) is a prevalent mental illness in youth with heterogeneous presentations and hazardous outcomes on family and society. Identifying potential biological markers that differentiate the various characteristics of the disorder may help in better understanding and managing the problem. This

work aims to explore the potential volumetric brain abnormalities in an Arab-Egyptian sample group of conduct-disordered youth with and without comorbid ADHD during late childhood and adolescence.
Methods: A total of 27 subjects with CD, 14 of whom also fulfilled the criteria for ADHD, and 20 healthy subjects were recruited. A validated Arabic version of the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) was carried out. Cortical reconstruction and automatic volumetric segmentation were performed with the FreeSurfer image analysis suite.
Results: Youth with CD, with and without ADHD, showed significantly lower cortical thicknesses and smaller subcortical volumes in most of the hemispheric areas. When the 2 patient groups were compared, youth with CD + ADHD had significantly greater cortical thicknesses but smaller subcortical volumes compared with youth with CD only.
Conclusions: CD, comorbid with ADHD, might prove to be a distinct phenotypic entity with different biological substrates and hence different needed management than CD only. ADHD, CD, NIMAG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S299.
CLINICAL AND NEUROCOGNITIVE PROFILES OF ADOLESCENTS WITH LATE-ONSET ADHD SYMPTOMS.
Sibley MH, Dick A, Graziano P, et al.
Objectives: Research indicates an adolescent-onset form of ADHD that emerges after age 12 years, with impairing symptoms that primarily manifest at school and remit before adulthood. It is unclear whether adolescent-onset and childhood-onset ADHD share etiology.
Methods: Teachers identified 36 ninth-grade students who displayed elevated ADHD symptoms and impairment. Semi-structured diagnostic interviews with parents and teenagers (KSADS-PL-DSM-5) confirmed teacher reports. Cases were classified as childhood or adolescent-onset based on mental health history with supplemental probes to determine symptom onset. Eighteen non–ADHD classmates were also recruited. Participants completed cognitive performance tasks, neuroimaging, and psychobehavioral rating scales. General linear models and Chi-square analyses examined group differences on outcomes.
Results: The teacher-identified ADHD sample group (81.8%) had no previous ADHD diagnosis, and 12 of 36 case subjects displayed late-onset symptoms. Late-onset cases were more likely to be female (41.7 vs 28.6%, OR = 1.79) and possess slightly lower IQs (mean = 90.50, SD = 9.78 vs mean = 96.33, SD = 12.92, d = 0.51). There were no group differences in comorbidity profile, trauma exposure, or ADHD subtype. Childhood-onset cases showed more severe executive functioning deficits on the Behavior Rating Inventory of Executive Function (BRIEF) (d = 0.77). Late-onset cases showed slower processing speed (d = 0.33) on a pattern comparison task. There were no group differences on working memory or inhibitory control tasks. Parents of late-onset ADHD case subjects spent more time assisting with academics (d = 0.38) and had higher academic expectations (d = 0.73). Childhood-onset parents had higher parenting stress (d = 0.88). Late-onset youth spent more time on electronics (d = 0.42). No differences were detected in exercise, pubertal development, or sleep. The presentation will include expanded statistics, plus neuroimaging and non–ADHD comparison data.
Conclusions: Adolescent-onset ADHD can be identified by teachers. Dispersion measures suggest that this subgroup had higher heterogeneity than the childhood ADHD group. Larger sample groups are needed to understand the variety of symptom etiologies that comprise adolescent-onset ADHD. Significant group differences indicate areas for future exploration. ADHD, ADOL, DIAG

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J Am Acad Child Adolesc Psychiatry. 2018;57:S253.
IS CANNABIS USE ASSOCIATED WITH WORSE INPATIENT OUTCOMES IN ADOLESCENTS WITH ADHD?
Patel RS, Makani RD, Patel P, et al.
Objectives: The objective of this presentation is to determine the impact of cannabis use disorder (CUD) on inpatient outcomes of ADHD in adolescents.

Methods: We used the Nationwide Inpatient Sample (NIS) from 2010 to 2014. We identified ADHD and CUD as primary and other diagnosis, respectively, using ICD-Clinical Modification codes. We used the binomial logistic regression model to generate adjusted ORs.
Results: We analyzed the hospital admissions of a total of 11,232 adolescents with ADHD from years 2010 to 2014, of which 1.79% had CUD. The mean age of the adolescents was 14.1 years (SD = 1.79). The prevalence of CUD was highest in ADHD in adolescents aged 15-18 years (73%) and common in whites (71%). A higher proportion of ADHD with CUD adolescents was transferred to an acute care hospital and skilled and/or other nursing facility (5.4 and 7.4% vs. 1.1 and 2.6%, respectively, $p < 0.001$). CUD increases the risk of inpatient charges > $12,247 (median) by 0.6 times (adjusted OR = 1.835; $p = 0.002$) and increases the risk of inpatient stay > 5 days (median) by 0.7 times (adjusted OR = 2.099; $p < 0.001$). The utilization of psychotropic medications was reduced by 0.8 times in adolescents with ADHD and CUD by 0.8 times (adjusted OR = 0.448; $p = 0.017$), and the implication of behavioral therapy in the management of adolescents with ADHD and CUD was reduced by 0.9 times (adjusted OR = 0.412; $p = 0.048$). In addition, there is a 2.8 times higher risk of comorbid alcohol abuse in adolescents with ADHD and CUD (adjusted OR = 17.141; $p < 0.001$).
Conclusions: Increased risk of substance use is a long-term implication of ADHD in adolescents. It has been determined that comorbid CUD in patients with ADHD not only increases the risk of acute inpatient care but also prolongs the inpatient stay, thus increasing the health care cost. It is noteworthy that comorbid CUD decreases the utilization of psychotropic medications and behavioral therapy in ADHD. Another major issue is the higher risk of comorbid alcohol abuse in adolescents with ADHD and CUD. ADOL, ADHD, SUD

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J Am Acad Child Adolesc Psychiatry. 2018;57:S229-S230.
OPPORTUNITIES AND CHALLENGES IN USING A MOBILE HEALTH (MHEALTH) INTERVENTION TO OPTIMIZE EARLY STIMULANT TREATMENT IN CHILDREN WITH ADHD: FINDINGS FROM THE MH-2□ÄÓ PILOT.
***Paschall ES, Marti FA, Cheung Y, et al*.**
Objectives: ADHD is a very common (prevalence 4+ó Γé¼ΓÇ£12% of US children ages 4+óΓé¼ΓÇ£17 years), chronic, debilitating, and costly neurodevelopmental illness. Efficacy of stimulants is well established, and the use of treatment guidelines is encouraged, but management of childhood ADHD remains poor, especially in community-based settings. Given near-universal access to smart phones in the United States, mobile health (mHealth) holds promise for improving quality of ADHD treatment in community-based settings. Pilot study was designed to evaluate the feasibility and acceptability of MH2TM, a web-based mobile health application (app) developed to optimize early stimulant treatment for children with ADHD.
Methods: MH2 was used in 2 community mental health centers and 1 general pediatrics clinic. Sample group included 25 low-income parents whose children were starting stimulant medication. Using a mixed-methods proof-of-concept study design, app feasibility was assessed over 3 follow-up medical visits. Data sources included the following: 1) after-visit parent surveys (demographic data and ratings of parent competence, treatment acceptability, and medication self-efficacy); and 2) time-stamped data from the app+ s user activity log (how often logging in, time spent on app, use of features). The app was available in English and Spanish.
Results: Data were aggregated across the first 3 episodes of care (baseline to first follow-up; visits 1+ 2; visits 2+ 3). All but one subject (parent) used the app on multiple days, although frequency and consistency of use varied widely. During interval 1, for instance, the days used ranged from 1 to 33 (from 4.8 to 80.5% of possible days), and total minutes used ranged from 0.2 to 119.8. Ratings of parent competence, treatment acceptability, and medical management self-efficacy improved an average of 2 3 points from baseline to end of the study, but range in each was extremely wide (eg, change in parent competency ranged from +22 to 10 over course of study).
Conclusions: Parent use of MH2s main features is feasible and was sustained during early medication titration. However, there was wide variability in use and outcomes ratings between subjects. Further study is needed to evaluate differences between low and high users and whether the level of use correlates with changes to competence, treatment acceptability, and medical management self-efficacy. ADHD, STIM, MDM

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J Am Acad Child Adolesc Psychiatry. 2018;57:S178.

THE EFFECT OF FRUSTRATION ON RESPONSE CONTROL IN CHILDREN WITH ADHD: THE IMPORTANCE OF SEX AND COMORBIDITY.

Seymour KE, Rosch KS, Mostofsky SH.

Objectives: Poor frustration tolerance is a significant impairment in children with ADHD. During frustrating tasks, children with ADHD show greater levels of frustration, are more likely to quit the task, and focus more on the negative aspects of the task compared with typically developing control (TDC) subjects. However, little is known about how frustration affects neurocognitive deficits such as response control in children with ADHD. The current study examined the effect of frustration on response control using a novel frustration paradigm.

Methods: Participants (ages 8–12 years) included TDC subjects (n = 38), children with ADHD only (n = 30), or children with ADHD plus comorbid ODD, an anxiety disorder, or a depressive disorder (comorbid, n = 31). Participants completed a novel frustration Go/No-Go paradigm with performance-based incentives delivered across 3 blocks, including a frustrative second block involving 50% rigged Go trials on which the stimuli did not move to the target. The primary dependent variable is commission error rate. To assess frustration during the task, participants completed affect ratings at 4 points during the task (baseline and after each block).

Results: Across the whole sample group, results revealed an increase in self-reported frustration [t(99) = ΓêÆ10.90, p < 0.001] from baseline to the end of block 2, and an increase in commission error rate [t(99) = ΓêÆ3.03, p = 0.003] from block 1 to block 2. A 3 Group x 2 Sex x 3 Block repeated measures analysis of covariance with age as a covariate was examined. Results showed a significant Group x Sex x Block interaction for commission error rate [F(4,184) = 2.51, p = 0.043]. Post hoc tests indicated that girls with ADHD showed the greatest increase in commission error rate with frustration (p = 0.002, d = 1.12), followed by TDC boys (p = 0.02, d = 0.47) and boys with comorbid conditions (p = 0.05, d = 0.43). In the frustration block, the girls with ADHD showed the highest commission error rate (28%).

Conclusions: Results suggest that the effect of frustration on response control in children with ADHD may be differential depending on child sex. In particular, girls with ADHD had the greatest difficulties when frustration was added to a response control task, which may have important implications for and associations with functional outcomes. ADHD, IMD, NEPSYC

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J Am Acad Child Adolesc Psychiatry. 2018;57:S235-S236.

DIFFERENCES IN DEMOGRAPHIC AND INPATIENT OUTCOMES IN HOSPITALIZED AUTISTIC TEENS WITH ADHD: A NATIONWIDE CASE-CONTROL STUDY.

Patel RS, Bhullar H, Amaravadi N, et al.

Objectives: The purpose of this study is to determine the differences in demographic pattern, inpatient outcomes, and comorbidities in patients with ASD with/without ADHD during hospitalization.

Methods: A retrospective analysis was performed using Nationwide Inpatient Sample data from 2012 to 2014. Patients ages 18 years with a primary diagnosis of autism and co-diagnosis of ADHD (N = 1285) were identified using ICD-9 diagnosis codes and control subjects with a diagnosis of autism only (N = 840). Multilevel logistic regression for hospital variability and comorbidities were used to calculate odds ratio, and discharge weight were applied to obtain national represent inpatient data.

Results: Majority of the cases (58.4%) were adolescents. Although 86.4% of cases were males, females had 3 times higher odds of comorbid ADHD (OR = 3.182 [95% CI = 2.350 £4.308]). African Americans had 2 times higher odds for co-diagnosis of ADHD (OR = 1.947 [95% CI = 1.521 £2.494]). There were higher odds of ADHD co-diagnosis in patients with ASD who were admitted in medium-size hospitals (OR = 1.693 [95% CI = 1.302 £2.200]) and rural nonteaching hospitals (2.756 [1.655 £4.591]). A higher proportion of cases (35.8%) were seen in the midwestern region of the United States. Psychosis was seen in 37.7% cases who had 2 times higher likelihood of comorbid psychosis compared with control subjects (OR = 2.019 [95% CI = 1.577 £2.584]). A higher proportion of case subjects (52.5 vs 42.9%; p < 0.001) had hospitalization of > 6 days per admission, and thus the cases subjects had higher odds for longer hospitalization compared with control subjects (OR = 1.605 [95% CI = 1.287 £2.001]). Cases also had higher odds for inpatient charges of > $18,034 per admission (OR = 1.379 [95% CI = 1.100 £1.729]) than control subjects.

Conclusions: Considering that males are easily identified with hyperactive symptoms, it is critical to examine females more carefully as girls with autism were 3 times more likely to have comorbid ADHD. Because of the inpatient outcomes and comorbidities seen in this study, the need to invest in versatile and tailored care continues. Comorbid ADHD in patients with ASD increases the likelihood of longer and higher hospitalization cost as a result of short-term inpatient care. Further research to develop clinical care models for early diagnosis and treatment of ADHD in autism is warranted to improve quality of health care. ASD, ADHD, ICP

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J Am Coll Nutr. 2018.

DIETARY PATTERNS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG IRANIAN CHILDREN: A CASE-CONTROL STUDY.

Abbasi K, Beigrezai S, Ghiasvand R, et al.

Objective: Associations between nutritional/dietary factors and mental disorders have been suggested. This study was conducted to assess the relation of major dietary patterns determined by factor analysis with attention-deficit/hyperactivity disorder (ADHD) in a group of Iranian preschool- and school-aged children.

Methods: This case-control study was conducted with 500 preschool- and school-aged children (4–12 years old) matched by age and sex, in Isfahan, Iran. Dietary intake was identified by a 168-item questionnaire, and major dietary patterns were identified by factor analysis. The multivariable logistic regression is used for the association of dietary patterns with the diagnosis of ADHD. ADHD diagnosis was carried out with the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Results: Two major dietary patterns were identified: healthy and Western. The healthy dietary pattern was rich in fruits, vegetables, vegetable oils, whole grains, legumes, and dairy products. The Western pattern was rich in processed meat, red meat, pizza, eggs, snacks, animal fat, hydrogenated fat, and salt. After controlling for potential confounders, children in the top quintile of the Western dietary pattern score had greater odds having ADHD, compared with those in the lowest quintile (odds ratio [OR] = 3.45; 95% confidence interval [CI], 1.17–18.3; ptrend = 0.03). The healthy pattern was inversely associated with ADHD (OR = 0.46; 95% CI, 0.38–0.91; ptrend = 0.01).

Conclusions: A significant independent association was found between the Western dietary pattern and the odds of ADHD. The healthy dietary pattern was associated with lower odds of having ADHD. Prospective studies are needed to confirm these findings

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Medicine (Baltimore). 2018 Sep;97:e12623.

EFFECTS OF NEUROFEEDBACK VERSUS METHYLPHENIDATE FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER PROTOCOL FOR A SYSTEMATIC REVIEW AND META-ANALYSIS OF HEAD-TO-HEAD TRIALS.

Yan L, Zhang J, Yuan Y, et al.

INTRODUCTION: Attention-deficit/hyperactivity disorder (ADHD) is developmental disorder characterized by inattention and/or hyperactivity/impulsivity. Psychostimulants, including methylphenidate (MPH), are recommended as a first-line pharmacological intervention, whereas neurofeedback (NF) has been proposed as a nonpharmacological option. The comparative effects of MPH and NF need further exploration. We will conduct a systematic review and meta-analysis of head-to-head randomized controlled trials (RCTs) comparing the efficacy and/or tolerability of MPH and NF in children/adolescents and adults with ADHD.

METHOD AND ANALYSIS: We will include published as well as unpublished data. Two investigators will independently search PubMed, OVID, ERIC, Web of Science, ClinialTrials.gov, and a set of Chinese databases, including CNKI, CQVIP, and WanFang for head-to-head RCTs comparing MPH and NF. Experts will be contacted for unpublished data. The primary outcome will be the efficacy on ADHD core symptoms, measured by the change in the severity of ADHD symptoms, from baseline to endpoint and, if available, at follow-up (at any available time point). Secondary outcomes will be: dropouts for any reasons; efficacy on neuropsychological measures (working memory, inattention, and inhibition). We will conduct subgroup analyses to assess the impact of the following variables: age; type of NF; language of publication;

comorbidities. Additionally, we will carry out meta-regression analyses to investigate the effect of sponsorship, year of publication, duration of intervention, and age of participants. Sensitivity analyses will be conducted to test the robustness of the findings. Risk of bias of individual studies will be assessed using the Cochrane risk of bias tool. Analyses will be performed using Comprehensive Meta-Analysis Software.
ETHICS AND DISSEMINATION: No ethical issues are foreseen. Results from this study will be published in a peer-reviewed journal and presented at relevant national and international conferences.
TRIALS REGISTRATION NUMBER: PROSPERO CRD42018090256

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Minerva Psichiatrica. 2018;59:144-1152.

STUDYING THE EFFECT OF COMBINATION THERAPY BY PRAMIPEXOLE AND METHYLPHENIDATE IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER, IN COMPARISON WITH THE PLACEBO AND METHYLPHENIDATE.

Riahi F, Tashakori A, Marashi SS.

BACKGROUND: In this article we studied the effect of combination therapy of pramipexole and methylphenidate in the treatment of attention-deficit hyperactivity disorder (ADHD) children regarding the mechanism of the effect of pramipexole and considering the mentioned problems and inadequacies in the present and current ADHD therapies.
METHODS: In a double blind randomized clinical trial study 30 children who suffered from ADHD have been selected among the patients referred to the psychiatric clinic of Ahvaz Golestan Hospital. The patients were randomly assigned in the case study group (methylphenidate and pramipexole) and or control group (placebo and methylphenidate), participants were examined before the start of treatment, and after two, four, and six weeks from the start of the treatment by the parent's Conners questionnaire.
RESULTS: The patients' mean age was 8.47-¦2.08. In the control group, in the second week, the final score of patients significantly decreased compared to week 0. That finding was significant for the fourth and sixth weeks as well as the previous week. In the case group, in the 2n d, 4t h, and 6t h weeks, the final score of the patients was significantly lower than the previous week. Comparison of the two groups showed that there was no significant difference between the scores of the two groups in the second and fourth weeks of the study (P>0.05). However, in the sixth week, the final score, and the total score, in the case group, were significantly lower than the control group (P<0.05).
CONCLUSIONS: Premipexylum and methylphenidate is probably more effective than methylphenidate alone in treating the ADHD disorder

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Mol Autism. 2018;9:26.

EU-AIMS LONGITUDINAL EUROPEAN AUTISM PROJECT (LEAP): THE AUTISM TWIN COHORT.

Isaksson J, Tammimies K, Neufeld J, et al.

EU-AIMS is the largest European research program aiming to identify stratification biomarkers and novel interventions for autism spectrum disorder (ASD). Within the program, the Longitudinal European Autism Project (LEAP) has recruited and comprehensively phenotyped a rare sample of 76 monozygotic and dizygotic twins, discordant, or concordant for ASD plus 30 typically developing twins. The aim of this letter is to complete previous descriptions of the LEAP case-control sample, clinically characterize, and investigate the suitability of the sample for ASD twin-control analyses purposes and share some 'lessons learnt.' Among the twins, a diagnosis of ASD is associated with increased symptom levels of ADHD, higher rates of intellectual disability, and lower family income. For the future, we conclude that the LEAP twin cohort offers multiple options for analyses of genetic and shared and non-shared environmental factors to generate new hypotheses for the larger cohort of LEAP singletons, but particularly cross-validate and refine evidence from it

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Neural Plasticity. 2018;2018.

MIXED-EFFECTS MODELING OF NEUROFEEDBACK SELF-REGULATION PERFORMANCE: MODERATORS FOR LEARNING IN CHILDREN WITH ADHD.

Zuberer A, Minder F, Brandeis D, et al.

Introduction. Neurofeedback (NF) has gained increasing popularity as a training method for children and adults with attention deficit hyperactivity disorder (ADHD). However, it is unclear to what extent children learn to regulate their brain activity and in what way NF learning may be affected by subject-and treatment-related factors.

Methods. In total, 48 subjects with ADHD (age 8.5-16.5 years; 16 subjects on methylphenidate (MPH)) underwent 15 double training sessions of NF in either a clinical or a school setting. Four mixed-effects models were employed to analyze learning: training within-sessions, across-sessions, with continuous feedback, and with transfer in which performance feedback is delayed.

Results. Age and MPH affected the NF performance in all models. Cross-session learning in the feedback condition was mainly moderated by age and MPH, whereas NF learning in the transfer condition was mainly boosted by MPH. Apart from IQ and task types, other subject-related or treatment-related effects were unrelated to NF learning.

Conclusion. This first study analyzing moderators of NF learning in ADHD with a mixed-effects modeling approach shows that NF performance is moderated differentially by effects of age and MPH depending on the training task and time window. Future studies may benefit from using this approach to analyze NF learning and NF specificity. The trial name Neurofeedback and Computerized Cognitive Training in Different Settings for Children and Adolescents With ADHD is registered with NCT02358941

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Neurologia, Neurocirugia y Psiquiatria. 2017;45:93-99.

ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN CHILDHOOD.

Ochoa-Madrigal MG, Valencia-Granados FJ, Hern+índez-Mart+¡nez HE.

Introduction: Attention deficit disorder (ADHD) is one of the most important diseases of the child psychiatric consultation, with a prevalence of up to 50%. It stands out from all the others for the great scientific interest since its first description in such a way that innumerable publications have been made around it in search of answers. Its worldwide prevalence oscillates around 4-15% with an epidemiological impact in the academic areas, social and family, nuanced by socio-cultural conditions.

Objective: Adequate diagnostic criteria are required for the adolescent and adult stages. The presence of comorbidity will also have to be assessed and patients should be given optimal treatment.

Methods: In order to better understand the construct of ADHD, a search of the available information was made for a better approach to this pathology.

Results: After an extensive review of the literature, the authors concluded that the diagnostic criteria of ADHD should be homogenized, reinforced activities aimed at detecting comorbidities, facilitating reference processes with specialists, and education of health professionals in first and second level of care, as well as teachers and parents.

Conclusions: The correct evaluation, detection and timely referral as well as proposal of the best treatment available to patients is essential to prevent the comorbidities associated with ADHD, without forgetting that it is a disorder of multifactorial etiology and should be handled as such

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Neurology. 2018;90:e1104-e1110.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MEDICATION AND SEIZURES.

Wiggs KK, Chang Z, Quinn PD, et al.

Objective Individuals with attention-deficit/hyperactivity disorder (ADHD) are at increased risk of seizures, but there is uncertainty about whether ADHD medication treatment increases risk among patients with and without preexisting seizures.

Methods We followed a sample of 801,838 patients with ADHD who had prescribed drug claims from the Truven Health MarketScan Commercial Claims and Encounters databases to examine whether ADHD medication increases the likelihood of seizures among ADHD patients with and without a history of seizures. First, we assessed overall risk of seizures among patients with ADHD. Second, within-individual concurrent analyses assessed odds of seizure events during months when a patient with ADHD received ADHD medication compared with when the same individual did not, while adjusting for antiepileptic medications. Third, within-individual long-term analyses examined odds of seizure events in relation to the duration of months over the previous 2 years patients received medication.
Results Patients with ADHD were at higher odds for any seizure compared with non-ADHD controls (odds ratio [OR] = 2.33, 95% confidence interval [CI] = 2.24-2.42 males; OR = 2.31, 95% CI = 2.22-2.42 females). In adjusted within-individual comparisons, ADHD medication was associated with lower odds of seizures among patients with (OR = 0.71, 95% CI = 0.60-0.85) and without (OR = 0.71, 95% CI = 0.62-0.82) prior seizures. Long-term within-individual comparisons suggested no evidence of an association between medication use and seizures among individuals with (OR = 0.87, 95% CI = 0.59-1.30) and without (OR = 1.01, 95% CI = 0.80-1.28) a seizure history.
Conclusions Results reaffirm that patients with ADHD are at higher risk of seizures. However, ADHD medication was associated with lower risk of seizures within individuals while they were dispensed medication, which is not consistent with the hypothesis that ADHD medication increases risk of seizures

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Neurophotonics. 2018;5.

ADAPTIVE ALGORITHM UTILIZING ACCEPTANCE RATE FOR ELIMINATING NOISY EPOCHS IN BLOCK-DESIGN FUNCTIONAL NEAR-INFRARED SPECTROSCOPY DATA: APPLICATION TO STUDY IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER CHILDREN.

Sutoko S, Monden Y, Funane T, et al.

Functional near-infrared spectroscopy (fNIRS) signals are prone to problems caused by motion artifacts and physiological noises. These noises unfortunately reduce the fNIRS sensitivity in detecting the evoked brain activation while increasing the risk of statistical error. In fNIRS measurements, the repetitive restingstimulus cycle (so-called block-design analysis) is commonly adapted to increase the sample number. However, these blocks are often affected by noises. Therefore, we developed an adaptive algorithm to identify, reject, and select the noise-free and/or least noisy blocks in accordance with the preset acceptance rate. The main features of this algorithm are personalized evaluation for individual data and controlled rejection to maintain the sample number. Three typical noise criteria (sudden amplitude change, shifted baseline, and minimum intertrial correlation) were adopted. Depending on the quality of the dataset used, the algorithm may require some or all noise criteria with distinct parameters. Aiming for real applications in a pediatric study, we applied this algorithm to fNIRS datasets obtained from attention deficit/hyperactivity disorder (ADHD) children as had been studied previously. These datasets were divided for training and validation purposes. A validation process was done to examine the feasibility of the algorithm regardless of the types of datasets, including those obtained under sample population (ADHD or typical developing children), intervention (nonmedication and drug/placebo administration), and measurement (task paradigm) conditions. The algorithm was optimized so as to enhance reproducibility of previous inferences. The optimum algorithm design involved all criteria ordered sequentially (0.047 mM mm of amplitude change, 0.029 mM mm/s of baseline slope, and 0.6 +ù interquartile range of outlier threshold for each criterion, respectively) and presented complete reproducibility in both training and validation datasets. Compared to the visual-based rejection as done in the previous studies, the algorithm achieved 71.8% rejection accuracy. This suggests that the algorithm has robustness and potential to substitute for visual artifact-detection

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Neuropsychiatr Enfance Adolesc. 2018.

DEVELOPMENTAL DYSMNESIA: A FORGOTTEN NEURODEVELOPMENTAL DISORDER.

Bussy G, Seguin C, Bonnevie I.

Introduction/objective: Memory disorders in adults are common after cerebral stroke, brain tumor, or major neurocognitive disorder. But in childhood, these disorders are less described in scientific literature and are perhaps less frequent. Many studies have described long-term memory disorder after hypoxic–ischemic events (see articles from Vargha-Kadhem and colleagues). This disorder is named developmental amnesia because the origin of difficulties is identified. But in a few cases (4 cases described currently) causes are unknown despite the same memory disorders. This neurodevelopmental disorder could be named: developmental dysmnesia. So, the question is: is the prevalence of developmental dysmnesia in the general population really low or is this an under-diagnosis? Temple and Richardson (2006) stated prevalence at around 5–6%, but in fact neuropsychologists never diagnose developmental dysmnesia.

Method: From literature review and description of two new cases which have have recently been identified (one with episodic dysmnesia and one with mixed dysmnesia), we postulate that developmental dysmnesia is an underdiagnosed neurodevelopmental disorder because of the presence of other developmental disorders such as ADHD, SLIΓÇª which become the tree that hides the forest; and because of low scholastic difficulties which are compensated for by more consequent personal effort.

Conclusion: Long-term memory can be perturbed in children without brain damage, which we have named developmental dysmnesia. We have demonstrated that many parameters generate few diagnostics of developmental dysmnesia which could be a neurodevelopmental disorder with the same prevalence as others. The diagnostic of memory disorder in children is difficult because complaints are not about memory, and/or scholastic difficulties are compensated. We have identified three types of developmental dysmnesia, based on the nature of the memory system that is disturbed: episodic dysmnesia, semantic dysmnesia and mixed dysmnesia (episodic and semantic memory disorders). Moreover, we could distinguish two sensorial modalities: verbal and/or visuo-spatial developmental dysmnesia. The systematic investigation of long-term memory problems in children with neurodevelopmental disorders (notably ADHD and dyslexia) must permit listing more cases of developmental dysmnesia in the future. We encourage all neuropsychologists and others professionals which working with children to assess long-term memory despite lack of complaints

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Neuropsychol Rev. 2018 Sep;28:341-58.

EXECUTIVE FUNCTION AND THEORY OF MIND IN CHILDREN WITH ADHD: A SYSTEMATIC REVIEW.

Pineda-Alhucema W, Aristizabal E, Escudero-Cabarcas J, et al.

In developmental research, the relationship between Executive Function (EF) and Theory of Mind (ToM) has been extensively assessed, and EF has been considered a condition for ToM. However, few researchers have studied the relationship between EF and ToM in clinical populations, especially that of Attention Deficit Hyperactivity Disorder (ADHD), a neurodevelopmental disorder characterized by symptoms of inattention and motor hyperactivity/impulsivity, in which EF is largely impaired. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model, 201 English and Spanish articles evaluating EF and ToM in ADHD were chosen. Fifteen papers met the inclusion criteria and were selected for further analysis. The first study dates from 2001. Most of the studies' designs are cross-sectional, include mostly male children, have a small sample size, and were conducted in European countries. Unlike tasks assessing EF, tasks assessing ToM were heterogeneous across studies. The EFs most correlated with ToM were inhibitory control, working memory, cognitive flexibility, and attention. Interest in studying the relationship between EF and ToM in ADHD is recent,but increasing based on new findings and tuning of ToM instruments. However, while an association between EF and ToM is indicated in ADHD, the degree of prediction and predictability of one over the other cannot yet be established because of the studies' heterogeneity

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Niger J Clin Pract. 2018 Sep;21:1132-38.

ORAL HEALTH STATUS AND ITS RELATION WITH MEDICATION AND DENTAL FEAR IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Pinar-Erdem A, Kuru S, Urkmez ES, et al.

Objective: The objective of this study was to determine the ora-dental health and its relation with medication and dental fear in a group of Turkish children with attention-deficit hyperactivity disorder (ADHD).

Subjects and Methods: The levels of dental fear of children were determined with The Dental Subscale of Children's Fear Survey Schedule (CFSS-DS). The oral and dental health evaluation was performed. This study included a total of 117 children aged between 6 and 15 years and they were examined under two groups as "ADHD" (n = 59) and "Control" (n = 58). Ora-dental health variables were compared between the groups and were also analyzed in accordance with dental fear and medication.

Results: ADHD children and the control group exhibited similar CFSS-DS scores (15-32). No significant differences existed in df(t)/df(s), DMF(T)/DMF(S), d/D values, and presence of the white spot lesions. ADHD children's Mutans streptococci and Lactobacillus quantities were found significantly higher than the control group. The incidence of parafunctional habits of the ADHD children was also found high.

Conclusions: ADHD children that were medicated exhibited similar dental caries prevalence and periodontal health status. Although ADHD group had similar dental-periodontal health status and dental fear level with the control group and using ADHD medicines did not make a significant effect on the ora-dental health parameters, the patients should be carefully followed up because they were categorized in high caries risk groups

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Niger J Clin Pract. 2018 Sep;21:1213-20.

THE EFFECTS OF PSYCHOSTIMULANTS ON ORAL HEALTH AND SALIVA IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A CASE-CONTROL STUDY.

Ertugrul CC, Kirzioglu Z, Aktepe E, et al.

Introduction: This study investigated the dental health problems and saliva characteristics of children under psychostimulant therapy for attention-deficit hyperactivity disorder (ADHD).

Materials and Methods: One hundred and twenty children aged 7-12 years were divided into three groups. Groups 1-2 comprised children diagnosed with ADHD: those who had not yet started psychostimulant therapy (Group 1) and those already receiving long-term psychostimulant therapy (Group 2). Group 3 comprised healthy, nonmedicated children. Possible side effects of psychostimulants were investigated at the beginning of study in Group 2 and after 3 months drug use in Group 1. Bruxism and dental erosion prevalence, salivary Streptococcus mutans count, buffering capacity, and stimulated salivary flow rate (SSFR) were measured, and salivary alpha-amylase, calcium, total protein, and proline-rich acidic protein (PRAP) levels were quantified in the beginning of the study. Data were analyzed using the Kruskal-Wallis test.

Results: The most frequently reported side effects of psychostimulants were decreased appetite, dry mouth, and increased fluid consumption. The prevalence of bruxism and dental erosion was higher in Groups 1 and 2 than in Group 3, but the differences were not significant ($P > 0.05$). In Group 2, subjective dry mouth feel was reported by 32.5% of patients and 17.5% had a very low SSFR. Salivary alpha-amylase, calcium, total protein, and PRAP levels were lower in Group 2 than the others, but the differences were not significant ($P > 0.05$).

Conclusions: ADHD and psychostimulant therapy do not appear to be significantly related to decreasing SSFR or protective saliva components against dental caries. However, a systematic investigation of the long-term safety of psychostimulants is needed. The most effective method of maintaining dental health of children with ADHD is frequent appointments focusing on oral hygiene practices accompanied by dietary analyses

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Nord J Psychiatry. 2018.

STANDARDIZATION AND CROSS-CULTURAL COMPARISONS OF THE SWEDISH CONNERS 3-« RATING SCALES.

Thorell LB, Chistiansen H, Hammar M, et al.

Purpose: The Conners Rating Scales are widely used in research and clinical practice for measuring attention deficit/hyperactivity disorder (ADHD) and associated problem behaviors, but country-specific norms are seldom collected. The current study presents the standardization of the Swedish Conners 3-« Rating Scales. In addition, we compared the Swedish norms to those collected in the U.S. and Germany.

Material and methods: The study included altogether 3496 ratings of children and adolescents aged 6–18 years from population-based samples.

Results: The scores obtained for the Swedish Conners 3-« showed satisfactory to excellent internal consistency for most subscales and excellent test–retest reliability. Across-informant correlations were modest. Cross-country comparisons revealed that aggression symptoms rated by teachers and ADHD symptoms rated by parents differed between Sweden, Germany and the U.S. Executive functioning deficits also varied as a function of rater and country, with German and Swedish teachers reporting increasing behavior problems with age, whereas a decrease was observed in the U.S. For some subscales, the observed cross-cultural differences were large enough for a child to be classified as being within the normal range (t-score <60) in one country and within the clinical range (t-score > 70) in another country.

Conclusion: The present study shows that the Swedish adaptation of the Conners 3-« provides consistent and reproducible scores. However, across-informant ratings were only modest and significant cross-cultural differences in scoring were observed. This emphasizes the need for multi-informant assessment as well as for national norms for rating instruments commonly used within child and adolescent psychiatry research and clinical settings

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Nutritional Neuroscience. 2018;21:641-47.

NUTRITIONAL AND ENVIRONMENTAL FACTORS IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD): A CROSS-SECTIONAL STUDY.

San MMn, I, Blumenfeld Olivares JA, Garicano VE, et al.

Objectives: Attention-deficit hyperactivity disorder (ADHD) has been related to nutrient deficiencies and unhealthy diets, and to date there is only one study that examined the relationship between the Mediterranean diet and ADHD. The aim was to determine the association between those environmental, nutritional, and body composition factors that may affect the pathogenesis and symptomatology of patients with ADHD in Spain.

Methods: A total of 89 children and adolescents (41 with diagnosed ADHD and 48 controls) were studied in an observation case–control study. Anthropometry, nutritional status, adherence to a Mediterranean diet, sedentary behaviour, and sleep were measured.

Results: Lower adherence to a Mediterranean diet was associated with ADHD diagnosis. Individuals with ADHD more often missed having a second serving of vegetables daily and showed reduced intakes of fish, pulses, and pasta or rice almost every day when compared with controls. Statistically significant differences ($P < 0.05$) were found for fish, cereal, no breakfast and commercially baked goods consumption. There were also statistically significant differences between ADHD individuals and controls when analysing sedentary behaviours and BMI ($P < 0.05$).

Conclusion: Low adherence to a Mediterranean diet might play a role in ADHD development. Not only specific nutrients but also the whole diet should be considered in ADHD. No clear association was found for anthropometry and sedentary behaviours

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Pediatr Ann. 2018 Aug;47:e311-e316.

UPDATE ON COMMON PSYCHIATRIC MEDICATIONS FOR CHILDREN.

Sharma A.

For children and adolescents with uncomplicated psychiatric disorders, pediatricians are often the first prescriber of psychiatric medications. Mental health disorders commonly treated by pediatricians include attention-deficit/hyperactivity disorder (ADHD), depression, and anxiety. There are several safe and effective first-line medications for these disorders. For ADHD, stimulants and nonstimulants can be used as first-line interventions. For anxiety and depression, selective serotonin reuptake inhibitors are well-established treatments and often well-tolerated. With appropriate support and training, pediatricians can increase access for children to necessary mental health treatments

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Pediatr Dermatol. 2018 Sep;35:560-65.

ITCHING AT NIGHT: A REVIEW ON REDUCING NOCTURNAL PRURITUS IN CHILDREN.

Boozalis E, Grossberg AL, Puttgen KB, et al.

The most common causes of chronic nocturnal itching in children are atopic dermatitis and psoriasis, with lichen simplex chronicus and prurigo nodularis contributing to lesser degrees. Despite the prevalence of nocturnal itching, its pathophysiology remains poorly understood. The most troubling consequence of itching at night is poor quality of sleep. Poor sleep quality in children with nocturnal itching has been linked to adverse neurocognitive, behavioral, and physiologic outcomes, including poor performance in school, attention deficit hyperactivity disorder, short stature, hypertension, obesity, and impaired immune function. There is no consensus on the best management of nocturnal itching in children. We conducted a review of the literature evaluating the efficacy of various treatment options for children with chronic nocturnal pruritus. Our review found three recently conducted randomized controlled trials and one case report demonstrating the efficacy of topical corticosteroids, oral melatonin, and clonidine in reducing nocturnal itching or improving sleep quality in children with nocturnal pruritus. Future research is needed to elucidate the pathophysiology of nocturnal itching to best develop targeted, effective treatment strategies

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Pediatr Int. 2018 Sep;60:820-27.

NEUROCOGNITIVE ASSESSMENT OF CHILDREN WITH NEURODEVELOPMENTAL DISORDERS: PRELIMINARY FINDINGS.

Kawabe K, Horiuchi F, Kondo S, et al.

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention and hyperactivity/impulsivity, and is often treated pharmacologically. It is necessary to use both subjective and objective assessments to diagnose and determine the efficacy of pharmacological treatment in children with ADHD, but cognitive assessment tools for ADHD are scarce. We examined a computer-administered, brief, and repeatable cognitive assessment tool: CogHealth. The aims of this study were to use the CogHealth battery, an objective assessment tool, to compare cognitive function between children with ADHD or ADHD + autism spectrum disorder (ASD) and healthy children and to assess improvements in cognitive function following pharmacological treatment.

METHODS: We measured the cognitive function of nine children with ADHD or ADHD + ASD using CogHealth and compared the results with those of 33 age-matched children from the community. Cognitive function comparisons were made before and after psychostimulant treatment with methylphenidate.

RESULTS: We detected significant cognitive abnormalities in the children with ADHD, compared with the control subjects. The children with pre-treatment ADHD had significantly more errors on the detection task (DT), and more anticipatory errors in the one card learning task, compared with control children. The children with ADHD significantly improved their accuracy on the one back test (OBT), and had significantly fewer errors, anticipatory errors, and shorter reaction times after osmotic-release oral system methylphenidate treatment.

CONCLUSION: The DT is a useful neurocognitive function assessment for children with ADHD, and the OBT can measure pharmacological treatment effectiveness in children with ADHD

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Pediatr Res. 2018.

CHILDREN'S LOW-LEVEL PESTICIDE EXPOSURE AND ASSOCIATIONS WITH AUTISM AND ADHD: A REVIEW.

Roberts JR, Dawley EH, Reigart JR.

Pesticides are chemicals that are designed specifically for the purpose of killing or suppressing another living organism. Human toxicity is possible with any pesticide, and a growing body of literature has investigated possible associations with neurodevelopmental disorders. Attention deficit disorder with or without hyperactivity (ADHD) and autism spectrum disorder (ASD) are two of these specific disorders that have garnered particular interest. Exposure to toxic chemicals during critical windows of brain development is a biologically plausible mechanism. This review describes the basic laboratory science including controlled pesticide dosing experiments in animals that supports a mechanistic relationship in the development of ADHD and/or ASD. Epidemiological relationships are also described for low-level pesticide exposure and ADHD and/or ASD. The available evidence supports the hypothesis that pesticide exposure at levels that do not cause acute toxicity may be among the multifactorial causes of ADHD and ASD, though further study is needed, especially for some of the newer pesticides

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Pharmaceutical Sciences. 2018;24:193-98.

ASSOCIATION BETWEEN LEVEL OF VITAMIN D WITH ENVIRONMENTAL AND BIOELEMENT FACTORS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Noorazar G, Mehdizadeh G, Ghaffari A, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a behavioral disorder. The exact pathophysiology of ADHD is not completely recognized. Previous studies have shown the role of different genetic and environmental factors in it. This study investigates the relationship between vitamin D and environmental factors in ADHD.

Methods: In this study, 182 children from 2 to 18 years with confirmed ADHD were allocated in this cross-sectional study. Patients with a history of any chronic disease, anticonvulsants and corticosteroids consumption were excluded from the study. The ADHD severity was assessed by Conners' parent scale test. The level of serum vitamin D, ferritin, iron, total iron binding capacity, zinc, magnesium, calcium and routine complete blood count (CBC) were measured.

Results: Although the results showed a U shaped pattern between vitamin D levels and ADHD severity, the correlation between vitamin D level did not show any significant relation with ADHD symptoms severity (p=0.786). Our data showed significant relation between level of vitamin D and ferritin in patients with ADHD (p=0.003). The analysis demonstrates significant relation between vitamin D level and duration of daily TV watching in children with ADHD (p=0.002).

Conclusion: The vitamin D supplementation may improve ADHD symptoms in patients with vitamin D deficiency. In addition, due to the proved effect of ferritin level in ADHD and significant relation with vitamin D level in this study, treatment of vitamin D deficiency is necessary in children with ADHD. Replacing TV watching by more outdoor activity may improve ADHD symptoms

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Phys Occup Ther Pediatr. 2018 Nov;38:444-56.

COGNITIVE-FUNCTIONAL (COG-FUN) DYADIC INTERVENTION FOR CHILDREN WITH ADHD AND THEIR PARENTS: IMPACT ON PARENTING SELF-EFFICACY.

Hahn-Markowitz J, Berger I, Manor I, et al.

AIM: The family context of children with ADHD plays a role in intervention outcomes, especially when parents are involved in treatment. Parental participation in evidence-based treatment for ADHD may play a role in

improving their own parenting self-efficacy (PSE) as well as child outcomes. This study examined the impact of Cognitive-Functional (Cog-Fun) intervention in occupational therapy (OT) for school-aged children with ADHD, on PSE.
METHODS: In this randomized controlled trial with crossover design, 107 children were allocated to intervention and waitlist control groups. Intervention participants (n = 50) received Cog-Fun after baseline assessment and waitlist controls (n = 49) received treatment 3 months later. Intervention participants received 3-month follow-up assessment. Treatment included 10 parent-child Cog-Fun weekly sessions. PSE was assessed with the Tool to measure Parenting Self-Efficacy (TOPSE).
RESULTS: All children who began treatment completed it. Mixed ANOVA revealed significant Time x Group interaction effects on TOPSE scales of Play and Enjoyment, Control, Self-Acceptance, Knowledge and Learning and Total score, which showed significant improvement with moderate treatment effects for the intervention group. Results were replicated in the control group after crossover.
CONCLUSION: The findings of this study suggest that Cog-Fun OT intervention may be effective for improving aspects of PSE among parents of children with ADHD

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Pratique Neurologique - FMC. 2018.
TIC DISORDERS AND TOURETTE SYNDROME.
Sanchez S, Humbertclaude V, Carme E, et al.
Tics and Gilles de la Tourette syndrome (TS) are common in childhood. They may be associated with various neuropsychiatric comorbidities including attention deficit hyperactivity disorder, obsessive–compulsive disorder, behavioral disturbances with impulse control disorder. Tic disorders represent a heterogeneous spectrum ranging from benign forms to more disabling situations with learning and quality of life impairment. In most patients with TS, tics progressively improve at adolescence, whereas comorbidities persist. Proper diagnosis and treatment of patients with tics involves appropriate evaluation and recognition, not only of tics, but also of these associated conditions. Pharmacological treatment is often not necessary

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Prax Kinderpsychol Kinderpsychiatr. 2018 May;67:315-32.
ATTACHMENT AND EXTERNALIZING BEHAVIOR PROBLEMS IN PRIMARY SCHOOL CHILDREN WITH ADHD.
Franke S, Kissgen R.
Attachment and Externalizing Behavior Problems in Primary School Children with ADHD When examining children with ADHD, attachment research does not usually differentiate between the different clinical pictures within the disorder. This study examines attachment and ADHD in children who display a simple or unspecified form of ADHD, in order to be able to draw specific conclusions about this particular group. Attachment, ADHD symptoms as well as externalizing behavior problems were assessed from 93 children aged five to nine years, 48 of whom had an ADHD diagnosis. The distributions of attachment representations between children with ADHD and those without ADHD differ greatly. In addition, externalizing behavior problems differ between attachment classifications. Attachment seems to be an important factor in the etiology of ADHD, however, ADHD as well as externalizing behavior problems as a global construct are too unspecific to determine the influence of attachment on the disorder. Subsequent studies should first focus on specific symptom patterns within the clinical picture whereas clinical practice should consider the parent-child relation an important factor in the development as well as the treatment of ADHD

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Prescriber. 2018;29:23-27.
DIAGNOSIS AND MANAGEMENT OF ADHD IN CHILDREN AND ADULTS.
Chaplin S.
In March, NICE updated its guidance on the diagnosis and management of attention deficit hyperactivity disorder (ADHD) for the first time in 10 years. This article provides a summary of the new guidelineΓÇÖs main recommendations

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Proc Natl Acad Sci U S A. 2018 Oct;115:9875-81.
SCREEN MEDIA USE AND ADHD-RELATED BEHAVIORS: FOUR DECADES OF RESEARCH.
Beyens I, Valkenburg PM, Piotrowski JT.
The diagnosis of attention-deficit/hyperactivity disorder (ADHD) among children and adolescents has increased considerably over the past decades. Scholars and health professionals alike have expressed concern about the role of screen media in the rise in ADHD diagnosis. However, the extent to which screen media use and ADHD are linked remains a point of debate. To understand the current state of the field and, ultimately, move the field forward, we provide a systematic review of the literature on the relationship between children and adolescents' screen media use and ADHD-related behaviors (i.e., attention problems, hyperactivity, and impulsivity). Using the Differential Susceptibility to Media effects Model as a theoretical lens, we systematically organize the existing literature, identify potential shortcomings in this literature, and provide directions for future research. The available evidence suggests a statistically small relationship between media and ADHD-related behaviors. Evidence also suggests that individual child differences, such as gender and trait aggression, may moderate this relationship. There is a clear need for future research that investigates causality, underlying mechanisms, and differential susceptibility to the effects of screen media use on ADHD-related behaviors. It is only through a richer empirical body that we will be able to fully understand the media-ADHD relationship

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Proc Natl Acad Sci U S A. 2018 Oct;115:9851-58.
HOW EARLY MEDIA EXPOSURE MAY AFFECT COGNITIVE FUNCTION: A REVIEW OF RESULTS FROM OBSERVATIONS IN HUMANS AND EXPERIMENTS IN MICE.
Christakis DA, Ramirez JSB, Ferguson SM, et al.
Attention deficit hyperactivity disorder (ADHD) is now among the most commonly diagnosed chronic psychological dysfunctions of childhood. By varying estimates, it has increased by 30% in the past 20 years. Environmental factors that might explain this increase have been explored. One such factor may be audiovisual media exposure during early childhood. Observational studies in humans have linked exposure to fast-paced television in the first 3 years of life with subsequent attentional deficits in later childhood. Although longitudinal and well controlled, the observational nature of these studies precludes definitive conclusions regarding a causal relationship. As experimental studies in humans are neither ethical nor practical, mouse models of excessive sensory stimulation (ESS) during childhood, akin to the enrichment studies that have previously shown benefits of stimulation in rodents, have been developed. Experimental studies using this model have corroborated that ESS leads to cognitive and behavioral deficits, some of which may be potentially detrimental. Given the ubiquity of media during childhood, these findings in humansand rodents perhaps have important implications for public health

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Psychiatr Danub. 2018 Mar;30:79-84.

CLINICAL CHARACTERISTICS AND COMORBIDITY OF PEDIATRIC TRICHOTILLOMANIA: THE STUDY OF 38 CASES IN CROATIA.

Klobucar A, Folnegovic-Smalc V, Kocijan-Hercigonja D, et al.

BACKGROUND: The main goal of this study was to analyse and show clinical characteristics and psychiatric comorbidity in 38 participants aged between 10 and 17 with DSM-IV diagnoses of Trichotillomania (TTM) that we were treating at Children's Hospital Zagreb from 2008 to 2017.
SUBJECTS AND METHODS: We analyzed the data obtained from semi-structured interviews by the criteria of DSM-IV, Youth Self Report (YSR) (Achenbach & Rescorla 2001) and survey that we created.
RESULTS: From 38 participants 21 were girls. The activities during which the participants state that they mostly pull hairs are as follows: doing homework and learning, working on PC, in the toilet, watching TV etc. The most common sites on the body from which participants pulled hair were scalp and among nonscalp sites eyebrows and eyelashes. We found nail biting in more than a half of participants. In 22 participants one or more comorbid disorder has been found, of which ADHD (n=6) and tics (n=5) are most co-occurring disorders. The internalized and externalized problems were nearly evenly represented. Trichophagia was reported by two participants. The results indicate that more than two thirds of participants isolate themselves during hair pulling and half of them try to hide consequences. Median time from the first occurrence of the symptoms to the first visit to a child psychiatrist caused by TTM problem was 9 months (min 5; max 24) what we consider a very long period of time that increased the probability of complications.
CONCLUSIONS: Knowledge about this disorder and cooperation among pediatric experts is extremely important for recognizing it at an early stage and starting the treatment especially considering habit-forming mechanism, the burden of an emotional distress and frequent comorbidity. Further research is needed

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Psychiatr Danub. 2018 Mar;30:2-10.

SUICIDE RISK IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Giupponi G, Giordano G, Maniscalco I, et al.

BACKGROUND: ADHD (Attention-deficit/hyperactivity disorder) is a common neurodevelopmental disorder that manifests itself during childhood with various combinations of symptoms, including inattention, hyperactivity and impulsivity. Research has shown that psychiatric comorbidities play an important role in the development of suicidal behavior and, recently, there has been a growing interest in a possible association between ADHD and suicide during both childhood and adulthood. Furthermore, some authors have shown a relationship between pharmacological treatments and suicide in patients affected by ADHD. AIMS: We conducted a selective review of current literature to explore the factors which contribute to suicidal behavior and self-harm in those with ADHD.
METHODS: We performed a PubMed/MEDLINE, Scopus, PsycLit, and PsycINFO search to identify all articles and book chapters on the topic up to 2017.
RESULTS: Several studies have showed that ADHD may be correlated with an increased suicide ideation and attempts.
CONCLUSIONS: Although differences in studies design and samples made the results difficult to compare and interpret, many studies indicate an association between ADHD and suicidal behavior. It remains controversial whether there is a direct relationship or whether the association depends on the increased prevalence of pre-existing comorbid conditions and individual and family dysfunctional factors

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Psychiatr Danub. 2018;30:310-16.

HOMOCYSTEINE, PYRIDOXINE, FOLATE AND VITAMIN B12 LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Altun H, Sahin N, et al.

Background: In our study, we aimed to evaluate the serum homocysteine levels, pyridoxine, folate and vitamin B12 levels in children with attention deficit hyperactivity disorders (ADHD).

Subjects and methods: This study included 30 newly diagnosed drug-naive children with ADHD (23 males and 7 female, mean age 9.3-¦1.8 years) and 30 sex-and age matched healthy controls. The diagnosis of ADHD was made according to DSM-V criteria. Children and adolescents were administered the Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version, the Conners' Parent Rating Scale-Revised, Long Form, the Conners' Teacher Rating Scale and the Wechsler Intelligence Scale for Children Revised (WISC-R) for all participants. Homocysteine, pyridoxine, folate and vitamin B12 levels were measured with enzyme-linked immunosorbent assay.
Results: Homocysteine, pyridoxine, folate and vitamin B12 levels were significantly lower in children with ADHD compared with their controls ($p<0.05$). A positive significant correlation was observed between the all WISC-R scores and vitamin B12 level in patients ($r=0.408$, $p=0.025$).
Conclusions: The results obtained in this study showed that reduced homocysteine, pyridoxine, folate and vitamin B12 levels could be a risk factor in the etiology of ADHD

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Psychiatr Psychol Klin. 2018;18:315-19.
THE VIRTUAL CLASSROOM TASK AS AN ALTERNATIVE ADHD DIAGNOSIS METHOD.
Cyranek L.
Nowadays, virtual reality is becoming one of the most innovative methods of diagnosis and therapy as well as psychological and neuropsychological rehabilitation. A virtual environment is created with the use of goggles generating a three-dimensional image. The device induces a state of immersion which can be explained as the sense of presence in a virtually arranged world. As a result of this phenomenon, virtual space tests have high ecological validity, which is an extremely significant aspect for tests employed in psychological diagnosis. The study presents the description of a Virtual Classroom Task applicable in the process of clinical diagnosis, using continuous performance tasks. The method is an alternative way to assess cognitive functions, especially in the case of children suffering from attention-deficit/hyperactivity disorder. The parameters assessed include, above all, attention processes and the inhibition of reaction. The development of virtual space tests creates an opportunity to extend the scope of the measurement techniques used to assess attention processes. Those tests are sophisticated systems aimed at examining the field of vision by following the head movement, especially while presenting a material accompanied by distractors. The stimuli making the task more difficult are visual and auditory. The Virtual Class Task uses also mixed, visual-auditory distractors. This kind of stimuli allows to assess the selectivity, stability or divisibility of attention. The diagnosis with the use of virtual reality test provides relevant information about the cognitive functioning of the subjects. Additionally, this kind of assessment is very interesting for children which is one more advantage worth mentioning. The high ecological validity of results allows for creating an action plan focused on improving the functioning of children with attention-deficit/hyperactivity disorder

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Psychiatry and Clinical Psychopharmacology. 2017;27:329-36.
ASSESSMENT OF RELATIONSHIP BETWEEN COMORBID OPPOSITIONAL DEFIANT DISORDER AND RECOGNITION OF EMOTIONAL FACIAL EXPRESSIONS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Kara H, et al.
Objectives: Attention-deficit/hyperactivity disorder (ADHD) is the most frequent neurobehavioural disorder in childhood. ADHD is associated with impaired academic performance, cognitive, and emotional deficits. Moreover, comorbid oppositional defiant disorder (ODD) is leading to more severe impairment in social performance. Social cognition involves recognition, encoding, and interpretation of emotions from faces. Basic facial expressions that include sadness, happiness, anger, disgust, fear, and surprise are the easiest emotions to recognize. We aimed to demonstrate facial expression recognition impairments that might occur more frequently in children with co-occurring ADHD/ODD than patients with ADHD only. Thus, children with the co-occurrence of ODD may suffer more severely from social and behavioural difficulties.
Methods: Forty patients diagnosed with ADHD and/or co-occurring ADHD/ODD according to DSM-IV-TR criteria were compared with a parallel (by gender, age, and educational state) 11 healthy children as a control

group in this study. Clear facial images of each emotion were used as well as two additional sets of photos include 50% blurred images and cropped eye images were added as distractors then all images represented with black and white tone for emotion recognition task via facial expression. Angry expressions presented as target expressions. DSM-IV-Based Screening and Rating Scale for Children and Adolescents with attention deficit and disruptive behaviour disorders, the Conners Teachers Rating Scale/ Revised Long Form and the Conners Parent Rating Scale/Revised Long Form were used to provide diagnostic objectivity.
Results: Control group statistically performed better than ADHD group on recognition of emotional facial expressions. Results showed no statistically significant differences between the ADHD and ADHD/ODD group on recognition of emotional facial expressions. However, according to results of emotion recognition task via facial expressions, there were statistically significant differences between pure ADHD and comorbid ADHD+ODD groups in happy and neutral expressions. ADHD/ODD group tend to attribute more meaning to neutral facial expressions. Additionally there was statistically significant difference between control group and ADHD group according to recognition of angry expressions. There were statistically significant differences between the groups according to recognition of sad expressions in all clear, blurred, and eye photographs.
Conclusions: Difficulties in recognizing emotional facial expressions were observed in children with ADHD. A statistically significant association was established between presence of ADHD and impaired recognition of facial emotion expressions independent from the scores of the disruptive behaviour rating scale. Comorbid ODD was not associated with recognition of emotional facial expressions including angry expressions. Recognition of angry expressions was not found as a predictor for disruptive behaviour disorders

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Psychiatry Clin Neurosci. 2018 Jul;72:531-39.

ASSOCIATIONS BETWEEN PROBLEMATIC INTERNET USE AND PSYCHIATRIC SYMPTOMS AMONG UNIVERSITY STUDENTS IN JAPAN.

Kitazawa M, Yoshimura M, Murata M, et al.

AIM: Research on the adverse effects of Internet use has gained importance recently. However, there is currently insufficient data on Japanese young adults' Internet use, so we conducted a survey targeting Japanese university students to research problematic Internet use (PIU). We also investigated the relationship between PIU and multiple psychiatric symptoms.
METHODS: A paper-based survey was conducted at five universities in Japan. Respondents were asked to fill out self-report scales regarding their Internet dependency using the Internet Addiction Test (IAT). Sleep quality, attention-deficit hyperactivity disorder (ADHD) tendency, depression, and anxiety symptom data were also collected based on respective self-reports.
RESULTS: There were 1336 responses and 1258 were included in the analysis. The mean IAT score (+/- SD) was 37.87 +/- 12.59; and 38.2% of participants were classified as PIU, and 61.8% as non-PIU. The trend level for young women showed that they were more likely to be classified as PIU than young men (40.6% and 35.2% respectively, P = 0.05). Compared to the non-PIU group, the PIU group used the Internet longer (P < 0.001), had significantly lower sleep quality (P < 0.001), had stronger ADHD tendencies (P < 0.001), had higher Depression scores (P < 0.001), and had higher Trait-Anxiety scores (P < 0.001). Based on multiple logistic regression analyses, the factors that contributed to an increased risk of PIU were: being female (odds ratio [OR] = 1.52), being older (OR = 1.17), having poor sleep quality (OR = 1.52), having ADHD tendencies (OR = 2.70), having depression (OR = 2.24), and having anxiety tendencies (OR = 1.43).
CONCLUSION: We found a high PIU prevalence among Japanese young adults. The factors that predicted PIU were: female sex, older age, poor sleep quality, ADHD tendencies, depression, and anxiety

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Psychiatry Res. 2018;270:281-85.

TEMPERAMENT AND CHARACTER PROFILES FOR CHILDREN WITH ADHD WITH AND WITHOUT TIC DISORDERS.

Kang NR, Kwack YS.

There is no research about whether ADHD with tic disorder that temperamental features that differ from the ADHD. This research aimed to identify temperament and character profiles for children with ADHD according to tic disorder by comparing them with a healthy control group. A discriminant analysis was conducted to identify whether temperament and character profiles can discriminate comorbidity. The sample consisted of three groups (N = 40 per group): ADHD alone, ADHD with tic disorder and age- and sex- matched healthy control. The parents of 120 children (mean age 8.57 -¦ 1.71 years) completed the Junior Temperament and Character Inventory (JTCI). The two ADHD groups showed higher novelty seeking and low persistence, self-directedness and cooperativeness than the control group. The ADHD alone group had lower scores for persistence and self-directedness than the other two groups. Temperament and character profiles were useful for discriminating ADHD from the control group. However, their discriminating power was relatively low for all three groups. Results indicated that differences in temperament and character in ADHD children were present according to comorbid tic disorders. JTCI's discriminating power for ADHD alone and ADHD with tic disorder was relatively lower than that of the combined ADHD group and the control group

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Psychiatry Res. 2018;270:544-46.

RNA-SEQ BLOOD TRANSCRIPTOME PROFILING IN FAMILIAL ATTENTION DEFICIT AND HYPERACTIVITY DISORDER (ADHD).

Lorenzo G, Braun J, Mu+¦oz G, et al.

We have carried an exploratory study by blood transcriptome to find RNA expression signatures in familial ADHD. Samples were collected from three cases with familial ADHD and their paired controls and evaluated by RNA-Seq. Transcriptome profiling identified 7 differentially expressed transcripts with a FDR <0.05 that were involved in pathways in Huntington's disease or axonal guidance signaling previously implicated in ADHD, and enriched for signal peptide, growth factor binding, and notably the lipid metabolism pathways. These findings show that blood transcriptome can have an associated signature and highlight a potential to use blood transcriptome to identify patterns of ADHD

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Psychiatry Res. 2018;270:117-22.

THEORY OF MIND AND EMOTION REGULATION DIFFICULTIES IN CHILDREN WITH ADHD.

Kalyoncu T, et al.

Social cognition deficits and emotion dysregulation (ED) are frequently separately studied in relation to ADHD. This study aimed to examine the link between theory of mind (ToM) abilities and ED in children with ADHD. Participants were 200 children aged 11-17 years (study group, n = 100; healthy controls, n = 100). Emotion regulation skills were quantified by using the Difficulties in Emotion Regulation Scale (DERS). ToM was quantified by three different tasks. Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) Disruptive Behavior Disorders Rating Scale parents form was used for determination of ADHD symptom severity (ADHD-SS). Children in the study group had more overall difficulties regulating their emotions than healthy controls. Within the study group, a significant correlation was found between the scores of DERS-total and ADHD-SS; and between the scores of DERS-total and gender. The linear regression showed that the predictor variables accounted for 56% of the variation in DERS-total. Unexpected Outcomes Test (UOT) scores significantly improved the accountability of the total variance when added to the linear regression. Our findings show that theory of mind deficits may partly explain ED in children with ADHD

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Psychol Assess. 2018 Oct.

DO WE NEED AN IRRITABLE SUBTYPE OF ADHD? REPLICATION AND EXTENSION OF A PROMISING TEMPERAMENT PROFILE APPROACH TO ADHD SUBTYPING.

Karalunas SL, Gustafsson HC, Fair D, et al.

Attention deficit hyperactivity disorder (ADHD) is emblematic of unresolved heterogeneity in psychiatric disorders—the variation in biological, clinical, and psychological correlates that impedes progress on etiology. One approach to this problem is to characterize subgroups using measures rooted in biological or psychological theory, consistent with the National Institute of Mental Health's research domain criteria initiative. Within ADHD, a promising application involves using emotion trait profiles that can address the role of irritability as a complicating feature for ADHD. Here, a new sample of 186 children with ADHD was evaluated using community detection analysis to determine if meaningful subprofiles existed and if they replicated those previously identified. The new sample and a prior sample were pooled for evaluation of (a) method dependence, (b) longitudinal assessment of the stability of classifications, and (c) clinical prediction 2 years later. Three temperament profiles were confirmed within the ADHD group: one with normative emotional functioning ('mild'), one with high surgency ('surgent'), and one with high negative affect ('irritable'). Profiles were similar across statistical clustering approaches. The irritable group had the highest external validity: It was moderately stable over time and it enhanced prospective prediction of clinical outcomes beyond standard baseline indicators. The irritable group was not reducible to ADHD + oppositional defiant disorder, ADHD + disruptive mood dysregulation disorder, or other patterns of comorbidity. Among the negative affect domains studied, trait proneness to anger uniquely contributed to clinical prediction. Results extend our understanding of chronic irritability in psychiatric disorders and provide prospects for a fresh approach to assessing ADHD heterogeneity focused on the distinction between ADHD with and without anger/irritability.

Public Significance Statement—This work identifies a group of children with ADHD and irritable mood who are at increased risk for negative outcomes. Addition of a specifier in the ADHD diagnostic criteria based on the presence or absence of irritability could be considered.

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Rehabil Psychol. 2018.

PSYCHOLOGICAL DIFFICULTIES AND PARENTAL WELL-BEING IN CHILDREN WITH MUSCULOSKELETAL PROBLEMS IN THE 2011/2012 NATIONAL SURVEY OF CHILDREN'S HEALTH.

Williams NA, Burnfield JM.

Objective: This study compared children with and without current musculoskeletal (MSK) problems on key indices of child psychological adjustment and parental well-being.

Research Method: Prevalence estimates of psychological problems were compared for children ages 2-17 years with and without current MSK problems in the 2011/2012 National Survey of Children's Health. Multivariate logistic regression analyses examined the effects of MSK problem severity on the risk of psychological concerns.

Results: Population level differences in prevalence estimates were observed in psychological difficulties. Children with MSK problems were disproportionally affected by anxiety problems, depression, behavioral/conduct problems, and ADHD compared to children without MSK problems. Compared to children with mild MSK problems, children with severe MSK problems were 2.74 times more likely to have anxiety problems (95% CI [1.35, 2.86], $p < .05$). No other significant differences were found among children with mild, moderate, or severe MSK problems. Regarding parental well-being, compared to children without MSK problems, children with MSK problems were more likely to have mothers and fathers who often experience parenting stress/aggravation and have poor physical and mental health.

Conclusions: Children with MSK problems are vulnerable to psychological difficulties that can affect their learning, development, and quality of life. Psychological screening and ensuring that these children receive effective mental health treatments should be a priority in pediatric health care settings. Consideration of parental physical and mental health is recommended in the assessment and treatment of children with MSK problems

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Reprod Toxicol. 2018 Mar;76:63-70.

PRENATAL EXPOSURE TO MATERNAL SMOKING DURING PREGNANCY AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN OFFSPRING: A META-ANALYSIS.

Dong T, Hu W, Zhou X, et al.

Some large population-based cohort studies highlighted the risk of maternal smoking during pregnancy (MSDP) for children attention-deficit/hyperactivity disorder (ADHD). However, the causality of this association is still controversial. Here we performed a meta-analysis trying to clarify the association between prenatal exposure to MSDP and ADHD in offspring. After publication screening, 27 eligible original articles with a total of 3076173 subjects were included. The results showed that either prenatal exposure to MSDP or smoking cessation during first trimester was significantly associated with childhood ADHD after adjusting for parental psychiatric history and social socioeconomic status. Smoking cessation before pregnancy, which was not significantly associated with childhood ADHD, was strongly recommended for female smokers planning to conceive. Inconsistent results were obtained in the meta-analysis on the risk of maternal passive smoking during pregnancy caused by paternal smoking. We also found that risk of MSDP for childhood ADHD varied across geographic regions

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Res Dev Disabil. 2018 Jun;77:12-23.

ACUTE AND CHRONIC EFFECT OF PHYSICAL ACTIVITY ON COGNITION AND BEHAVIOUR IN YOUNG PEOPLE WITH ADHD: A SYSTEMATIC REVIEW OF INTERVENTION STUDIES.

Suarez-Manzano S, Ruiz-Ariza A, Torre-Cruz M, et al.

BACKGROUND: Young people with attention deficit hyperactivity disorder (ADHD) often have learning and behavioral control difficulties. AIM: The aim of this review is analyse the acute and chronic effect of physical activity (PA) on the cognition and behaviour of children and adolescents with ADHD.

METHODS: Studies were identified in five databases (PubMed, SPORTDiscus, ProQuest, Web of Science, and SCOPUS), from January 2000 through to January 2017. A total of 16 interventional studies met the inclusion criteria.

RESULTS/CONCLUSIONS: PA practice of 20-30min (intensity 40-75%) produces a positive acute effect on processing speed, working memory, planning and problem solving in young people with ADHD. However, these effects on behaviour are contradictory and vary depending on age. Chronic PA practice (>/=30min per day, >/=40% intensity, >/=three days per week, >/=five weeks) further improves attention, inhibition, emotional control, behaviour and motor control. The results must be treated with caution, because only 25% of the studies used confounders.

IMPLICATION: More research is needed to justify the causes of these effects. It is necessary to establish programs with regard to the duration, intensity, kind of exercise, and time of PA to improve cognition and behaviour in young people with ADHD taking into account potential confounders

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Rev Neurol. 2018;67:195-202.

CHILDREN'S AND ADOLESCENTS□ÇÖ PERCEPTION OF THEIR QUALITY OF LIFE IN CASES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH AND WITHOUT PHARMACOLOGICAL TREATMENT AND IN CONTROLS.

Lòpez-Villalobos JA, Garrido-Redondo M, et al.

Introduction. Health-related quality of life perceived by children and teenagers is important to assess the effects of therapeutic intervention.

Aim. To analyze quality of life, comparing cases of attention deficit hyperactivity disorder (ADHD) treated with methylphenidate, untreated cases and controls.

Subjects and methods. Sampling of 228 participants between 8 and 14 years-old. Consecutive sampling in ADHD according to DSM-IV criteria (ADHD Rating Scales IV) and random sampling of matched controls by sex and age. Evaluation of quality of life using KIDSCREEN-52 (children version). ANOVA with Bonferroni correction was used.

Results. There is a moderate significant correlation between greater intensity of ADHD symptoms and worse quality of life, except in the dimension of physical well-being. Cases of untreated ADHD have significantly worse quality of life than controls on psychic well-being, mood, autonomy school environment and social acceptance. Cases of treated ADHD present similar results, except in the school environment and psychological well-being. The cases of ADHD treated only differ significantly from ADHD not treated in having a better school environment.
Conclusions. The cases of ADHD present dimensions of KIDSCREEN-52 with worse quality of life than controls and the cases of ADHD treated with methylphenidate only differ significantly from those not treated in presenting better results in the school environment

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Revista de Psicopatología y Psicología Clínica. 2018 Aug;23:79-88.
RECONOCIMIENTO DE EXPRESIÓN FACIAL EMOCIONAL EN EL TRASTORNO DE DÉFICIT DE ATENCIÓN E HIPERACTIVIDAD EN LA INFANCIA = RECOGNITION OF EMOTIONAL FACIAL EXPRESSION IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN CHILDHOOD.
Oliva-Macías M, Parada-Fernández P, Amayra I, et al.
The main symptoms of attention deficit/hyperactivity disorder (ADHD) are inattention, hyperactivity and impulsivity. In addition to cognitive and behavioral deficits present in ADHD, having difficulties in social skills has also been observed in different studies. The objective of this study was to analyze performance in recognizing emotional facial expression in this group. For this, a clinical group with ADHD was compared to a control group. Emotional facial expression recognition tools were applied. No statistically significant differences were found between groups in non-contextualized static emotions. However, differences were found in non-contextualized dynamic emotions, contextualized scenarios and secondary social skills. In addition, a more comprehensive analysis identified a subgroup of children with ADHD that performed better than the other ADHD group of children and similarly to the control group

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SAGE Open Medical Case Reports. 2016;4.
UNGUAL FIBROMA IN 12-YEAR-OLD BOY WITH HYPOMELANOTIC MACULES, INTELLECTUAL DISABILITY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER POSSIBLE TUBEROUS SCLEROSIS.
Glavan N, Ljubi-ii-ç-Bistrovi-ç I, Grahovac B, et al.
Objective: To report a case of a 12-year-old boy with intellectual disability and attention deficit hyperactivity disorder, who came to surgery for an examination due to a minor bulge on the left thumb, which had been growing for the previous month. His mother denied any trauma.
Methods: After the removal of the clinically ambiguous bulge and a pathohistological confirmation that it was a periungual fibroma, complete patient analysis was performed due to the presence of hypomelanotic macules and a suspected tuberous sclerosis.
Results: Considering the presence of hypomelanotic macules, as one of the main criteria, possible TS diagnosis was set.
Conclusion: Early detection of the symptoms of TS enables a timely provision of protocols for further patient monitoring, which affects the patient's morbidity and mortality

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Scand J Psychol. 2018 Jun;59:273-80.
DOES PARENTAL MENTAL HEALTH MODERATE THE EFFECT OF A TELEPHONE AND INTERNET-ASSISTED REMOTE PARENT TRAINING FOR DISRUPTIVE 4-YEAR-OLD CHILDREN?
Fossum S, Cunningham C, Ristkari T, et al.
This study explores the moderators affecting the success of an Internet-based and telephone assisted remote parent training intervention and compares them to an educational control group. We prospectively identified 464 parents who reported at a health check that their 4-year-old children showed elevated levels of

externalizing behavior. The moderators explored included parental attention deficit and hyperactivity disorder (ADHD) and parental distress. The dependent variables were child externalization scores and self-reported parenting skills. The measures were completed at baseline, six and 12-months follow-up. The 232 families randomized to active treatment received 11 Internet-based training sessions with weekly phone calls from a coach. The other 232 families had access to a website that provided general positive parenting advice and one 45-minute phone-call from a coach. Using hierarchical linear models, we explored if the parental ADHD or parental distress modified the treatment effects on child externalizing behavior or parenting skills. The results showed that none of the independent variables moderated intervention effects on child externalizing behavior or parenting skills. The lack of significant moderator effects could have been due to the treatment's personalization, the format's flexibility and adaptability to when and how the parents wanted to complete the sessions or the relatively low levels of ADHD and parental distress among the participants

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Scand J Psychol. 2018 Oct;59:511-17.

ERRORS ON A COMPUTER TASK AND SUBCLINICAL SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Christensen KE, Lundwall RA .

Previous reports have found increased error rate for children with attention-deficit/hyperactivity disorder (ADHD) on response time (RT) computer tasks. Here we attempt the conceptual replication and extension of two studies that examined error rate in a general population of children (N = 203). Study 1 followed Johnstone and Galletta but considered associations between scores on a dimensional measure of ADHD symptoms (rather than comparing those with or without an ADHD diagnosis) and the frequency of commission and omission errors. Study 2 followed Shiels, Tamm & Epstein and examined post-error adjustment in the same group of children as for Study 1. Study 1 did not replicate previous findings of no increase in errors of commission in those with higher ADHD symptoms (Johnstone & Galletta). Instead, we found that younger children with lower ADHD symptoms were more likely to make commission errors, while omission errors did not vary with age. Study 2 replicated the previous finding of less RT slowing in children with more ADHD symptoms, extending this finding to a general population of children. Namely, as ADHD symptoms increase, RT slowing is less likely, putting children with higher ADHD symptoms at risk of additional errors. Overall, we extend previous ADHD research to typically developing children with ADHD symptoms

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Scand J Psychol. 2018 Oct;59:483-95.

EFFECTS OF THE EXAT NEUROPSYCHOLOGICAL MULTILEVEL INTERVENTION ON BEHAVIOR PROBLEMS IN CHILDREN WITH EXECUTIVE FUNCTION DEFICITS.

Rantanen K, Vierikko E, Nieminen P.

This is a clinical intervention study of children with executive function (EF) deficits. A neuropsychological multimodal group intervention called EXAT (rehabilitation of EXecutive function and ATtention) was developed at the Psychology Clinic of the University of Tampere. Based on the principles of neuropsychological rehabilitation and behavioral modification, EXAT combines child group training, parent training, and teacher consultations. The aims of this study were to investigate behavior problems before and after the intervention in children attending EXAT and in controls, and to compare intervention effects in hyperactive, inattentive, and EF subgroups based on the primary deficit described in the referral. The participants were 86 children (6-12 years) with a mean IQ of 91.4 attending EXAT and 45 controls. The participants' parents and teachers completed the Conners' Rating Scales-Revised. In addition, the Strengths and Difficulties Questionnaire was completed by the parents attending EXAT. The parents reported statistically significant decreases with medium effect sizes for the CPRS-R subscales for impulsivity, hyperactivity, and oppositional behavior. In the controls within the same time interval, there was increase in restless and impulsive behavior, and a decrease in total problems. The teachers reported positive changes after the intervention in ADHD symptoms and anxiousness/shyness, but the effects sizes were small. The

intervention effects were larger in the hyperactive subgroup. Positive intervention effects were related to a younger age, lower IQ, and simultaneous learning support. In conclusion, E

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Sch Psychol Q. 2018 Oct.

BRIEF HOMEWORK INTERVENTION FOR ADOLESCENTS WITH ADHD: TRAJECTORIES AND PREDICTORS OF RESPONSE.

Breaux RP, Langberg JM, Bourchtein E, et al.

In the present study, we sought to examine response trajectories to brief (11-week) school-based homework interventions and factors that may help schools predict responses. Participants included 222 middle-school students (72% boys; Mage = 12.00 years, SD = 1.02) who had been diagnosed with attention-deficit/hyperactivity disorder (ADHD) and had received either a contingency-management or skills-based intervention for homework problems. Both interventions included 16 20-min student meetings with a school counselor and two parent meetings. Trajectories of response for ratings of homework problems and assignment completion were examined from baseline to a 6-month follow-up using growth-mixture models. Baseline variables routinely measured in school settings, including grade-point average (GPA), math and reading achievement, and externalizing and internalizing symptoms, were examined as predictors of treatment-response trajectories. The majority of students (68–81%) showed positive treatment response across outcomes. However, trajectories of students who did not respond to intervention were identified for each outcome. Baseline GPA significantly predicted trajectories for all outcomes and achievement scores significantly predicted trajectories of teacher-reported homework performance and parent-reported homework problems, such that youth with relatively higher baseline GPAs and achievement were most likely to respond. In contrast, neither externalizing nor internalizing symptoms were significant predictors of response trajectories. Schools can use GPA and academic-achievement data to determine whether brief school-based interventions for homework problems are likely to succeed. Students with ADHD who display severe academic impairment (i.e., GPA lower than 2.0 at baseline) may benefit from a more long-term, intensive intervention

Impact and Implications: The majority of students with ADHD displayed a significant and positive response to a brief homework intervention, according to both parent and teacher ratings and the percentage of assignments turned in (68–81% across outcomes). Students with ADHD and severe academic impairment, as indicated by a grade-point average (GPA) below 2.0 at baseline, are less likely to respond and may require more intensive interventions to address homework problems and academic impairment

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Sleep Med. 2018.

SLEEP PHENOTYPES IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Miano S, Amato N, Foderaro G, et al.

Objective: A case-control study was performed to test the hypothesis that children with attention deficit hyperactivity disorder (ADHD) have chronic sleep deprivation and may be classified into specific sleep-related phenotypes.

Methods: Thirty outpatients with ADHD (nine females, mean age 10.1 -¦ 2.1 years) were recruited consecutively, and given a comprehensive sleep assessment, including blood exams, sleep questionnaires, laboratory video-polysomnographic recordings (v-PSG), multiple sleep latency tests, and one-week actigraphy. The PSG parameters were compared to those of 25 age-matched controls (12 females, mean age 10.34 -¦ 1.54 years) who underwent only the v-PSG.

Results: ADHD children were classified as follows: a narcolepsy-like phenotype was found in four; delayed sleep onset insomnia in five; obstructive sleep apnea (OSA) in 15; periodic limb movements in eight, and sleep epileptiform discharges in 10 children. All subjects had a total sleep time shorter than 9 h at actigraphy, ferritin levels lower than 60 mcg/L, and a history of sleep problems (mainly OSA and insomnia). Compared to controls, the ADHD group had a higher apnea-hypopnea index at PSG.

Conclusions: A full sleep assessment in children with ADHD confirmed the validity of the sleep phenotypes hypothesis, and revealed a much higher percentage of sleep problems than that found in the literature.

Beyond the sleep phenotypes, all children reported a history of sleep problems and slept less than 9 h per night, indicating chronic sleep deprivation that should be evaluated as a possible unifying marker of ADHD

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Sleep Med. 2018;52:75-79.

LAST NIGHT'S SLEEP IN RELATION TO ACADEMIC ACHIEVEMENT AND NEUROCOGNITIVE TESTING PERFORMANCE IN ADOLESCENTS WITH AND WITHOUT ADHD.

Cusick CN, Isaacson PA, Langberg JM, et al.

Objectives/background: Objectives were to (1) examine previous night's sleep in relation to next day performance on standardized academic achievement and neurocognitive assessments in adolescents, and (2) explore whether previous night's sleep is differentially associated with testing performance for adolescents with and without attention-deficit/hyperactivity disorder (ADHD).

Participants/methods: Participants were 300 adolescents (ages 12–14 years; 55% male). Approximately half (53.6%) were diagnosed with ADHD. Adolescents provided ratings of their previous night's sleep quality, sleep duration, and number of night wakings and were administered standardized tests of processing speed and working memory, as well as word reading, numerical operations, and math fluency academic achievement.

Results: In analyses controlling for sex, race, medication use, time of testing, and ADHD group status, more night wakings the previous night were associated with significantly lower numerical operations and math fluency achievement scores and marginally lower working memory scores. Previous night's sleep was not associated with processing speed or reading achievement. ADHD status did not moderate sleep in relation to academic/neurocognitive performance. Participants reporting 2 night wakings the previous night had slightly over half a standard deviation lower scores on average compared to participants reporting 0 night wakings.

Conclusions: This preliminary study suggests that previous night's wakings are associated with poorer mathematics performance the next day, regardless of ADHD status. This may be due to the detrimental effect of interrupted and fragmented sleep on attention and executive control. These findings have implications for clinicians and educators when considering contextual factors that may impact academic and neurocognitive testing performance

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Br J Psychiatry. 2018 Sep;213:526-34.

YOUNG ADULT MENTAL HEALTH AND FUNCTIONAL OUTCOMES AMONG INDIVIDUALS WITH REMITTED, PERSISTENT AND LATE-ONSET ADHD.

Agnew-Blais JC, Polanczyk GV, Danese A, et al.

Background: Attention-deficit hyperactivity disorder (ADHD) is associated with mental health problems and functional impairment across many domains. However, how the longitudinal course of ADHD affects later functioning remains unclear.

Aims: We aimed to disentangle how ADHD developmental patterns are associated with young adult functioning.

Method: The Environmental Risk (E-Risk) Longitudinal Twin Study is a population-based cohort of 2232 twins born in England and Wales in 1994–1995. We assessed ADHD in childhood at ages 5, 7, 10 and 12 years and in young adulthood at age 18 years. We examined three developmental patterns of ADHD from childhood to young adulthood—remitted, persistent and late-onset ADHD—and compared these groups with one another and with non-ADHD controls on functioning at age 18 years. We additionally tested whether group differences were attributable to childhood IQ, childhood conduct disorder or familial factors shared between twins.

Results: Compared with individuals without ADHD, those with remitted ADHD showed poorer physical health and socioeconomic outcomes in young adulthood. Individuals with persistent or late-onset ADHD showed poorer functioning across all domains, including mental health, substance misuse, psychosocial, physical

health and socioeconomic outcomes. Overall, these associations were not explained by childhood IQ, childhood conduct disorder or shared familial factors.
Conclusions: Long-term associations of childhood ADHD with adverse physical health and socioeconomic outcomes underscore the need for early intervention. Young adult ADHD showed stronger associations with poorer mental health, substance misuse and psychosocial outcomes, emphasising the importance of identifying and treating adults with ADHD

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Lancet Psychiatry. 2018;5:727-38.

COMPARATIVE EFFICACY AND TOLERABILITY OF MEDICATIONS FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN, ADOLESCENTS, AND ADULTS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS.

Cortese S, Adamo N, Del GC, et al.

Background The benefits and safety of medications for attention-deficit hyperactivity disorder (ADHD) remain controversial, and guidelines are inconsistent on which medications are preferred across different age groups. We aimed to estimate the comparative efficacy and tolerability of oral medications for ADHD in children, adolescents, and adults.
Methods We did a literature search for published and unpublished double-blind randomised controlled trials comparing amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil with each other or placebo. We systematically contacted study authors and drug manufacturers for additional information. Primary outcomes were efficacy (change in severity of ADHD core symptoms based on teachers' and clinicians' ratings) and tolerability (proportion of patients who dropped out of studies because of side-effects) at timepoints closest to 12 weeks, 26 weeks, and 52 weeks. We estimated summary odds ratios (ORs) and standardised mean differences (SMDs) using pairwise and network meta-analysis with random effects. We assessed the risk of bias of individual studies with the Cochrane risk of bias tool and confidence of estimates with the Grading of Recommendations Assessment, Development, and Evaluation approach for network meta-analyses. This study is registered with PROSPERO, number CRD42014008976.
Findings 133 double-blind randomised controlled trials (81 in children and adolescents, 51 in adults, and one in both) were included. The analysis of efficacy closest to 12 weeks was based on 10 068 children and adolescents and 8131 adults; the analysis of tolerability was based on 11 018 children and adolescents and 5362 adults. The confidence of estimates varied from high or moderate (for some comparisons) to low or very low (for most indirect comparisons). For ADHD core symptoms rated by clinicians in children and adolescents closest to 12 weeks, all included drugs were superior to placebo (eg, SMD −1·02, 95% CI −1·19 to −0·85 for amphetamines, −0·78, −0·93 to −0·62 for methylphenidate, −0·56, −0·66 to −0·45 for atomoxetine). By contrast, for available comparisons based on teachers' ratings, only methylphenidate (SMD −0·82, 95% CI −1·16 to −0·48) and modafinil (−0·76, −1·15 to −0·37) were more efficacious than placebo. In adults (clinicians' ratings), amphetamines (SMD −0·79, 95% CI −0·99 to −0·58), methylphenidate (−0·49, −0·64 to −0·35), bupropion (−0·46, −0·85 to −0·07), and atomoxetine (−0·45, −0·58 to −0·32), but not modafinil (0·16, −0·28 to 0·59), were better than placebo. With respect to tolerability, amphetamines were inferior to placebo in both children and adolescents (odds ratio [OR] 2·30, 95% CI 1·36–3·89) and adults (3·26, 1·54–6·92); guanfacine was inferior to placebo in children and adolescents only (2·64, 1·20–5·81); and atomoxetine (2·33, 1·28–4·25), methylphenidate (2·39, 1·40–4·08), and modafinil (4·01, 1·42–11·33) were less well tolerated than placebo in adults only. In head-to-head comparisons, only differences in efficacy (clinicians' ratings) were found, favouring amphetamines over modafinil, atomoxetine, and methylphenidate in both children and adolescents (SMDs −0·46 to −0·24) and adults (−0·94 to −0·29). We did not find sufficient data for the 26-week and 52-week timepoints.
Interpretation Our findings represent the most comprehensive available evidence base to inform patients, families, clinicians, guideline developers, and policymakers on the choice of ADHD medications across age groups. Taking into account both efficacy and safety, evidence from this meta-analysis supports methylphenidate in children and adolescents, and amphetamines in adults, as preferred first-choice medications for the short-term treatment of ADHD. New research should be funded urgently to assess long-term effects of these drugs.

Funding Stichting Eunethydis (European Network for Hyperkinetic Disorders), and the UK National Institute for Health Research Oxford Health Biomedical Research Centre

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Lancet Psychiatry. 2018;5:689-90.
INTRIGUING FINDINGS REGARDING THE ASSOCIATION BETWEEN ASTHMA AND ADHD.
Agnew-Blais J.

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Lancet Psychiatry. 2018;5:824-35.
TRENDS IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER MEDICATION USE: A RETROSPECTIVE OBSERVATIONAL STUDY USING POPULATION-BASED DATABASES.
Raman SR, Man KKC, Bahmanyar S, et al.
Background: The use of medications to treat attention deficit hyperactivity disorder (ADHD) has increased, but the prevalence of ADHD medication use across different world regions is not known. Our objective was to determine regional and national prevalences of ADHD medication use in children and adults, with a specific focus on time trends in ADHD medication prevalence.
Methods: We did a retrospective, observational study using population-based databases from 13 countries and one Special Administrative Region (SAR): four in Asia and Australia, two in North America, five in northern Europe, and three in western Europe. We used a common protocol approach to define study populations and parameters similarly across countries and the SAR. Study populations consisted of all individuals aged 3 years or older between Jan 1, 2001, and Dec 31, 2015 (dependent on data availability). We estimated annual prevalence of ADHD medication use with 95% CI during the study period, by country and region and stratified by age and sex. We reported annual absolute and relative percentage changes to describe time trends.
Findings: 154-À5 million individuals were included in the study. ADHD medication use prevalence in 2010 (in children aged 3–18 years) varied between 0-À27% and 6-À69% in the countries and SAR assessed (0-À95% in Asia and Australia, 4-À48% in North America, 1-À95% in northern Europe, and 0-À70% in western Europe). The prevalence of ADHD medication use among children increased over time in all countries and regions, and the absolute increase per year ranged from 0-À02% to 0-À26%. Among adults aged 19 years or older, the prevalence of any ADHD medication use in 2010 varied between 0-À003% and 1-À48% (0-À05% in Asia and Australia, 1-À42% in North America, 0-À47% in northern Europe, and 0-À03% in western Europe). The absolute increase in ADHD medication use prevalence per year ranged from 0-À0006% to 0-À12%. Methylphenidate was the most commonly used ADHD medication in most countries.
Interpretation: Using a common protocol and data from 13 countries and one SAR, these results show increases over time but large variations in ADHD medication use in multiple regions. The recommendations of evidence-based guidelines need to be followed consistently in clinical practice. Further research is warranted to describe the safety and effectiveness of ADHD medication in the short and long term, and to inform evidence-based guidelines, particularly in adults. Funding: None

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Tidsskr Nor Laegeforen. 2018 Jan;138.
DRUG TREATMENT OF A.
Vogt H, Lunde C.

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Turk Psikiyatri Derg. 2017;28:268-77.

THE PSYCHOMETRIC PROPERTIES OF TURKISH VERSION OF AUTISM SPECTRUM SCREENING QUESTIONNAIRE IN CHILDREN AGED 6-18 YEARS.

Kose S, Ozbaran B, Yazgan Y, et al.

OBJECTIVE: The objective of this study is to determine the psychometric properties of the Turkish version of the Autism Spectrum Screening Questionnaire (ASSQ-TR) and to find the best cutoff score for Pervasive Developmental Disorder (PDD) cases.

METHOD: Children between 6 to 18 years old with diagnoses of PDD, Obsessive Compulsive Disorder (OCD), and Attention Deficit Hyperactivity Disorder (ADHD) were included. The healthy control (HC) group was recruited from children who did not have any psychiatric complaints or history. Furthermore, parents of 268 children filled the ASSQ-TR. Of the children, 51 were PDD, 67 were ADHD, 50 were OCD, and 100 were HC. In order to show the reliability of the ASSQ-TR, Cronbach's alpha values and test-retest were evaluated. ROC analyses was carried out to show concurrent validity and to determine the cutoff score.

RESULTS: The Cronbach's alpha of ASSQ-TR is 0,86, while the test-retest reliability is r: 0,98. Total ASSQ-TR scores of children with PDD (27,96+/-9,5) were significantly higher than other groups (p<0,001). ROC analysis of ASSQ-TR showed the area under curve to be 0,97 with a cutoff of 16, having the maximum sensitivity (94,1%), specificity (89,0%), and 90,7% diagnostic accuracy of PDD versus HC scores.

CONCLUSIONS: Our pilot data showed that ASSQ-TR is a reliable instrument that successfully differentiates clinically diagnosed PDD from HC. This instrument might therefore be useful for the screening of PDD in school-aged children in Turkish populations

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Turk Psikiyatri Derg. 2018;29:31-35.

NEUROPEPTIDE Y LEVELS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Hekim BO, Guney E, Goker Z, et al .

OBJECTIVE: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in adolescence, however, the etiology has not been described. Neuropeptide Y (NPY) is one potential factor that may be involved in the etiology of ADHD. The goal of this study was to evaluate NPY levels in children with ADHD and compare the findings to healthy controls.

METHODS: Forty-eight ADHD patients and 40 healthy controls were included in this study. The age range of ADHD patients was 6 to 16 years. All patients were diagnosed according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).

RESULTS: The NPY levels of children with ADHD were compared to healthy controls but were not significantly different (t (86)= -0.887, p= 0.378). NPY levels were similar (F= 0.191, p= 0.826) between ADHD presentations, and included 8 children with predominantly hyperactive-impulsive type (14.3%), 14 children with predominantly inattentive type (30.4%), and 26 children with a combined type (55.4%). There was also no difference between ADHD patients using medical treatment, ADHD patients not using medical treatment, and control subjects in terms of NPY levels (F= 0.572, p= 0.566). There was a significant positive correlation between age and NPY levels in the ADHD group (r= 0.349, p= 0.015).

CONCLUSION: This study demonstrated that the NPY levels of ADHD subjects were not different than those of controls. Future studies with homogeneous phenotypes and a larger sample population are needed

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World J Biol Psychiatry. 2018;19:101-11.

HYPERACTIVITY IN MOTOR RESPONSE INHIBITION NETWORKS IN UNMEDICATED CHILDREN WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Massat I, Slama H, Villemonteix T, et al.

Objectives: Hypo/reduced activity in motor response inhibition (RI) cerebral networks was recently proposed as a promising specific neurobiological marker of attention deficit-hyperactivity disorder (ADHD). Before adopting such a pattern as a key diagnosis tool, we aim to replicate in an independent study the mechanisms underlying reduced RI-related activity in ADHD, after controlling for potentially confounding effects.

Methods: In this fMRI study, we investigated the neural networks mediating successful and failed motor RI in children with ADHD and typically developing children (TDC) using the stop-signal task (SST) paradigm.
Results: In contrast to hypofrontality predictions, children with ADHD exhibit increased neural activity during successful response inhibition in an RI-related brain network encompassing the indirect and/or hyperdirect pathways between the basal ganglia and cortex. Voxel-based morphometry analyses have further evidenced reduced grey matter volume in the left caudate in children with ADHD, which paralleled higher functional responses. Finally, connectivity analyses disclosed tighter coupling between a set of cortical regions and the right caudate as well as the right IFG, networks involved in successful RI.
Conclusions: Hypo/reduced activity in RI cerebral networks in children with ADHD cannot at this time be considered as a systematic biomarker for ADHD

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Z Kinder- Jugendpsychiatr Psychother. 2018;46:298-304.

TAILORING PARENT-CHILD INTERACTION THERAPY (PCIT) FOR OLDER CHILDREN: A CASE STUDY.

Briegel W.

Parent-Child Interaction Therapy (PCIT) is an evidence-based intervention designed for families of 2-to 6-year-old children with disruptive behavior disorders. This article illustrates the application of PCIT in a 10-year-old boy with attention defi cit/hyperactivity disorder (ADHD) and oppositional defi ant disorder (ODD). Both parents and the patient attended PCIT sessions. The course of therapy included minor changes to the PCIT protocol. After 13 PCIT sessions, the patient displayed disruptive behaviors within normal limits, and 12 months later he no longer met diagnostic criteria for ODD. Results remained stable at a 17-month follow-up assessment. This case study suggests that the use of PCIT in families of children with ODD markedly older than the recommended age range might be a promising approach for improving family functioning and reducing behavior problems. Further research with larger samples of older children with ODD is needed to replicate and elaborate the findings of this case study

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ORIGINAL CONTRIBUTION

Behavioral and cognitive effects of docosahexaenoic acid in drug-naïve children with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled clinical trial

Alessandro Crippa[1] · Alessandra Tesei[1] · Federica Sangiorgio[1] · Antonio Salandi[1] · Sara Trabattoni[1] · Silvia Grazioli[1,2] · Carlo Agostoni[3] · Massimo Molteni[1] · Maria Nobile[1]

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Abstract
This study aimed to investigate the efficacy of docosahexaenoic acid (DHA) dietary supplementation on behavior and cognition in school-aged, drug-naïve children with attention-deficit/hyperactivity disorder (ADHD). A total of 50 participants with ADHD aged 7 to 14 were enrolled in a 6-month randomized, placebo-controlled clinical trial and received either DHA or placebo. The primary outcome measure was the change in the ADHD rating scale IV Parent Version–Investigator (ADHD-RS-IV) after 4 and 6 months. Secondary outcome measures included Conners Parent Rating Scale-revised, other behavioral rating scales including quality of life and global functioning, and computerized cognitive tasks. Baseline assessment also addressed the blood fatty acids profile. No superiority of DHA supplement to placebo was observed on ADHD-RS-IV, the a priori primary outcome. DHA supplementation showed a significant, nonetheless quite small, effect on children's psychosocial functioning, emotional problems, and focused attention. Neither major nor minor adverse events were reported throughout the trial. This study shows that 6-month DHA supplementation has no beneficial effect on the symptoms of ADHD in school-aged, drug-naïve children with an established diagnosis of ADHD. Nevertheless, the 6 months treatment with supplemental DHA appears to have small positive effects on other behavioral and cognitive difficulties, which, in light of the absence of side-effects, could be reasonably followed up in future intervention studies. (https://clinicaltrials.gov/ct2/show/NCT01796262: The Effects of DHA on Attention Deficit and Hyperactivity Disorder (DADA)).

Keywords Attention-deficit/hyperactivity disorder (ADHD) · Docosahexaenoic acid (DHA) · Fatty acids · Cognition · Behavior

Introduction

Attention-deficit/hyperactivity disorder (ADHD), characterized by age-inappropriate and persistent inattention, excessive motor activity, and impulsivity, is one of the most common neurodevelopmental disorders with 7.2% of children affected worldwide ([1]; even though the prevalence in Italy is approximately 1%, based on the National Institute of Health' reports [2]). ADHD is a heterogeneous condition and its etiology has genetic and environmental components. With respect to the latter, the possible effect of nutrition on clinical manifestations of ADHD has attracted, during recent years, the attention of clinicians, researchers, and families. In particular, growing interest has been given to the potential role of polyunsaturated fatty acids (PUFAs) for understanding the pathogenesis of the disorder and as a possible coadjutant approach to pharmacological treatment [3]. At the biological level, omega-3 PUFAs are a crucial part of neuronal phospholipid membranes, and, as precursors of eicosanoids, can influence the quality of development [4]. Docosahexaenoic acid (DHA), in particular, is relevant for membrane fluidity and the release of neurotransmitters [5], and it can have anti-inflammatory properties through

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the production of a class of lipid mediators (the "specialized pro-resolving mediators," [6]). Moreover, DHA is the most abundant PUFA in brain gray matter, providing for the 15–20% of the total fatty acid composition in the frontal areas. This is particular meaningful with respect to ADHD because DHA could potentially be linked to executive functions, such as focused attention, planning, and inhibition, which are primarily located in the frontal cortex and are known to be impaired in ADHD (see, for example, [7]).

Although these findings could motivate clinical trials that used DHA, the large majority of studies that have explored the efficacy of PUFA supplementation in ADHD utilized mixed omega-3 fatty acids, such as DHA, eicosapentaenoic acid, and alpha-linoleic acid (for systematic meta-analyses of available data, see [8–12]). Indeed, to the best of our knowledge, the only clinical trial that used DHA in ADHD was the study of Voigt and colleagues [13]. In that work, 54 children between the ages of 6 and 12 years received either DHA supplementation (345 mg per day) or placebo for 4 months. The study did not show improvements in any measures of ADHD symptoms, in spite of a significant increase of plasma phospholipid DHA level in the supplemented group. It is worth mentioning that Voigt and colleagues used DHA as augmentation therapy to the stimulant medication, because all participants were receiving maintenance therapy throughout the trial, withheld 24 h before the testing session. Therefore, no studies have examined yet the effect of DHA supplementation as monotherapy in ADHD. Given the lack of literature and the above-mentioned considerations about the plausible role of DHA in ADHD, we aimed to investigate the efficacy of DHA dietary supplementation on behavior and cognition in school-aged, drug-naïve children with ADHD in a randomized, placebo-controlled clinical trial. Based on the previous observation that it may take up to 3 months for the cerebral membranes to recover a normal fatty acid composition from a PUFA deficiency [14], we extended the trial duration from four to 6 months compared to the study of Voigt and colleagues.

Method

The present work is a 6-month, randomized, placebo-controlled, double-blind intervention trial investigating the efficacy of supplementation with DHA in children aged 7 to 14 with ADHD ('The Effects of DHA on Attention Deficit and Hyperactivity Disorder (DADA)'). The trial was registered at ClinicalTrials.gov as NCT01796262. This study received approval by the ethics committee of our institute and was, therefore, performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments, with written informed consent and assent from all caregivers and participants, respectively. Data collection began in June 2012 and ended in October 2014. Figure 1 shows the schematic overview of the design of the present study, including all the measures collected and the flows of participants through the study.

Participants

Participants aged 7 to 14 were recruited from the Child Psychopathology Unit at our institute over a 22-month period. The study coordinator contacted 128 parents by phone to invite children to participate in the study protocol. Of these, 50 children with ADHD and their parents agreed to participate. The main reason for declining to participate was a child's refusal to have his or her blood sampled. All participants were diagnosed by a child neuropsychiatrist in accordance with the diagnostic and statistical manual of mental disorders criteria (fourth ed., text rev.; [15]). A child psychologist experienced in the diagnosis of ADHD (AC) confirmed independently the diagnosed by through direct observation and the administration of the semi-structured interview Development and Well-Being Assessment (DAWBA; [16]). According to the clinical assessment, 15.7% of children met the criteria for the ADHD inattentive subtype, 33.3% fulfilled criteria for the hyperactive–impulsive subtype, and 51% had the combined subtype. The Wechsler Intelligence Scale for Children–III or –IV [17, 18] was used to obtain the Full Scale Intelligence Quotient (FSIQ) or FSIQ scores. Only participants with FSIQ or estimated FSIQ scores higher than 80 were included. Moreover, all children were required to be drug-naïve and not have consumed omega-3/omega-6 supplements during the 3 months prior to the recruitment. Exclusion criteria were a history of seizures, other neurological disorders, or diagnosed genetic disorders. All participants were Caucasian and had normal or corrected-to-normal vision.

Procedure

Participants were assigned a study number and randomly allocated by an independent third person to either the supplement or the placebo group using a computer-generated randomization scheme. Children, parents, and study investigators were blinded to the randomization until completion of data collection and analysis. All participants were assessed at our institute's Child Psychopathology Unit at baseline and after 4 and 6 months. At baseline, blood samples were obtained by collecting drops of blood from a fingertip after a minimum 1-h fast. The participants filled out the Pubertal Developmental Scale [19]. Weekly frequency of fish consumption was then collected. Last, data on parental employment were used as a measure of socioeconomic status

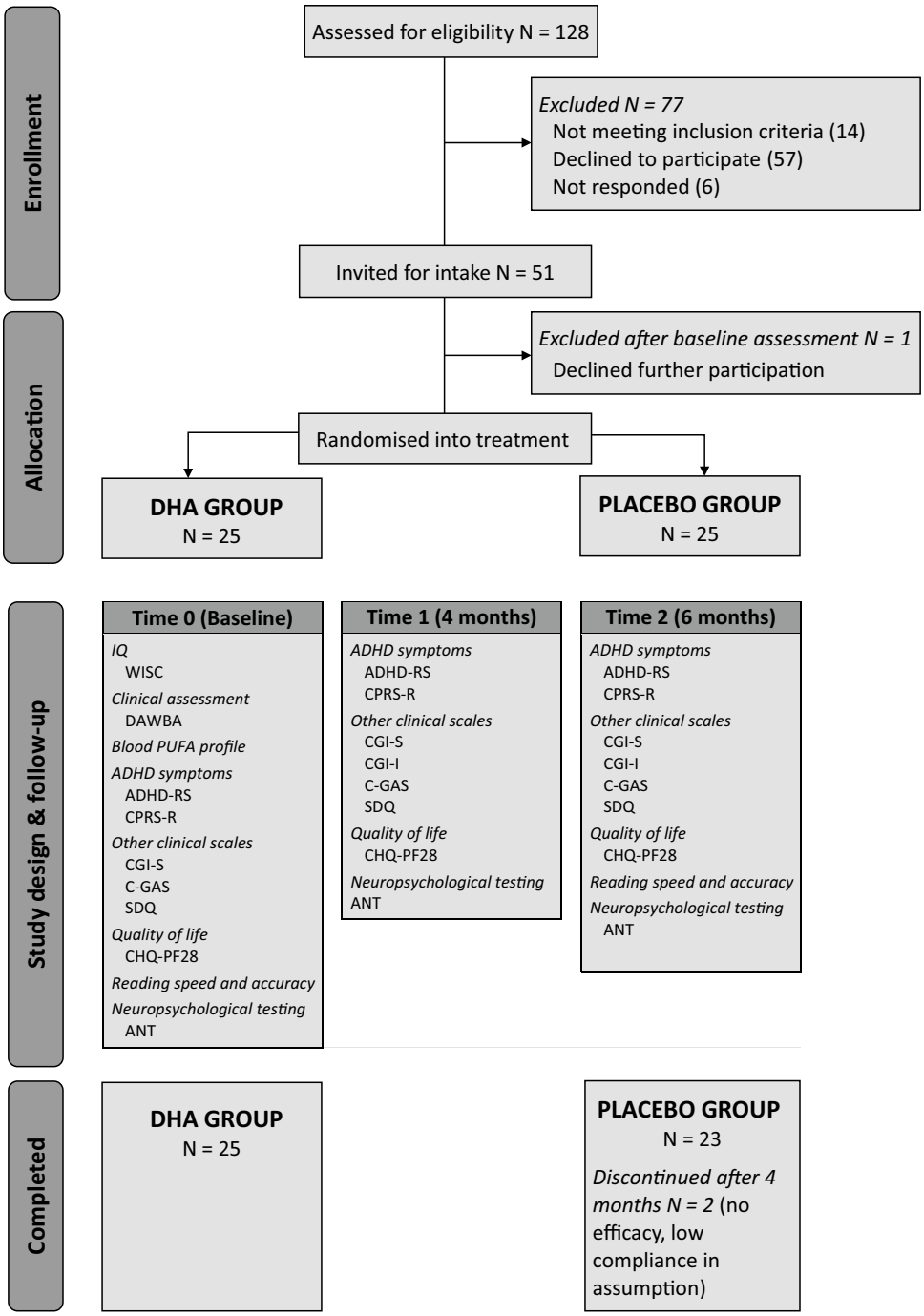

Fig. 1 Schematic overview of the study design, with a list of measures collected at each time point. ADHD-RS, ADHD Rating Scale; ANT, Amsterdam Neuropsychological Tasks; C-GAS, Children Global Assessment Scale; CGI-I, Clinical Global Impression-*Improvement scale;* CGI-S, Clinical Global Impression-Severity scale; CHQ-PF28, Child Health Questionnaire-Parent Form; CPRS-R, Conners' Parent Rating Scale-Revised; DAWBA, Development and Well-Being Assessment; DHA, docosahexaenoic acid; SDQ, Strengths and Difficulties Questionnaire; WISC, Wechsler Intelligence Scale for Children

and coded according to the Hollingshead 9-point scale for parental occupation [20].

At each visit, measurement of clinical parameters including height without shoes, weight in light clothing, and blood pressure (systolic and diastolic) were taken. After that, participants completed a battery of cognitive tests in a single session of approximately 50 min. While children were completing these tasks, parents and investigators filled out the behavioral and clinical rating scales, respectively. Between each visit, parents visited our institute monthly to receive the treatment supply for the following four weeks, check compliance, and report any adverse events.

Intervention

Active supplement consisted of two soft gelatin pearls per day providing a dose of 500 mg algal DHA. Placebo treatment consisted of two pearls per day containing 500 mg wheat germ oil. The placebo was stabilized with a low concentration of Vitamin E. The placebo pearls matched the

DHA ones in touch, smell, and size. Either the supplement or the placebo was provided in six identical boxes labeled with an identifying code and in compliance with good manufacturing process. Duration of treatment was 6 months. This period was chosen as long-chain PUFA levels in the brain can take up to 3 months to recover from a deficiency state [14, 21]. Compliance was assessed by weighting the leftover products that parents returned to the investigators on a monthly basis and was defined as taking more than 70% of the provided capsules. Participants were asked to maintain their usual diet throughout the intervention period and, in particular, to avoid foods enriched with EPA or DHA during the supplementation.

Outcome measures

The a priori primary outcome was the ADHD rating scale IV Parent Version–Investigator [22], used to assess parent ratings of ADHD behaviors.

As secondary outcomes, different measures of behavior and functioning, and cognition were used. Indeed, parents also completed the Conners' Parent Rating Scale–R [23] to investigate ADHD symptoms. For this questionnaire, ADHD index, Conners' Global Index restless–impulsive, Conners' Global Index emotional lability, Conners' Global Index total, DSM-IV inattentive, DSM-IV hyperactive–impulsive, and DSM-IV total were considered as dependent measures. Modifications of the Strengths and Difficulties Questionnaire (SDQ; [24]) score were considered possible improvements regarding the emotional and behavioral difficulties associated with the disorder. To rate the impact of ADHD on quality of life, the Child Health Questionnaire–Parent Form 28 item [25] was completed by the parents. The Child Health Questionnaire (CHQ) is a well-validated measure of quality of life, comprising an overall summary score for psychosocial functioning, as well as subscales that assess self-esteem, impact of the disorder on the parents, and participation in family activities. The children's global functioning was evaluated by a clinician using the Clinical Global Impression—severity Scale (CGI; [26]) and the Children's Global Assessment Scale (C-GAS; [27]). Moreover, the clinician used the CGI– improvement [26] at 4 and 6 months after supplementation had been initiated to compare the patients' general clinical condition to the period before the introduction of supplement use. Finally, an abbreviated battery of cognitive tests from the Amsterdam Neuropsychological Tasks (ANT; [28]) program was used to assess executive function domain. Participants completed four computerized tasks, always administered in the same order: baseline speed, focused attention 4 letters, shifting attentional set–visual, and sustained attention. Baseline speed measured simple response times to stimulus presence. In the focused attention test, participants had to respond (pressing the "yes" key) to one target letter among four letters presented on the screen at the same time, only when it was displayed in the relevant diagonal positions. The visual set-shifting task investigated three basic cognitive variables: vigilance, inhibition, and cognitive flexibility. Lastly, the sustained attention task assessed the fluctuation of attention over time. For further details about the dependent measures considered for these tasks, the reader is referred to Crippa et al. [29]. Reading skills were also assessed at baseline, and after 6 months of supplementation using word and non-word reading subtests from the Italian standardized Battery for the Assessment of Developmental Reading and Spelling Disorders [30]; both reading speed (syllables/seconds) and reading accuracy (number of errors) were registered.

Blood collection and fatty acid profiles analysis

Drops of blood from fingertips were collected at baseline from all children to evaluate the fatty acid profile. This method was chosen because whole blood is more easily obtainable than other components such as plasma and red blood cells, and the whole blood fatty acid composition offers a more balanced picture of the status of circulating PUFA in relation to fat dietary intakes [31, 32]. Whole blood samples were directly subjected to transmethylation for gas chromatography analysis, using a well-validated protocol [33]. Fatty acids from 14 to 24 carbons were detected, and fatty acid values were then expressed as a percentage of total fatty acids. We report here single fatty acid data for main omega-3 and omega-6, expressed as percentage of total fatty acids. The arachidonic acid(AA)/EPA and AA/DHA ratios were calculated as reliable indexes of the functional effects of long-chain PUFAs [34]. Last, the sum of EPA and DHA (the "omega-3 index"; [35]) and the sum of saturated fatty acids, monounsaturated fatty acids, and PUFAs, respectively, were also reported. For further details about the fatty acid profile analysis in relation to patients with neurodevelopmental disorders, the reader is referred to Crippa and colleagues [29].

Statistical analysis

Primary analyses were intent-to-treat, including all randomized study participants, and were conducted using SAS statistical software package, version 9.4 (SAS Institute Inc., Cary, NC, USA). Baseline between-group differences on the demographic variables, clinical questionnaires, cognitive measures, and blood fatty acid levels were analyzed using Chi square analysis, Mann–Whitney, or independent-samples *t* test, according to the distributional nature of the data. Effect of DHA versus placebo supplementation on outcome variables was investigated using linear mixed modeling. This statistical technique allows participants with missing data or

dropouts to be included in the analysis. Each outcome variable was individually assessed with the same mixed model design, including a fixed treatment group effect, a fixed time effect, and a treatment by time interaction, estimating the average group specific intercepts, rates of change over time, and group specific differences in those rates, respectively. In order to determine effect size estimates of DHA effect across the trial visits, eta-squared values for both main effects and for treatment by time interaction were computed and reported, with values of 0.01 considered small effects, 0.06 considered medium effects, and 0.14 considered large effects [36]. Detection of possible outliers was based on median value and interquartile range (IQR), namely every value lower than the 25th quartile minus 3 × IQR or greater than the 75th quartile plus 3 × IRQ was identified as an outlier and therefore removed. Between-group differences on CGI-improvement score were assessed using Kruskal–Wallis analysis. The significance level was two tailed ($p < 0.05$) for all analyses. No correction was applied for family wise error rate, as comparisons were strictly planned before the study's initiation and only the comparisons associated with a significant main effect on the linear mixed-model analysis were calculated. The present study was designed to detect a change in performance of 0.8 standard deviation, with 25 participants assigned to each group (power = 80%; $p < 0.05$). Cohen's d effect sizes were calculated to define effect size of DHA versus placebo supplementation between baseline and the end of treatment using the formula:

$$d = M_{\text{change-DHA}}/\text{SD}_{\text{DHA}} - M_{\text{change-placebo}}/\text{SD}_{\text{placebo}}$$

where $M_{\text{change-DHA}}$ is the change score (i.e., the mean of difference between pretest and posttest means) for the DHA group, $M_{\text{change-placebo}}$ is the mean of the change scores for the placebo group, SD_{DHA} and $\text{SD}_{\text{placebo}}$ are the standard deviation of DHA group scores and placebo group scores, respectively [37]. Effect size was interpreted as small with Cohen's d values between 0.2 and 0.5, medium with values between 0.5 and 0.8, and larger above 0.08, following the benchmarks proposed by Cohen [36].

Results

Baseline characteristics

Data on the demographic variables and blood fatty acid levels at baseline are summarized in Table 1. DHA and placebo group did not significantly differ in any of the demographic variables (all $p > 0.05$). Fish consumption per week before the supplementation was also not different between groups, as reported by parents ($\chi^2(3) = 1.032$, $p > 0.05$).

With respect to the fatty acid profile, two children (both in the DHA group) among the 50 participants recruited could not be analyzed due to insufficiency of the absorbed blood sample. When compared with participants in the placebo group, children in the DHA group had significantly higher levels of AA/EPA ratio (DHA group: 16.80 ± 18.14 vs. placebo group: 12.18 ± 9.66, $p = 0.045$). No other difference was found in fatty acid concentrations. All the participants had abnormally lower blood level of DHA at baseline compared to a control group of 22 healthy developing children matched by gender, age, and IQ [29]. Ratings of ADHD symptoms and other associated difficulties that often co-occur with the ADHD were similar in the two groups at baseline, with the exception of higher impact of symptoms on functioning evaluated by SDQ in DHA group ($p = 0.045$). Lastly, with respect to cognitive measures, children in the DHA group showed more false alarms in the focused attention task (false alarms relevant non-target, $p = 0.032$; false alarms irrelevant target, $p = 0.013$), and less flexibility in the visual set-shifting task compared to participants in the placebo group ($p = 0.029$).

Table 1 Demographics and blood fatty acid levels of the participants at baseline assessment

	DHA	Placebo
N	25	25
Females: males	2: 23	2: 23
Age	11.06 ± 1.85	10.91 ± 1.42
IQ	103 ± 13.045	104.48 ± 13.79
SES	58 ± 17.02	50.2 ± 19.82
BMI	18.51 ± 2.42	19.46 ± 3.13
% 18:2n-6 (LA)	22.34 ± 2.58	22.28 ± 2.27
% 20:4n-6 (AA)	9.34 ± 1.78	9.38 ± 2.27
% 20:5n-3 (EPA)	0.81 ± 0.38	1.24 ± 0.99
% 20:6n-3 (DHA)	1.68 ± 0.40	1.73 ± 0.53
DHA/EPA	2.49 ± 0.68	3.16 ± 1.58
AA/EPA	16.80 ± 18.14	12.18 ± 9.66
AA/DHA	5.72 ± 1.07	5.72 ± 1.70
SFA	34.07 ± 3.92	33.82 ± 4.03
MUFA	27.43 ± 3.59	27.56 ± 4.15
PUFA	37.38 ± 4.48	37.98 ± 3.77

IQ intelligence quotient, *SES* socio economic status, *BMI* body mass index, *LA* linoleic acid, *AA* arachidonic acid, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *SFA* saturated fatty acids, *MUFA* monounsaturated fatty acids, *PUFA* polyunsaturated fatty acids

Adverse events and treatment adherence

Over the course of the 6 months, no instances of either major or minor adverse events were reported. The mean compliance over the study, determined by monthly pearl counts of the number returned divided by number of pearls prescribed, was 83.2%. Two children, both in the placebo group, discontinued taking the study pearls after 4 months, due to no

observed efficacy and increasing difficulty in swallowing the capsules. Three further participants, one in the DHA group and two in the placebo group, did not reach the requested level of compliance (i.e., taking at least 70% of the prescribed pearls), and were therefore excluded from the efficacy outcomes analyses.

Efficacy outcomes: primary outcome measures

As can be seen in Table 2, the linear mixed-model analysis did not find any significant difference on ADHD rating scale, the a priori primary outcome, between the treatment groups ($p > 0.05$).

Indeed, a main effect of time was observed on the hyperactivity–impulsivity scale and on total score of the ADHD rating scale, with participants in both groups showing improvements over the 6 months, as shown in Fig. 2.

Efficacy outcomes: secondary outcome measures

With respect to the secondary behavioral outcomes, the linear mixed-model analysis further showed a main effect of time on the SDQ Hyperactivity scale and on SDQ total difficulties score, on the CGI severity, on the C-GAS, and on Conners' ADHD index, Conners' Global Index restless–impulsive, Conners' Global Index total, DSM-IV hyperactive–impulsive scale, and DSM-IV total (see Table 2). This suggests that children across groups displayed ameliorations of both symptoms and general functioning over the study. Moreover, as depicted in Fig. 3, significant interactions occurred between treatment condition and time. The linear mixed-model analysis revealed that children in the DHA group showed amelioration in CHQ Psychosocial summary between the baseline and the end of supplementation ($p < 0.01$) and improved in parental ratings of emotional problems on SDQ over the study (baseline vs. 4-month visit, $p < 0.05$; baseline vs. end of treatment, $p < 0.05$). The effect size of these interaction effects (eta squared) was 0.04 and 0.05, respectively, denoting small interaction effects. Consistently, pre-post effect sizes (Cohen's d) were also small, 0.013 and − 0.23, respectively. Children in placebo group showed improvement in the CHQ Parental impact-Time scale between the baseline and the 4-month visit ($p < 0.05$), but this amelioration was not sustained at the end of supplementation.

With respect to the other secondary cognitive endpoints, the linear mixed-model analysis revealed a main effect of time on several ANT scores: reaction time in baseline speed task; reaction time of correct responses, false alarms relevant non-target, and false alarms irrelevant target in the focused attention 4-letters task; reaction time of inhibition, reaction time of flexibility, number of errors inhibition, and number of errors flexibility in visual set-shifting; tempo × series and false alarms in the sustained attention task. Not surprisingly, a main effect of time was also found on non-word reading speed (see Table 3).

Finally, the linear mixed-model analysis showed a significant interaction between treatment condition and time on number of misses and false alarms irrelevant target in focused attention 4-letters task. As can be seen in Fig. 4, participants supplemented with DHA showed a decrease of misses in the focused attention 4-letters task at the 6-month visit (end of treatment vs. baseline, $p < 0.01$; end of treatment vs. 4-month visit, $p < 0.05$), whereas children in the placebo group displayed a lower number of misses at the 4-month ($p < 0.05$) but not at the 6-month visit ($p > 0.05$). Likewise, children in the DHA group showed a reduction of false alarms irrelevant target in the focused attention 4-letters task at the end of supplementation (end of treatment vs. baseline, $p < 0.001$; end of treatment vs. 4-month visit, $p < 0.05$). These interaction effects ranged small to medium in size, with eta-squared values of 0.7 and 0.3, and Cohen's d values of − 0.30 and − 0.28, respectively.

Discussion

The objective of the present clinical trial was to investigate the efficacy of 6-month supplementation with DHA as only medication on behavior and cognition in school-aged children with ADHD. To date, this is to the best of our knowledge the first study that explored the effect of DHA as monotherapy in a drug-naïve clinical sample. Differently from previous studies investigating the efficacy of PUFA supplementation in ADHD by means of mixed omega-3 fatty acids, we decided to use exclusively DHA because it is relevant for regulating both membrane fluidity and synaptic transmission [5] and it represents the 15–20% of the total fatty acid composition in the frontal lobes.

Overall, this is a substantially negative study. The results of the present randomized, placebo-controlled clinical trial did not show evidence of benefit on the a priori primary outcome measure—the ADHD rating scale IV—. Furthermore, the results did not show any significant treatment effects on other measures of ADHD symptoms, such as Conners Parents Rating Scale.

However, with respect to the secondary behavioral outcome variables, supplementation with DHA led to a slight but significant amelioration of children's psychosocial functioning as judged by parents, and to a decrease of parent-rated emotional problems in the selected study population. The size of these effects of 0.13 and 0.23, while statistically significant, was nevertheless quite small. These results are in line with those reported by previous meta-analyses, suggesting an absent or marginal effect of PUFA supplementation on ADHD behavioral manifestations [8–11]. Lastly,

Table 2 Behavioral measures per treatment group

	Baseline		4-month visit		6-month visit		Treatment		Time		Treatment × Time		Pre-post effect size
	DHA	Placebo	DHA	Placebo	DHA	Placebo	*F*	η^2	*F*	η^2	*F*	η^2	*d*[a]
Primary outcome measure													
ADHD rating scale													
Hyperactivity—impulsivity scale	15.36 (5.45)	14.48 (5.23)	11.42 (5.02)[b]	10.86 (6.63)[b]	11.29 (5.28)[b]	11.38 (7.61)[b]	0.15	0.00	14.74***	0.20	0.22	0.00	− 0.19
Inattention scale	14.20 (5.11)	17.28 (5.98)	14.38 (4.51)	14.95 (6.55)	13.63 (5.86)	14.95 (7.55)	0.82	0.01	1.17	0.02	0.79	0.01	0.06
Total	29.56 (9.46)	31.76 (9.76)	25.79 (8.67)[b]	25.81 (11.89)[b]	24.92 (10.28)[b]	26.33 (14.19)[b]	0.08	0.00	8.00**	0.11	0.20	0.00	− 0.09
Secondary outcome measures													
Strengths and difficulties questionnaire													
Emotional problem scale	3.36 (2.68)	2.56 (1.50)	2.79 (2.08)	2.81 (0.98)	2.33 (1.52)	2.38 (2.25)	0.62	0.01	2.03	0.03	3.78*	0.05	− 0.23
Conduct problem scale	3.52 (1.64)	3.80 (1.76)	3.71 (1.68)	3.76 (2.23)	3.25 (1.70)	3.43 (2.18)	0.13	0.00	1.47	0.02	0.20	0.00	0.03
Hyperactivity scale	8.12 (3.09)	7.80 (1.76)	6.96 (2.53)[b]	7.26 (2.28)[b]	6.74 (2.05)[b]	6.89 (2.26)[b]	0.01	0.00	5.16**	0.05	0.01	0.01	− 0.19
Peer problems scale	3.16 (4.63)	2.40 (1.68)	2.17 (2.08)	2.14 (1.68)	2.09 (2.24)	2.10 (1.79)	0.17	0.00	1.16	0.02	0.03	0.00	− 0.04
Prosocial scale	7.56 (2.20)	7.24 (2.37)	7.00 (1.89)	7.48 (2.42)	7.00 (1.93)	7.38 (2.52)	0.14	0.00	1.17	0.02	1.07	0.02	− 0.10
Impact	3.72 (2.95)[c]	2.28 (1.84)[c]	3.00 (2.48)	3.24 (2.59)	2.38 (2.28)	2.86 (2.37)	0.13	0.00	1.38	0.02	3.06	0.04	− 0.32
Total difficulties score	18.16 (8.47)	16.56 (3.64)	15.75 (5.76)[b]	15.65 (4.65)[b]	14.54 (5.02)[b]	14.05 (6.34)[b]	0.15	0.00	5.54**	0.03	0.98	0.02	− 0.25
Conners' parents rating scales													
ADHD index	72.24 (8.53)	75.00 (11.63)	69.58 (10.78)[b]	69.33 (10.34)[b]	66.54 (10.21)[b]	70.67 (12.77)[b]	0.41	0.00	3.48*	0.05	1.61	0.02	− 0.24
CGI: restless-impulsive	68.16 (9.72)	70.96 (11.46)	66.00 (11.17)[b]	64.48 (10.77)[b]	62.04 (10.14)[b]	64.81 (13.71)[b]	0.21	0.00	5.99**	0.08	1.54	0.02	− 0.09
CGI: emotional lability	59.88 (14.08)	58.88 (14.55)	55.54 (8.55)	55.76 (13.02)	51.92 (8.01)	57.10 (15.97)	0.18	0.00	2.63	0.04	2.02	0.03	− 0.41
CGI: total	65.48 (14.09)	69.52 (12.49)	63.91 (10.66)[b]	63.95 (11.52)[b]	60.30 (9.31)[b]	64.05 (14.25)[b]	0.45	0.01	5.73**	0.05	1.11	0.02	− 0.03
DSM IV: inattentive	68.64 (15.09)	73.48 (13.78)	69.48 (10.46)	70.57 (11.48)	67.22 (10.84)	69.90 (14.37)	0.40	0.01	1.77	0.01	0.29	0.01	0.02
DSM IV: hyperactive-impulsive	67.36 (14.10)	69.96 (12.28)	64.48 (13.20)[b]	61.52 (13.11)[b]	60.17 (10.03)[b]	63.43 (17.77)[b]	0.01	0.00	8.35***	0.06	2.57	0.04	− 0.09
DSM IV: total	70.79 (12.34)	74.08 (12.28)	69.04 (12.19)[b]	68.10 (12.14)[b]	65.48 (10.67)[b]	69.48 (15.64)[b]	0.14	0.00	4.16*	0.04	1.76	0.03	− 0.14
Child Health Questionnaire													
Physical functioning	0.31 (0.62)	0.18 (0.92)	0.56 (0.00)	0.46 (0.32)	0.36 (0.84)	0.53 (0.15)	0.07	0.00	0.82	0.02	0.90	0.02	− 0.03
Role—physical	0.24 (0.58)	0.17 (0.83)	0.45 (0.00)	0.11 (0.90)	0.23 (1.08)	0.37 (0.38)	0.23	0.00	0.01	0.00	1.03	0.02	− 0.03
General health	0.74 (0.91)	0.89 (0.64)	0.95 (0.62)	0.84 (0.67)	0.89 (0.86)	0.82 (1.13)	0.04	0.00	0.80	0.01	1.07	0.01	0.04
Bodily pain	− 0.13 (1.25)	0.06 (0.84)	0.33 (0.74)	0.29 (0.80)	0.27 (0.77)	0.20 (0.98)	0.33	0.00	1.07	0.02	0.41	0.01	0.08
Role—emotional/behavioral	− 1.08 (1.77)	− 0.74 (1.94)	− 0.77 (1.48)	− 1.46 (1.73)	− 0.65 (1.09)	− 1.14 (1.75)	0.36	0.00	1.16	0.02	2.87	0.04	0.18
Parental impact—time	− 0.06 (0.99)	− 0.09 (1.34)	0.19 (0.67)	− 0.26 (1.04)	0.18 (0.74)	0.14 (0.87)	0.00	0.00	1.55	0.03	3.53*	0.03	0.02
Parental impact—emotional	− 0.70 (0.87)	− 0.51 (0.99)	− 0.36 (0.82)	− 0.87 (0.95)	− 0.24 (0.52)	− 0.45 (1.06)	0.73	0.01	2.42	0.01	3.01	0.05	0.10
Self-esteem	− 0.69 (1.21)	− 0.61 (0.54)	− 0.39 (0.86)	− 0.82 (0.96)	− 0.48 (0.99)	− 0.66 (1.03)	0.83	0.00	0.20	0.00	1.87	0.03	0.03
Mental health	− 2.02 (1.32)	− 1.65 (1.33)	− 1.62 (1.28)	− 1.82 (1.40)	− 1.28 (0.96)	− 1.41 (1.48)	0.01	0.00	2.70	0.04	1.64	0.02	0.11
Behavior	− 1.52 (0.86)	− 1.17 (0.91)	− 1.28 (1.00)	− 1.16 (1.18)	− 1.07 (0.90)	− 1.29 (1.41)	0.39	0.00	1.33	0.01	0.69	0.02	0.12

Table 2 (continued)

	Baseline		4-month visit		6-month visit		Treatment		Time		Treatment × Time		Pre-post effect size
	DHA	Placebo	DHA	Placebo	DHA	Placebo	*F*	η^2	*F*	η^2	*F*	η^2	*d*[a]
Physical summary	0.77 (0.64)	0.70 (0.80)	1.00 (0.35)	0.85 (0.74)	1.01 (0.41)	0.91 (0.55)	0.08	0.00	0.31	0.01	2.14	0.01	− 0.01
Psychosocial summary	− 1.46 (1.01)	− 1.19 (0.99)	− 1.20 (1.00)	− 1.63 (1.24)	− 1.05 (0.86)	− 1.46 (1.06)	0.32	0.00	1.11	0.02	4.21*	0.04	0.13
Children' Global Assessment Scale	67.52 (9.97)	68.76 (7.68)	72.21 (11.39)[b]	69.29 (7.91)[b]	73.25 (10.06)[b]	69.80 (8.04)[b]	0.84	0.01	3.99*	0.06	1.70	0.02	0.23
Clinical Global Impression-Severity	3.8 (0.87)	4.08 (0.91)	3.58 (0.93)[b]	3.67 (0.97)[b]	3.25 (0.74)[b]	3.71 (1.10)[b]	1.06	0.01	3.63*	0.05	1.10	0.02	− 0.06

CGI Conners' Global Index

[a]Cohen's d

[b]Main effect of time

[c]Between-group baseline difference

*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

as regards the secondary cognitive outcome measures, the results indicated a small, significant benefit of DHA on focused attention, as shown by the decrease of misses and false alarms in the supplemented group. Again, the effect size of these modifications, ranging from 0.28 to 0.30, was rather small. Although limited in size, we feel that this result of the present trial confirms the conclusion of the meta-analysis of Cooper et al. [12], which disclosed limited evidence of benefit of omega-3 in cognition only in children who had deficient levels of PUFAs. Indeed, all the children recruited in this trial had abnormally lower blood levels of DHA at baseline compared to 22 healthy developing peers matched by gender, age, and IQ [29]. Future studies assessing the impact of DHA on cognitive functioning should focus on subgroups of children with ADHD who are omega-3 deficient at baseline. Nonetheless, compared to pharmacological treatment effect size ranging from 0.6 for non-stimulant medication to 1.52 for stimulant medication [38], the effect of DHA supplementation on secondary outcomes disclosed in this trial is overall quite modest.

Comparison of results of the present trial with previous findings about effect of PUFA supplementation is limited by the fact that only one clinical trial has previously used DHA in ADHD [13]. The present results deviate from findings of Voigt and colleagues, where no statistical between-group differences were reported in any of the behavioral or cognitive performances evaluated after 4 months of DHA supplementation. There are several possible reasons for these differences. First, the measures of outcome used in the two studies were not identical. With regard to behavior, we found an effect of DHA on difficulties frequently associated with the disorder, such as the CHQ and SDQ, not included in the study of Voigt and colleagues. Indeed, the authors used two parental rating scales, the Child Behavior Checklist and the Conners' Rating Scales. It is important to note that, in line with Voigt and colleagues, the results of the present study did not reveal an effect of DHA on parents' ratings of behavior on Conners' Rating Scales. With respect to cognition, we did not find an effect of DHA supplementation on sustained attention (assessed by ANT), in agreement with Voigt and colleagues (measured by Test of Variable Attention). The present significant findings about the benefit of DHA on cognitive functions are restricted to focused attention. Another cause of difference in findings might be that the dose of the DHA supplementation in the present study was higher (500 mg vs. 345 mg per day) and given for a longer period (6 vs. 4 months), compared to the trial of Voigt et al. There is still some controversy whether larger doses of DHA further improve ADHD symptoms and over the role of the trial duration [8–12]. Although the meta-analytical results are not entirely concordant, we feel that differences in intervention between

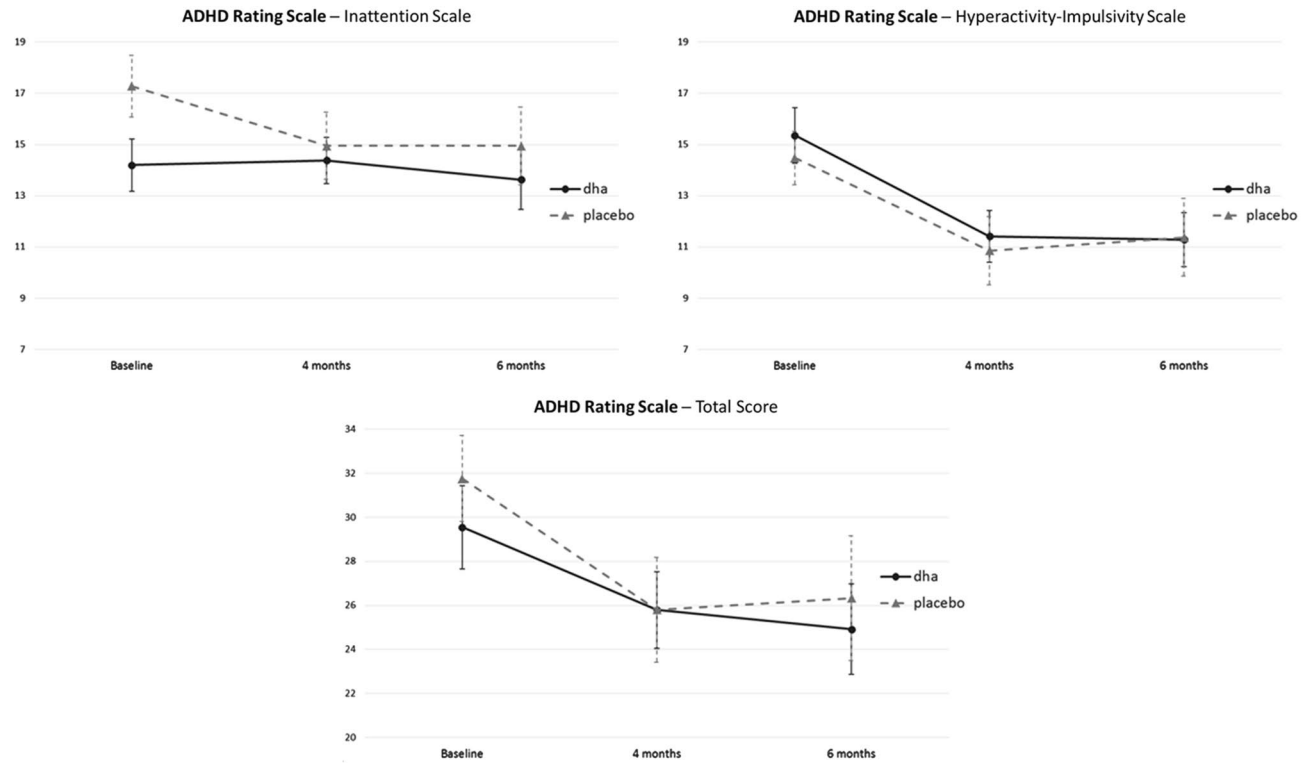

Fig. 2 Change in the a priori primary outcome measures, ADHD Rating Scale, in DHA and in placebo group. The linear mixed-model analysis demonstrated a main effect of time on the hyperactivity–impulsivity scale (higher right panel, $p < 0.001$) and on total score of the ADHD rating scale (lower panel, $p < 0.01$), with participants in both groups showing similar improvements over the 6 months. No significant effect of treatment condition was found ($p > 0.05$)

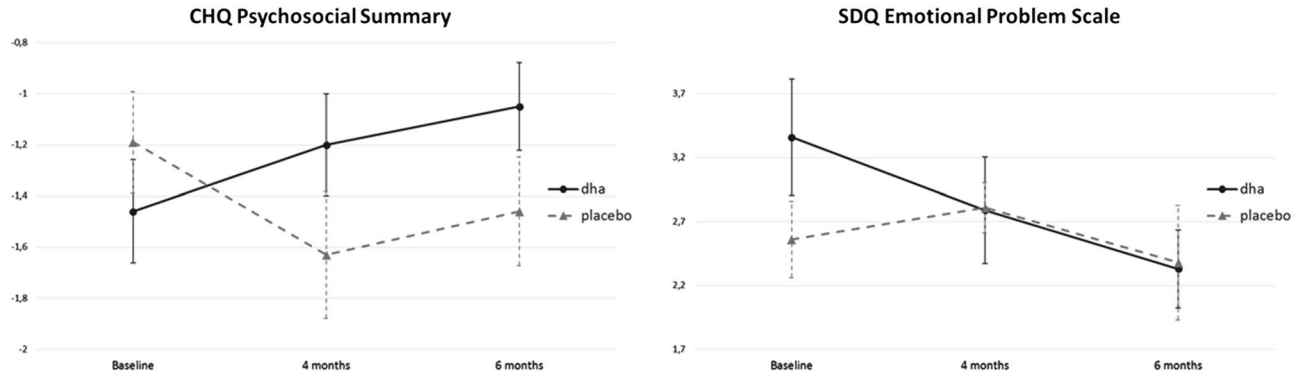

Fig. 3 Change in secondary behavioral outcome measures in DHA and in placebo group showing interactions between treatment condition and time. The linear mixed-effect analysis revealed that children in DHA group showed amelioration in the Child Health Questionnaire–Parent Form (CHQ) Psychosocial summary between the baseline and the end of supplementation (left panel; $p = 0.008$) and improved in parental ratings of emotional problem on the Strengths and Difficulties Questionnaire (SDQ) over the study (right panel; baseline versus 4-month visit, $p = 0.049$; baseline versus end of treatment, $p = 0.017$)

this study and the work of Voigt and colleagues might have led to divergent conclusions. Finally, it is worth remembering as a possible confounding factor that participants of Voigt and others were taking stimulant medication throughout the trial, whereas children recruited in the present study were drug-naïve. The present findings are also in line with the observations of a previous cross-sectional study, where we analyzed the relationship between PUFA status, cognitive, and behavioral traits in a mixed sample of children with ADHD—then recruited

Table 3 Cognitive measures per treatment group

	Baseline		4-month visit		6-month visit		Treatment		Time		Treatment × Time		Pre-post effect size
	DHA	Placebo	DHA	Placebo	DHA	Placebo	d^a	η^2	F	η^2	F	η^2	d[a]
Other outcome measures													
Reading Abilities													
Word reading speed (syll/sec)	3.03 (1.17)	2.68 (1.01)	–	–	3.32 (1.25)	2.96 (1.03)	1.62	0.01	1.30	0.01	0.07	0.00	0.02
Word reading accuracy (errors)	4.16 (4.44)	5.68 (4.49)	–	–	4.29 (3.95)	4.14 (4.60)	0.27	0.00	1.94	0.01	1.74	0.01	0.20
Non-word reading speed (syll/sec)	1.85 (0.78)	1.55 (0.45)	–	–	1.99 (0.63)[b]	1.73 (0.54)[b]	2.08	0.01	5.28*	0.04	0.01	0.00	0.00
Non-word reading accuracy (errors)	6.4 (4.65)	7.04 (6.27)	–	–	7.38 (5.01)	7.38 (6.97)	0.11	0.00	0.53	0.00	0.97	0.01	0.13
ANT—baseline speed													
RT (msec)	351.88 (70.16)	342.68 (74.74)	377.79 (93.80)[b]	366.48 (79.24)[b]	351.13 (64.70)[b]	357.81 (58.83)[b]	0.08	0.00	3.97*	0.06	0.66	0.01	− 0.20
SD of RT	136.42 (78.52)	129.6 (87.79)	159.13 (114.93)	152.05 (115.29)	124.46 (64.52)	141.86 (100.58)	0.00	0.00	1.28	0.02	0.38	0.01	− 0.24
ANT—focused attention 4 letters													
RT correct responses (msec)	1049.56 (347.56)	971.64 (332.64)	988.17 (393.38)[b]	951.05 (314.15)[b]	876.38 (237.87)[b]	921.00 (267.24)[b]	0.00	0.00	15.44***	0.11	1.61	0.03	− 0.30
SD of correct responses RT	484.75 (284.95)	395.73 (185.81)	421.46 (277.02)[b]	381.41 (216.19)[b]	341.36 (223.74)[b]	372.06 (199.03)[b]	0.30	0.00	5.70**	0.08	3.31	0.05	− 0.34
Misses	3.24 (2.82)	2.84 (2.59)	2.38 (1.66)	1.48 (1.44)	1.54 (1.32)	2.43 (2.25)	0.44	0.00	2.51	0.03	4.99*	0.07	− 0.30
False alarms relevant non-target	1.36 (1.38)[c]	0.56 (0.77)[c]	0.57 (0.73)[b]	0.29 (0.46)[b]	0.30 (0.56)[b]	0.19 (0.40)[b]	4.57*	0.04	9.13***	0.11	1.22	0.03	− 0.14
False alarms irrelevant target	2.56 (3.68)[c]	1.00 (0.91)[c]	1.43 (1.31)[b]	0.86 (1.46)[b]	0.78 (0.95)[b]	0.76 (1.00)[b]	4.05	0.03	5.88**	0.05	3.51*	0.03	− 0.28
ANT—visual set-shifting													
RT inhibition (msec)	376.08 (317.30)	333.96 (188.29)	162.09 (145.86)[b]	244.05 (153.71)[b]	164.68 (126.58)[b]	215.05 (154.72)[b]	0.73	0.00	8.83***	0.08	0.64	0.01	− 0.08
RT flexibility (msec)	672.72 (325.09)	616.98 (263.95)	511.23 (217.14)[b]	481.60 (174.16)[b]	445.85 (163.30)[b]	418.64 (171.86)[b]	0.22	0.00	11.42***	0.14	0.02	0.00	0.15
Number of errors inhibition	8.28 (5.49)	7.36 (7.31)	4.17 (4.53)[b]	4.30 (4.86)[b]	5.67 (6.20)[b]	3.90 (4.82)[b]	0.89	0.00	9.12***	0.09	1.38	0.01	0.01

Table 3 (continued)

	Baseline		4-month visit		6-month visit		Treatment		Time		Treatment × Time		Pre-post effect size
	DHA	Placebo	DHA	Placebo	DHA	Placebo	d^a	η^2	F	η^2	F	η^2	d^a
Number of errors flexibility	21.56 (12.18)[c]	14.96 (11.74)[c]	18.09 (13.35)[b]	12.85 (10.79)[b]	15.04 (12.39)[b]	9.75 (11.32)[b]	3.08	0.02	16.09***	0.20	0.36	0.01	− 0.15
ANT—sustained attention date													
Tempo X series	15.29 (3.28)	14.37 (4.06)	13.05 (2.80)[b]	13.19 (3.55)[b]	12.24 (4.02)[b]	12.04 (4.02)[b]	0.16	0.00	12.16***	0.16	2.07	0.02	− 0.11
SD	3.71 (1.55)	3.51 (1.51)	2.92 (1.24)[b]	3.14 (1.62)[b]	2.69 (1.49)[b]	2.85 (1.62)[b]	0.01	0.00	10.90***	0.17	0.96	0.01	− 0.06
Misses	34.80 (24.60)	37.68 (26.60)	29.09 (19.17)	35.57 (21.77)	32.26 (19.79)	37.14 (22.61)	0.24	0.00	0.34	0.00	0.01	0.00	− 0.06
False alarms	25.36 (18.12)	22.00 (16.67)	17.96 (11.68)[b]	17.38 (9.95)[b]	18.96 (18.10)[b]	12.86 (7.05)[b]	1.88	0.01	3.93*	0.05	0.68	0.01	0.23
Coefficient of variation	0.24 (0.07)	0.24 (0.08)	0.22 (0.06)	0.22 (0.07)	0.21 (0.07)	0.22 (0.06)	0.06	0.00	3.14	0.05	0.20	0.00	− 0.00

ANT Amsterdam neuropsychological task, *RT* reaction time, *SD* standard deviation

[a]Cohen's d

[b]Main effect of time

[c]Between-group baseline difference

*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

for the present clinical trial—and typically developing children [29]. In that study, we observed an association between higher level of DHA and lower parental rates of ADHD symptoms, lower clinical scores of severity, and a better global functioning measured by CHQ. In the present work, we extended those findings by suggesting that children with ADHD may benefit from DHA supplementation in terms of a better quality of life, as rated by their parents. Finally, with respect to the safety of the supplement used, no adverse events were reported by children and their parents, indicating a good tolerance for the dosage of both the DHA and the placebo.

The present work has several limitations. First, the study was limited by its small sample size. As elegantly calculated by Bloch and Qawasmi in their meta-analysis [8], a clinical trial should recruit approximately 330 participants to reliably detect the effect of omega-3 supplementation in light of an effect size of 0.31. Although the present study was underpowered, small but significant evidence of efficacy of DHA were ascertained. However, we cannot exclude that our sample size could have been unable to detect further significant benefits. In addition, we emphasize that in the present study the significance testing was not adjusted for multiple comparisons, because many of the outcome measures were intercorrelated. Small sample size could, therefore, have led to false-positive results, whereas one recent, well-powered study ($n = 162$) did not find any effect of mixed supplementation of DHA and eicosapentaenoic acid on behavioral symptoms or cognition [39]. Therefore, the results of the present study need to be replicated in a larger, independent sample. It is also fundamental to acknowledge the significant between-groups difference at baseline in the focused attention task that also showed an interaction between time and treatment condition. Children in the DHA group showed more false alarms of those in the placebo group, as shown in Fig. 4. This difference and other slight differences (although not statistically significant) on tests or questionnaires at baseline could have affected the findings of this trial, with children in the DHA group having more possibility of improvement. Finally, we cannot confirm the treatment adherence with blood samples throughout or at the end of the trial.

Keeping these limitations in mind, the present trial shows that 6-month DHA supplementation has no beneficial effect on the symptoms of ADHD in school-aged, drug-naïve children with an established clinical diagnosis. However, beyond the overall negative outcome, the 6 months treatment with supplemental DHA appears to have small positive effects on other behavioral and cognitive difficulties related to ADHD. In light of the absence of side-effects proved by this trial, these small benefits of DHA could be reasonably followed up in future intervention studies.

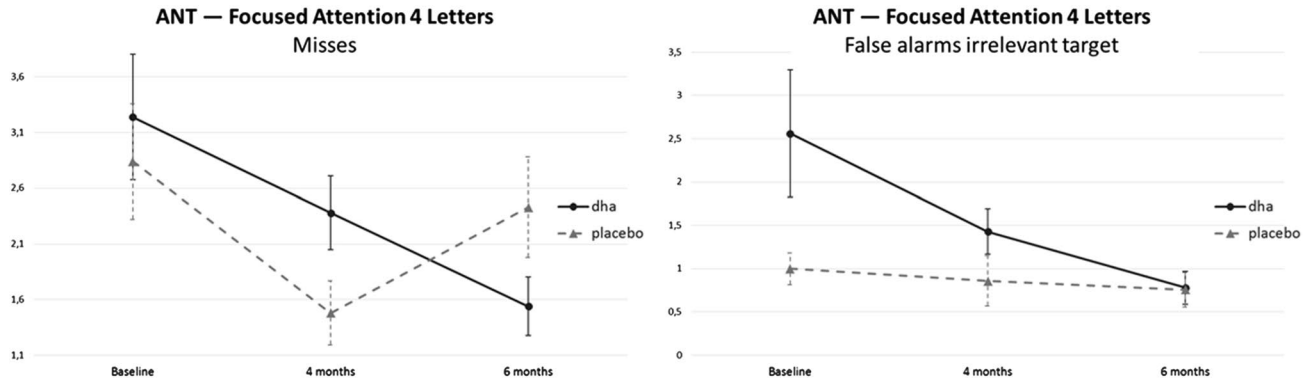

Fig. 4 Change in secondary outcome cognitive measures in DHA and in placebo group showing interactions between treatment condition and time. With respect to the Amsterdam Neuropsychological Tasks (ANT), participants supplemented with DHA showed a decrease of misses in focused attention 4-letters task at the 6-month visit (left panel; end of treatment versus baseline, $p=0.006$; end of treatment versus 4-month visit, $p=0.044$), whereas children in placebo group displayed a lower number of misses at the 4-month ($p=0.032$) but not at the 6-month visit ($p>0.05$). Furthermore, children in DHA group showed a reduction of false alarms irrelevant target in focused attention 4-letters task at the end of supplementation (right panel; end of treatment versus baseline, $p<0.001$; end of treatment versus 4-month visit, $p=0.028$). Children in the DHA group showed more false alarms in the focused attention task ($p=0.013$) also at baseline evaluation

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Review article

Adverse drug events related to mood and emotion in paediatric patients treated for ADHD: A meta-analysis

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ABSTRACT

Background: ADHD is frequently comorbid with anxiety and mood disorders, which may increase the severity of inattention and hyperactivity symptoms. Emotional symptoms (anxiety, irritability, mood lability) also affect patients without comorbidity or emerge as adverse drug events. The influence of ADHD drugs on emotional symptoms demands investigation to improve therapies.

Methods: Systematic review of trials reporting adverse events in patients pharmacologically treated for ADHD. Meta-analysis of the occurrence of irritability, anxiety, apathy, reduced talk, sadness, crying, emotional lability, biting nails, staring, perseveration, euphoria. Meta-regression analysis.

Results: Forty-five trials were meta-analysed. The most frequently reported outcomes were irritability, anxiety, sadness, and apathy. Methylphenidates, especially immediate-release formulations, were most studied; amphetamines were half as studied and were predominantly mixed amphetamine salts. Reports on atomoxetine were scant. Meta-analysis showed that methylphenidates reduced the risk of irritability, anxiety, euphoria, whereas they worsened the risk of apathy and reduced talk; amphetamines worsened the risk of emotional lability. Factors influencing risks were study year and design, patients' sex and age, drug dose and release formulation.

Limitations: Possible discrepancy between adverse events as indicated in clinical trials and as summarised herein. Confounding due to the aggregation of drugs into groups; uninvestigated sources of bias; incomplete lists of adverse events; lack of observations on self-injury.

Conclusions: Methylphenidates appeared safer than amphetamines, although younger patients and females may incur higher risks, especially with high-dose, immediate-release methylphenidates. Only atomoxetine holds a black-box warning, but amphetamines and methylphenidates also did not show a safe profile regarding mood and emotional symptoms.

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is among the commonest neurodevelopmental disorders, affecting 7.2% of children worldwide (Thomas et al., 2015) with a significant impact on familial, relational, and school functioning in more than one setting. ADHD is often associated with other comorbid mental disorders including major depressive disorder (MDD), 9–38%; bipolar disorder, 10–11%; and anxiety/social anxiety disorder (Anderson et al., 1987; Kessler et al., 2006; Kunwar et al., 2007; Tzang and Chang, 2009). Greater severity in the manifestation of symptoms associated with ADHD has been observed for individuals with ADHD and comorbid mental health disorders (Kuhne et al., 1997; Spencer et al., 2007). Furthermore, in ADHD patients who do not present with co-occurring mental health disorders, high levels of emotional symptoms, including anxiety, frustration intolerance, irritability, and mood lability are also observed (Shaw et al., 2014). These commonly associated features also cause considerable distress to individuals and their families.

Stimulant medications, including various drugs of the methylphenidate and amphetamine classes, are considered as first-line

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medications for the treatment of ADHD. Their activity is based on the strengthening of dopamine signals that are crucial to focus and to maintain attention (Arnsten and Pliszka, 2011; Arnsten and Rubia, 2012). Both methylphenidate and amphetamine are called "stimulants" since they potentiate dopamine signals. Methylphenidate acts only by increasing the intensity and duration of naturally-occurring dopaminergic signals (Volkow et al., 2002); amphetamine acts as methylphenidate and also by inducing a non-natural release of dopamine (Groves et al., 1979). This implies on one side that amphetamine can be more efficacious than methylphenidate, on another side that it can be less safe and may have a potential for abuse, which is negligible for methylphenidate in oral use (Volkow and Swanson, 2003). The commonest adverse effects of stimulants include decreased appetite, insomnia, stomach ache, and headache (Groenman et al., 2017). Stimulants are also associated with other adverse effects, including increased risk of growth retardation in weight and height of children, tics, increases in blood pressure, and possible abuse or misuse (Groenman et al., 2017). These drugs are often contraindicated in patients with comorbid disorders, including Tourette's syndrome and bipolar disorder, as well as in patients at risk for substance abuse (McIntyre, 2009; Rizzo et al., 2013). Further, some investigators advise caution in prescribing these products to patients with comorbid disorders that pose no explicit contraindication, such as tic disorders and anxiety (Blouin et al., 2010; Pringsheim and Steeves, 2011) and this is a matter of open debate. In particular, data do not seem to connect tics and stimulants (Cohen et al., 2015), and a previous meta-analysis showed beneficial effects of stimulants on anxiety (Coughlin et al., 2015). Suicidal ideation is an issue that may be present in ADHD patients with comorbid psychiatric disorders, especially depression and bipolar disorders. The presence of suicidal ideation in ADHD patients is currently a strict contraindication for the use of any methylphenidate in Europe.

Atomoxetine is the most commonly prescribed "non-stimulant" medication for the treatment of ADHD. While stimulants act on dopamine, atomoxetine potentiates naturally-occurring norepinephrine signals involved in the maintenance of attention (Arnsten and Pliszka, 2011). Atomoxetine is recommended as monotherapy for the treatment of ADHD for youths who do not respond well to stimulants (Pliszka et al., 2006; Shier et al., 2013), followed by bupropion, clonidine, or guanfacine (Wolraich et al., 2011). Atomoxetine may also be prescribed for individuals with ADHD and comorbidities including tics, mania, and suicidal ideation (Garnock-Jones and Keating, 2009; Reichart and Nolen, 2004), even though the effect of atomoxetine on mania and suicidal ideation has not yet been clarified. Atomoxetine has been associated with increased risk of suicidal behaviour in youths (Bangs et al., 2014) and the manufacturer of Strattera reported a warning on suicidal ideation. Both European and American labels for atomoxetine report a black-box warning regarding suicidal ideation in child and adolescent ADHD patients. Nevertheless, non-stimulant medication continues to be considered as a first-line treatment for individuals with comorbidities (Hah and Chang, 2005; Shier et al., 2013).

Although randomised controlled trials in children and adults with ADHD conclusively show that both groups of medications lead to clinically significant reductions in symptoms of ADHD (Storebø et al., 2015; Punja et al., 2016; Schwartz and Correll, 2014), what has not been defined is whether stimulants and atomoxetine also lead to reduced or increased severity of mood and emotional features. The action of stimulant and non-stimulant drugs on core symptoms of ADHD is thought to happen predominantly in the prefrontal cortex (Arnsten and Rubia, 2012); however, these drugs also diffuse to other regions of the brain. Dopamine has a crucial role also in the mesolimbic system, where it regulates reward-dependent behaviours. Norepinephrine is a key neurotransmitter in the limbic system and in the brainstem, which pair cognitive functions with emotional and autonomic responses. Drugs acting on dopamine and norepinephrine may thus have important effects on mood and emotion (Nestler and Carlezon, 2006; Dremencov et al., 2009). The detection of putative iatrogenic psychiatric symptoms is complicated by the fact that they may superimpose over patients' psychiatric comorbidities.

Researchers have already studied some of these aspects: drug-induced anxiety was investigated with respect to stimulant medications (amphetamines and methylphenidates), finding that stimulants were beneficial for the reduction of anxiety (Coughlin et al., 2015). One recent meta-analysis dealt with the symptom of irritability, analysing whether treatments for ADHD increased or reduced it (Stuckelman et al., 2017). Although methylphenidate was found to reduce irritability, a sizeable worsening effect caused by amphetamines was reported. Aside from these two focused meta-analyses, no comprehensive review covered the broad spectrum of treatment-emergent mood or emotional adverse events in relationship with ADHD treatment for children and adolescents. Due to the high prevalence of ADHD, of ADHD with comorbid mood and anxiety disorders, and of ADHD with mood and/or emotional symptoms, and in view of the increasing rate of use of stimulants and atomoxetine for the treatment of ADHD, a broad systematic review of the published literature on the effect of stimulants and atomoxetine on emotional symptoms is warranted. One possibility for such investigation is to evaluate the occurrence of adverse events in clinical trials.

2. Methods

2.1. Study aims and outcomes

In order to assess the effects of stimulants and atomoxetine on anxiety and mood symptoms in children and adolescents, we conducted a systematic review and meta-analysis of randomised controlled trials. Our primary aim was to quantify, in the context of efficacy trials, the effects of stimulants and atomoxetine on treatment-emergent adverse events concerning mood and emotional symptoms. Adverse events are usually indicated in clinical trials using Low Level Terms of the MedDRA dictionary (www.meddra.org). Therefore, we obtained our categories of adverse events by identifying in the studies we examined all the most frequently used Low Level Terms. In so doing we grouped together all similar Low Level Terms comprised under the same High Level Term categories of the MedDRA, as they refer to similar adverse events (see examples below). Since adverse events are reported by a restricted set of Low Level Terms across all clinical trials, a formal consensus procedure was deemed not necessary. The collection and grouping of Low Level Terms resulted in the following categories of events, which constitute the outcomes investigated in this work: irritability; anxiety; apathy or sedation or dullness or drowsiness (from now on: apathy); reduced talkativeness or less talk (from now on: talking less); sadness; proneness to crying or tearfulness or crying (from now on: crying); mood lability or mood instability or emotional lability, not otherwise specified (from now on: emotional lability); biting nails or nailbiting or nail-biting (from now on: biting nails); staring or daydreaming (from now on: staring); perseveration or fixation (from now on: perseveration); euphoria or racing thoughts (from now on: euphoria).

2.2. Data collection

Relevant publications were identified from the PubMed database through a literature search using the following terms: (atomoxetine OR amphetamine OR lisdexamphetamine OR dextroamphetamine OR methylphenidate OR dexmethylphenidate)(mood OR emotion OR affect OR anxiety OR irritability)(child OR children OR adolescent OR paediatric). Additional literature was collected from cross-references of both original and review articles, for a total of 1118 manuscripts. The search was not restricted by date and all relevant papers published up to July 2017 were retrieved. Next, two reviewers independently assessed studies for eligibility and discrepancies were resolved by consensus. Selection criteria for inclusion were: randomised placebo-

controlled clinical trials on human subjects, conducted in children and adolescents, with the primary aim of assessing clinical drug effects, also evaluating adverse events on emotional and mood symptoms. Selection criteria for exclusion were: articles in languages different from English; letters, commentaries, reviews, case reports; studies on addiction or substance abuse disorders; studies not reporting the numbers of adverse events. Studies dealing with ADHD plus specific psychiatric comorbidities and/or dealing with patients assuming specific psychoactive drugs not prescribed for ADHD were also excluded, as they would have introduced a specific bias connected with possible alternative explanations for adverse events. Lastly, full texts were screened and sorted to ensure they reported useful data. By this procedure, we excluded all studies focused on mood and emotional symptoms that used psychological scales or similar rating instruments, as they could not provide numbers of patients affected/unaffected by discrete adverse events.

2.3. Data extraction and description

We sought measures of adverse events regarding emotional or mood symptoms which were presented as, or could be converted to, numbers of patients who experienced adverse events. Standardised data recording forms were developed for this purpose and data were extracted manually from each selected report by two independent reviewers. After data extraction, disagreements were resolved by consultation between the first and last two authors. Descriptive data were collected for all included studies: study type and design, duration, exclusion criteria, percentage of male subjects, age of subjects, number of subjects treated with reference and experimental treatments, the nature of each treatment, minimum and maximum doses of experimental treatments, and numbers and percentages of patients treated with either reference or experimental treatments who experienced treatment-emergent adverse events included in the following outcomes: irritability, anxiety, apathy, talking less, sadness, crying, emotional lability, biting nails, staring, perseveration, and euphoria.

2.4. Meta-analysis

In order to carry out a meta-analysis, we excluded manuscripts that, although quantitative, did not provide complete data on both an experimental and a placebo treatment or baseline condition. To avoid the inflation of data from control groups, manuscripts reporting on multiple experimental treatments were used as follows: a) if they reported on different treatments (methylphenidates, amphetamines, and atomoxetine) control groups were included once for each treatment, as analyses are conducted separately; b) if they reported on the same treatment, with different-dosing arms, control groups were compared only against the highest dose; c) if they reported on the same treatment, in different formulations (immediate or controlled release), control groups were compared only against the controlled release formulation, as it represents the most clinically relevant choice for maintenance therapies; d) for the only manuscript (Sonuga-Barke, 2009) that reported on two treatment arms with different methylphenidate controlled-release formulations, after consultation between the first and last author, the size and number of events of the control group was split in half (rounding by coin flip) in order to conduct both comparisons. Meta-analyses compared the numbers of patients who experienced each outcome (adverse event), while grouping treatments into three therapeutic categories: amphetamines, atomoxetine, and methylphenidates. Among results, we chose not to report the effect of treatment for all drug classes pooled together: methylphenidates, amphetamines, and atomoxetine have different mechanisms of action, therefore the hypothesis of a common effect could be misleading. For meta-analysis, the Mantel-Haenszel risk ratio (RR) and 95% confidence interval (CI) were calculated in random effects models, using study sample sizes as trial weight. This choice was made to compensate for the possible heterogeneity in design and instruments used by studies to collect adverse events. A RR = 1 indicates a lack of association between the experimental treatment and the specific adverse event; a RR > 1 indicates a detrimental effect of the experimental treatment at increasing the occurrence of the adverse event; a RR < 1 indicates a protective effect of the experimental treatment at reducing the occurrence of the adverse event. Subgroup analyses with post-hoc comparisons were conducted in order to detect significant differences in RR between drug classes. Heterogeneity between studies was measured using the I^2 statistic: $p < 0.10$ was considered indicative of statistically significant heterogeneity and an I^2 value of 40% or more was considered indicative of sizeable heterogeneity. Sensitivity analyses were performed to determine the variability of pooled results. Begg's funnel plots were drawn to show potential risks of publication bias in each sub-analysis; Egger's tests were used to statistically assess the asymmetry of funnel plots; $p < 0.05$ was considered indicative of statistically significant asymmetry. Review Manager 5.3 (Copenhagen, the Nordic Cochrane Centre, the Cochrane Collaboration) was used to conduct this meta-analysis. In order to further investigate potential factors that influenced the study outcomes, we probed the association between the results of the meta-analyses and the essential characteristics of studies by random effects meta-regression of risk (as ln of RRs) against: sample size (as inverse variance of RR), publication year, study design (parallel groups or cross-over), drug dose, drug release, average patient age, and male percentage. Meta-regressions were carried out separately for each outcome and each drug group; R-squared values and p values of the models are reported in the results for significant models, together with Beta coefficients and p values of significantly associated independent variables. Analyses were conducted by SPSS v.22 (IBM, Chicago, USA) with the addition of the MetaReg package (http://mason.gmu.edu/~dwilsonb/ma.html).

3. Results

3.1. Qualitative analysis

After the first selection step, 98 manuscripts were selected. Full text screening and sorting led to the exclusion of one manuscript which lacked a text source and of 33 manuscripts which reported measures of emotional or mood events that were either qualitative or, although quantitative, did not allow us to count numbers of patients who experienced single events. We then excluded 19 manuscripts which did not provide complete data on study outcomes in both an experimental and a paired-control treatment. Forty-five manuscripts reported numbers of patients or data which could be converted to numbers of patients, who experienced adverse events to a control and to one or more experimental treatments; 18 of these dealt with more than one experimental treatment. The detail of selection procedures is reported in Fig. 1. Table 1 reports the essential characteristics of included studies. All studies dealt with populations of children and adolescents affected by ADHD (following our inclusion criteria). Exclusion criteria were not stated by 16% studies, while 53% of the studies excluded all subjects with comorbidities and the remaining ones had more specific criteria. All studies except one were randomised trials, with a cross-over design predominant (58%) over parallel-groups; trials lasted 6.0 weeks on average. Regarding average daily administered doses, atomoxetine was used at 0.5–2 mg/kg. Lisdexamphetamine was always used with a weight-independent dosing of 30–70 mg; mixed amphetamine salts were also used independent from weight, at 5–40 mg, except for one study which adjusted dosing by weight to 0.3–0.6 mg/kg. Dextroamphetamine was used at 5–25 mg. Immediate-release methylphenidate was used at doses ranging from 7.5–60 mg, with an average

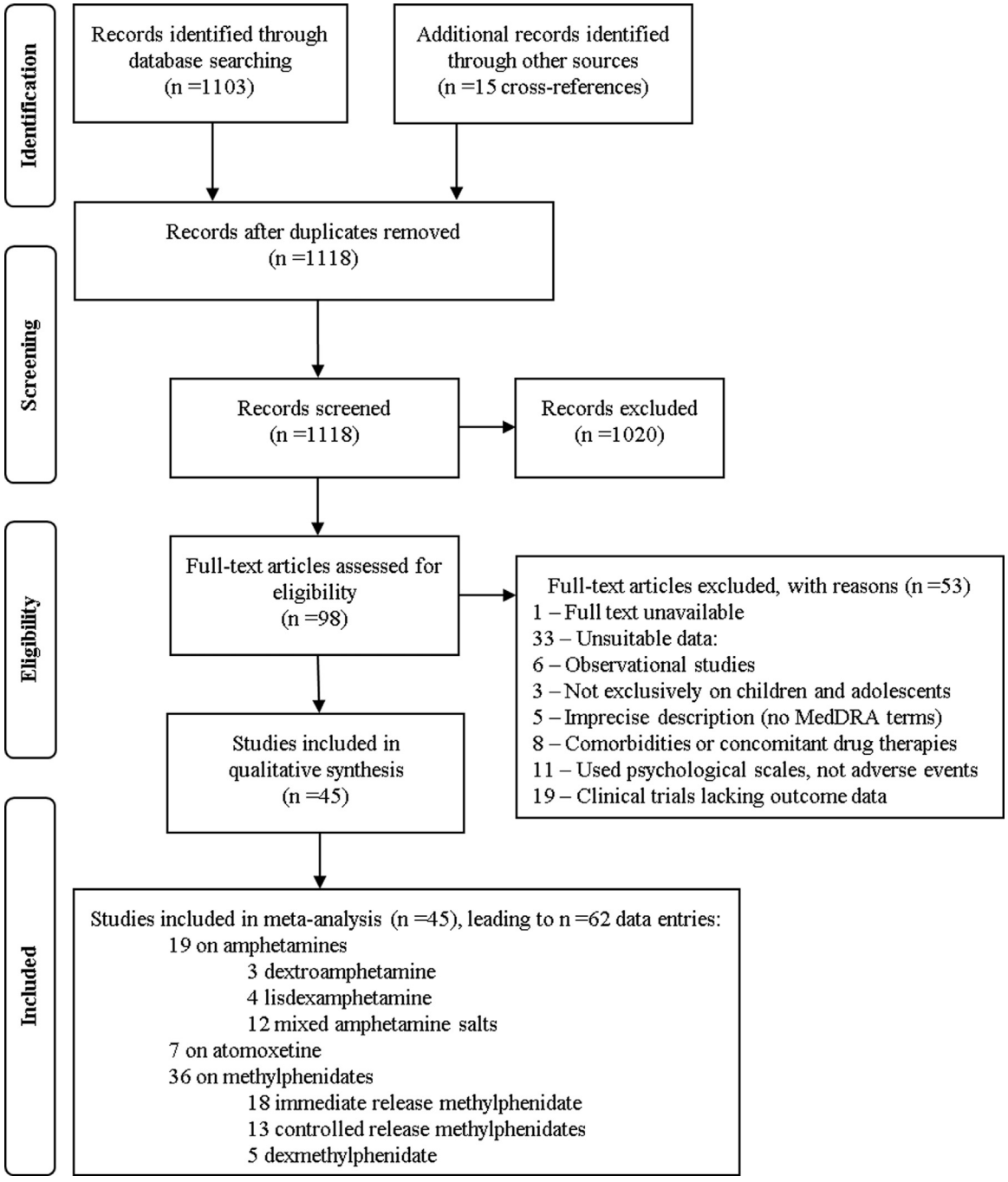

Fig. 1. Study selection flow-chart following the PRISMA standard.

dosing of 12–31 mg; the weight-adjusted methylphenidate dose varied slightly, between 0.3and 1.5 mg/kg and on average it was 0.72–0.78 mg/kg. Controlled-release methylphenidate was used at 5–60 mg, with an average of 14–54 mg, or 0.5–2 mg/kg. Dexmethylphenidate was used weight-independently at 10–40 mg.

Regarding the outcomes of meta-analysis, the most frequently investigated adverse events were irritability (89% of studies) followed by anxiety and sadness (53%), apathy (49%), biting nails and crying (36%), emotional lability and talking less (33%), staring (29%), euphoria (24%), and perseveration (11%).

With respect to self-injury-related events, 90% of studies did not provide any data. Only five studies reported specific data, of which three observed no event, one study reported seven cases of self-injury in patients treated with atomoxetine, and one study reported one case in a patient treated with lisdexamphetamine.

3.2. Meta-analyses

By extracting cohorts separately from manuscripts which reported on multiple treatment arms, we obtained seven data entries on atomoxetine, 19 on amphetamines (three dextroamphetamine, four lisdexamphetamine, and 12 mixed amphetamine salts), 36 on

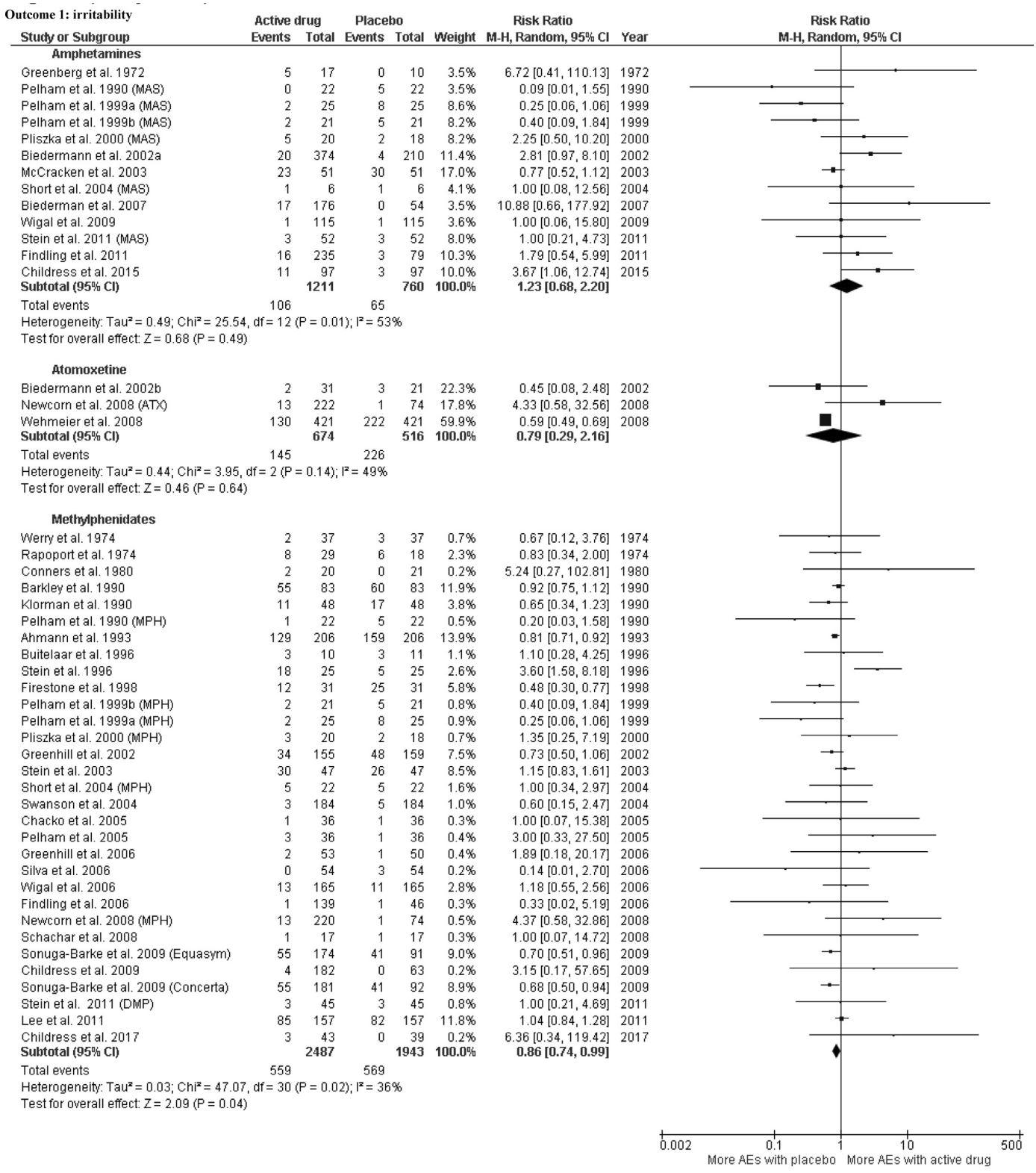

Fig. 2. Forest plots of adverse events for the outcome: irritability. Active treatments vs. placebo.
Legend: The funnel plot is available in Supplemental Fig. 1.

methylphenidates (18 immediate release, 13 controlled release, and 5 dexmethylphenidate). Forest plots of meta-analysis results are available in Figs. 2–12; studies that are indicated with no events in the meta-analysis Forest plots are only those that explicitly reported zero events. Studies that did not clarify whether events were investigated or not, are reported in the study selection flow chart (Table 1) as lacking outcome data and are not comprised in the meta-analysis. Funnel plots are available in Supplemental Figs. 1–11. Here below, we report as text the

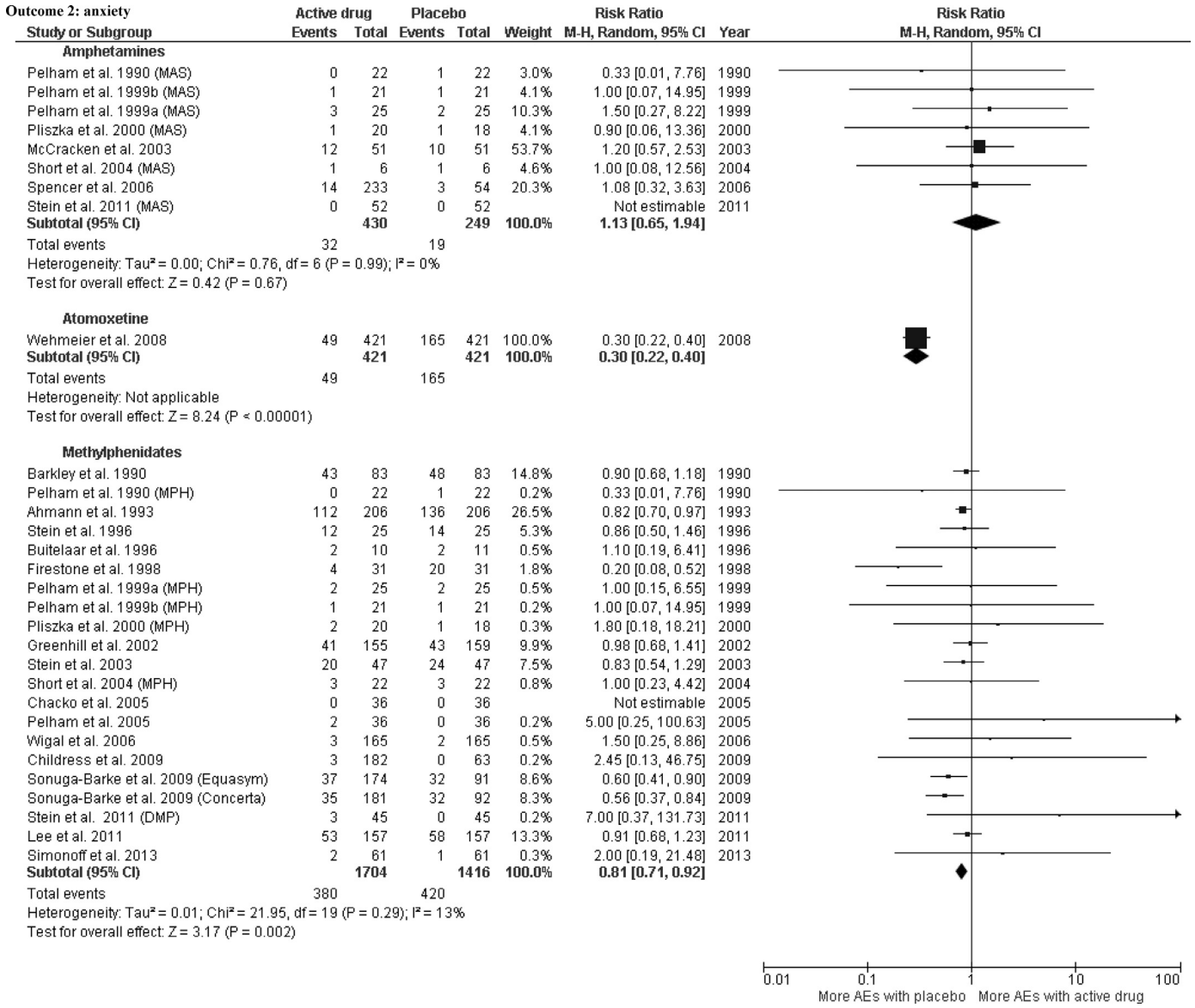

Fig. 3. Forest plots of adverse events for the outcome: anxiety. Active treatments vs. placebo.
Legend: The funnel plot is available in Supplemental Fig. 2.

results from meta-analyses for all outcomes, and results of the heterogeneity tests and Egger's tests only for significant outcomes. A full version comprising all non-significant results is available in Supplemental Table 1 (Fig. 12).

3.2.1. Outcome 1: irritability

Irritability was not significantly influenced by treatment with amphetamines (13 studies, RR = 1.23, 95%C.I. 0.68–2.20, Z = 0.68, $p = 0.49$) or atomoxetine (3 studies, RR = 0.79, 95%C.I. 0.29–2.16, Z = 0.46, $p = 0.64$). It was significantly reduced by treatment with methylphenidates (31 studies, RR = 0.86, 95%C.I. 0.74–0.99, Z = 2.09, $p = 0.04$), with moderate heterogeneity $\chi^2(30) = 47.1$, $p = 0.02$, $I^2 = 36\%$. Subgroup analysis evidenced no significant difference between drug classes, $\chi^2(2) = 1.4$, $p = 0.50$. The funnel plot of methylphenidates was asymmetrical, Egger's test scored $B = 0.72$, $p < 0.01$.

3.2.2. Outcome 2: anxiety

Anxiety was not significantly influenced by treatment with amphetamines (8 studies, RR = 1.13, 95%C.I. 0.65–1.94, $Z = 0.42$, $p = 0.67$). Atomoxetine was found protective in one study (RR = 0.30, 95%C.I. 0.22–0.40, $Z = 8.24$, $p < 0.001$). Anxiety was reduced by treatment with methylphenidates (21 studies, RR = 0.81, 95%C.I. 0.71–0.92, $Z = 3.17$, $p = 0.002$), without significant heterogeneity $\chi^2(19) = 22.0$, $p = 0.29$, $I^2 = 13\%$. Subgroup analysis evidenced a significantly different effect between atomoxetine and other treatments, $\chi^2(2) = 41.4$, $p < 0.001$. The funnel plot of methylphenidates was asymmetrical, Egger's test scored $B = 0.77$, $p < 0.01$.

3.2.3. Outcome 3: sadness

Sadness was not significantly influenced by treatment with amphetamines (7 studies, RR = 1.90, 95%C.I. 0.91–3.95, $Z = 1.72$, $p = 0.09$) or methylphenidates (21 studies, RR = 1.08, 95%C.I. 0.93–1.26, $Z = 1.05$, $p = 0.30$). It was reduced by treatment with

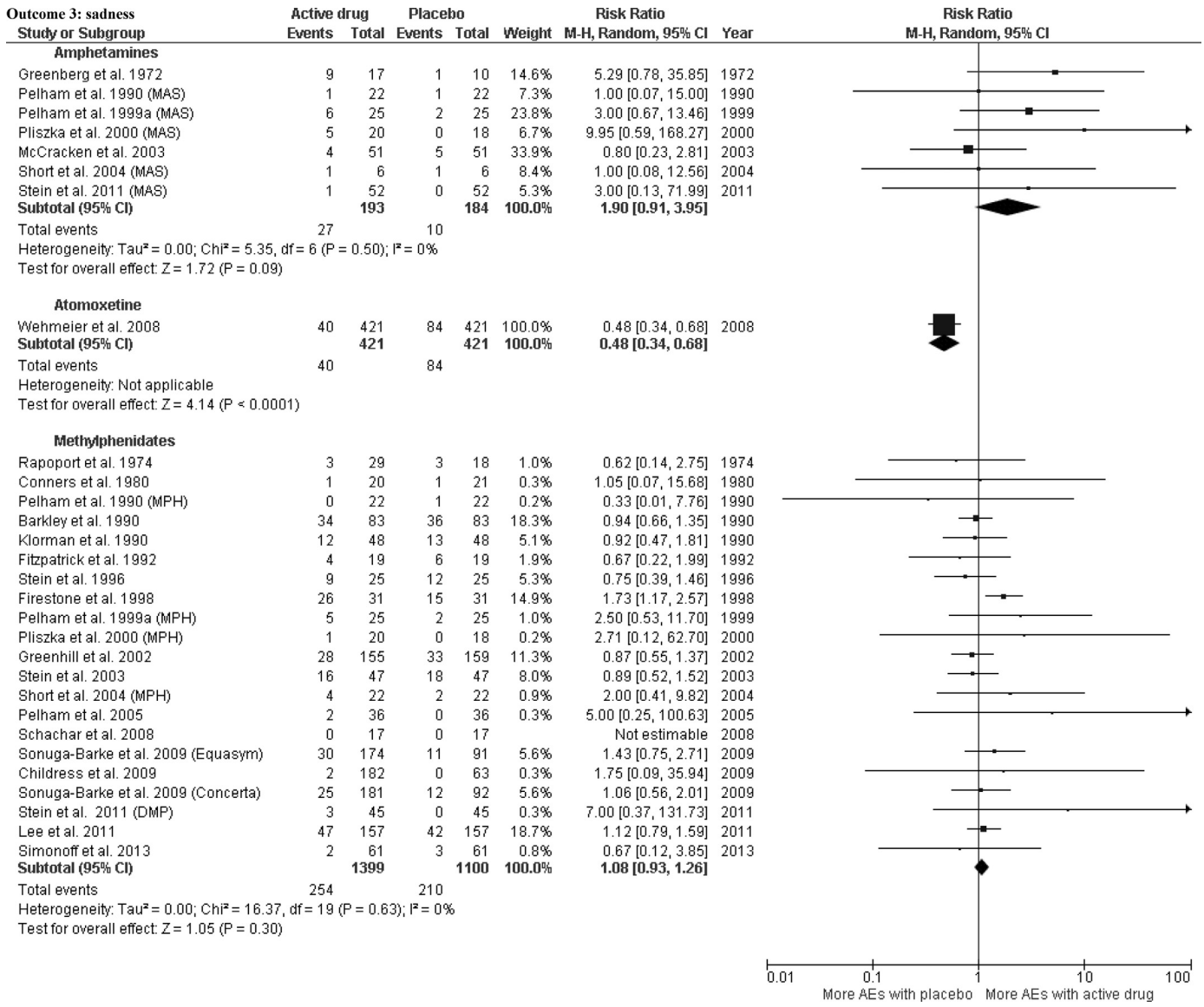

Fig. 4. Forest plots of adverse events for the outcome: sadness. Active treatments vs. placebo.
Legend: The funnel plot is available in Supplemental Fig. 3.

atomoxetine in one study (RR = 0.48, 95%C.I. 0.34–0.68, $Z = 4.14$, $p < 0.001$). Subgroup analysis evidenced a significantly different effect between atomoxetine and other treatments, $\chi^2(2) = 21.0$, $p < 0.001$.

3.2.4. Outcome 4: apathy

Apathy was not significantly influenced by treatment with amphetamines (8 studies, RR = 1.55, 95%C.I. 0.94–2.56, Z = 1.72, $p = 0.08$) or atomoxetine (2 studies, RR = 1.65, 95%C.I. 0.08–35.21, Z = 0.32, $p = 0.75$); it was increased by methylphenidates (16 studies, RR = 1.27, 95%C.I. 1.03–1.58, Z = 2.19, $p = 0.03$), without evidence of heterogeneity among studies $\chi^2(15) = 14.6$, $p = 0.48$, $I^2 = 0\%$. Subgroup analysis evidenced no significant difference between drug classes, $\chi^2(2) = 0.54$, $p = 0.76$. The funnel plot of methylphenidates was asymmetrical, Egger's test scored $B = 0.83$, $p < 0.01$.

3.2.5. Outcome 5: biting nails

The outcome of biting nails was not significantly influenced by treatments, either with amphetamines (6 studies, RR = 1.05, 95%C.I. 0.47–2.34, $Z = 0.11$, $p = 0.91$), or atomoxetine (1 study, RR = 0.71, 95%C.I. 0.39–1.30, $Z = 1.11$, $p = 0.27$), or methylphenidates (14 studies, RR = 0.96, 95%C.I. 0.81–1.16, Z = 0.39, $p = 0.70$). Subgroup analysis evidenced no significant difference between drug classes, $\chi^2(2) = 0.98$, $p = 0.61$.

3.2.6. Outcome 6: crying

The outcome of crying was not significantly influenced by treatments, either with amphetamines (5 studies, RR = 0.86, 95%C.I. 0.28–2.63, $Z = 0.27$, $p = 0.79$), or methylphenidates (15 studies, RR = 1.01, 95%C.I. 0.84–1.22, $Z = 0.16$, $p = 0.88$). Subgroup analysis evidenced no significant difference between drug classes, $\chi^2(2) = 0.08$, $p = 0.77$.

3.2.7. Outcome 7: emotional lability

Emotional lability was increased by amphetamines (5 studies, RR 3.82, 95%C.I. 2.02–7.22, $Z = 4.14$, $p < 0.001$) with no evidence of heterogeneity among studies, $\chi^2(4) = 3.46$, $p = 0.48$, $I^2 = 0\%$. No significant effect of atomoxetine (2 studies, RR = 0.73, 95%C.I. 0.12-4.44, $Z = 0.34$, $p = 0.73$) or methylphenidates (8 studies, RR = 1.40, 95%C.I. 0.87–2.27, $Z = 1.39$, $p = 0.17$) was found. Subgroup analysis evidenced a significantly different effect between atomoxetine and other treatments, $\chi^2(2) = 7.24$, $p = 0.03$. The funnel plot of amphetamines was not asymmetrical, with Egger's test $p = 0.12$.

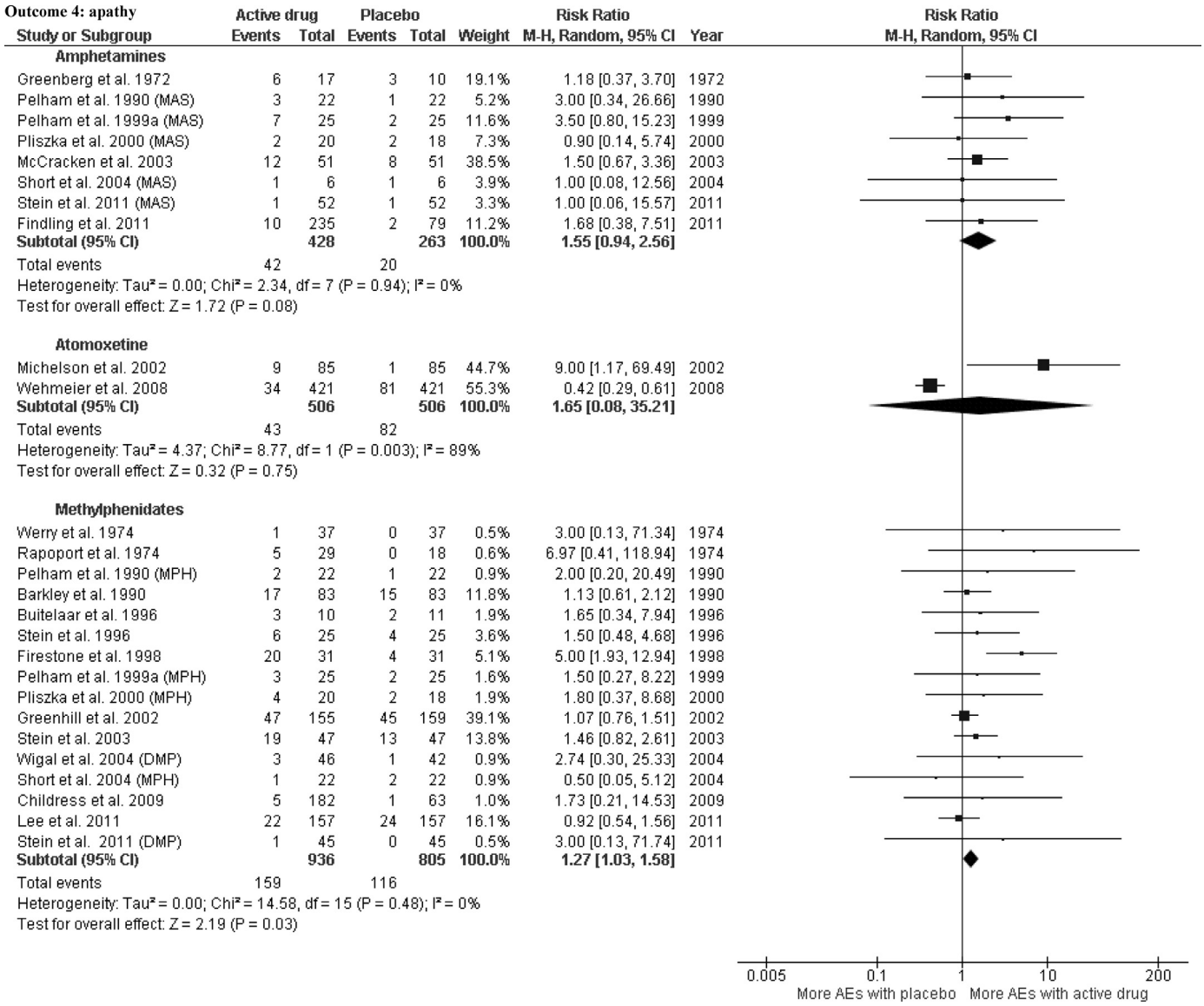

Fig. 5. Forest plots of adverse events for the outcome: apathy. Active treatments vs. placebo.
Legend: The funnel plot is available in Supplemental Fig. 4.

3.2.8. Outcome 8: talking less

With respect to talking less, amphetamines had no significant effect (5 studies, RR = 2.29, 95%C.I. 0.62–8.48, $Z = 1.24$, $p = 0.21$). Atomoxetine was found protective in one study (RR = 0.37, 95%C.I. 0.23–0.61, $Z = 3.93$, $p < 0.001$); methylphenidates had a detrimental effect (13 studies, RR = 1.53, 95%C.I. 1.15-2.04, $Z = 2.92$, $p = 0.003$), without evidence of heterogeneity among studies, $\chi^2(12) = 11.4$, $p = 0.50$, $I^2 = 0\%$. Subgroup analysis evidenced a significantly different effect between atomoxetine and other treatments, $\chi^2(2) = 24.94$, $p < 0.001$. Funnel plots of both atomoxetine and methylphenidates were not asymmetrical, with Egger's test $p = 0.50$ and 0.52, respectively.

3.2.9. Outcome 9: staring

The outcome of staring was not significantly influenced by treatments, either with amphetamines (4 studies, RR = 1.39, 95%C.I. 0.46–4.17, $Z = 0.58$, $p = 0.56$), or methylphenidates (12 studies, RR = 0.94, 95%C.I. 0.82–1.08, $Z = 0.90$, $p = 0.37$). Subgroup analysis evidenced no significant difference between drug classes, $\chi^2(1) = 0.48$, $p = 0.49$.

3.2.10. Outcome 10: euphoria

Euphoria was not significantly influenced by treatment with amphetamines (2 studies, RR = 1.94, 95%C.I. 0.29–12.76, Z = 0.69, $p = 0.49$). It was reduced by atomoxetine in one study (RR = 0.58, 95%C.I. 0.39–0.86, $Z = 2.70$, $p = 0.007$), and by methylphenidates (7 studies, RR = 0.77, 95%C.I. 0.59–1.00, $Z = 1.98$, $p = 0.05$), with no evidence of heterogeneity among studies $\chi^2(6) = 6.42$, $p = 0.38$, $I^2 = 6\%$. Subgroup analysis showed no significant difference between drug classes, $\chi^2(2) = 2.45$, $p = 0.29$. The funnel plot of methylphenidates was not asymmetrical, with Egger's test $p = 0.22$.

3.2.11. Outcome 11: perseveration

Perseveration was not significantly influenced by treatments, either with amphetamines in one study (RR = 0.50, 95%C.I. 0.06–4.15, $Z = 0.64$, $p = 0.52$), or methylphenidates (4 studies, RR = 0.84, 95%C.I. 0.45–1.57, $Z = 0.54$, $p = 0.59$). It was reduced by atomoxetine in one study (RR = 0.31, 95%C.I. 0.17–0.57, $Z = 3.79$, $p < 0.001$). Subgroup analysis evidenced no significant difference between drug classes, $\chi^2(2) = 5.10$, $p = 0.08$.

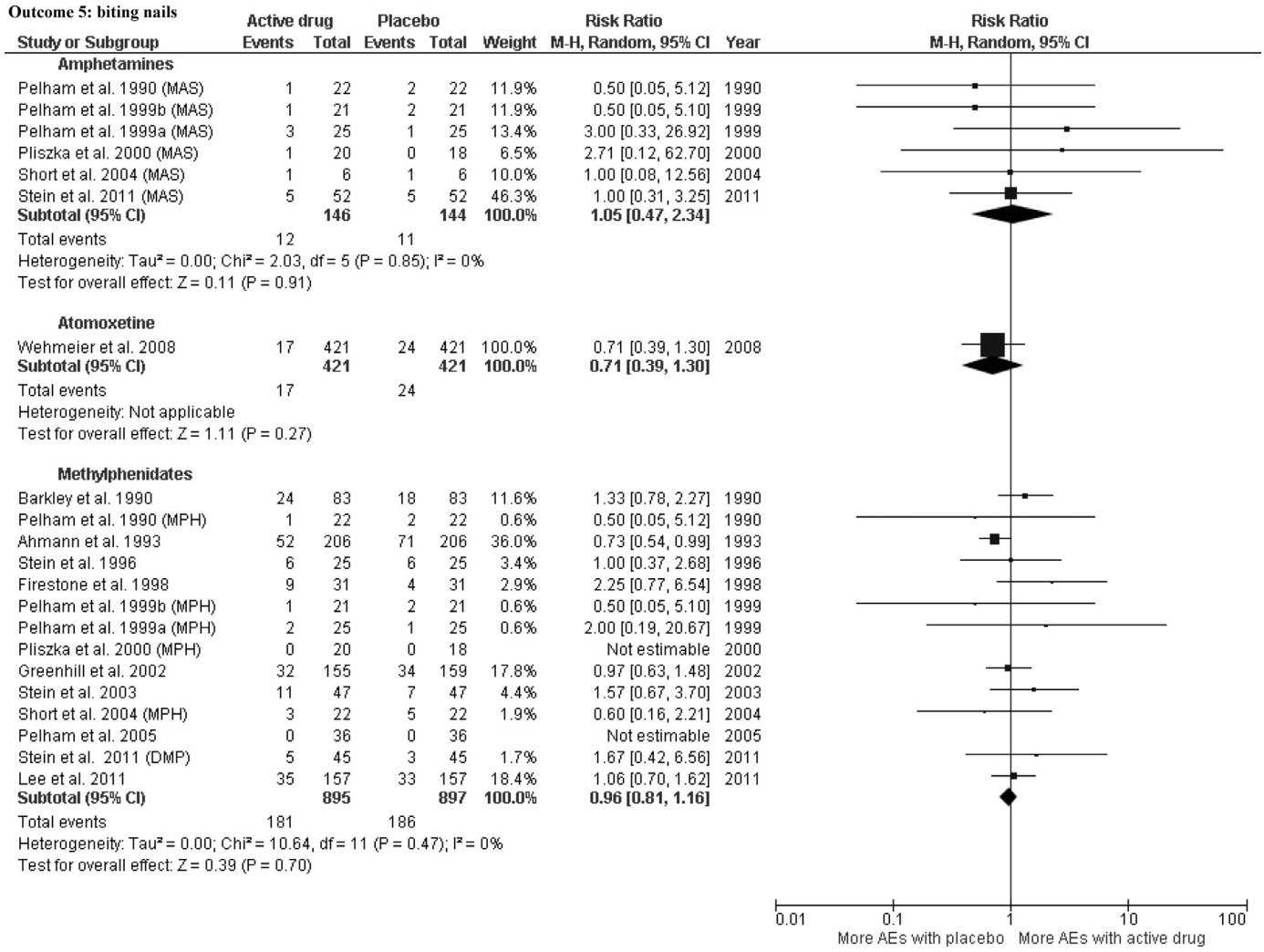

Fig. 6. Forest plots of adverse events for the outcome: biting nails. Active treatments vs. placebo.
Legend: The funnel plot is available in Supplemental Fig. 5.

3.3. Meta-regressions

Results of meta-regressions are reported only for models with significant equations.

3.3.1. Outcome 1: irritability

The RR of irritability with amphetamine treatment (model $R^2 = 0.98$, $p < 0.001$) was higher in parallel-group studies ($B = 0.18$, $p = 0.012$) conducted in more recent years ($B = 1.35$, $p < 0.001$).

3.3.2. Outcome 3: sadness

The RR of sadness with methylphenidate treatment (model $R^2 = 0.67$, $p < 0.001$) was lower in studies with more male patients ($B = -0.81$, $p < 0.001$) and older patients ($B = -0.30$, $p = 0.050$), whereas the risk was higher with immediate-release formulations ($B = 0.62$, $p = 0.006$) as compared to controlled-release ones.

3.3.3. Outcome 6: crying

The RR of crying with methylphenidate treatment (model $R^2 = 0.64$, $p < 0.001$) was lower in studies with more male patients ($B = -0.61$, $p = 0.032$) and older patients ($B = -0.38$, $p < 0.027$), whereas the RR was higher with higher methylphenidates doses ($B = 0.44$, $p < 0.036$).

4. Discussion

A vast prevalence of adverse events involving mood alterations and disturbances of emotion is reported throughout clinical studies on the pharmacotherapy of ADHD, even when selection criteria are set to exclude patients with comorbidities (Martinez-Raga et al., 2017). This duality opens an interesting question as to whether drug treatments for ADHD may also improve comorbid mood/emotion symptoms (as shown in Coughlin et al., 2015; Stuckelman et al., 2017) through an amelioration of ADHD symptoms, or conversely whether they treat ADHD at the cost of developing disturbances of mood and/or emotion (as reported by Blouin et al., 2010; Pringsheim and Steeves, 2011). Most clinical studies to date have dealt with such events heterogeneously and have come to different conclusions, hence a systematic analysis of the existing information is in order. We here described the impact of drugs used to treat ADHD on a broad range of adverse events considered to be connected with symptoms of mood and/or emotion. By identifying the adverse events most commonly investigated in clinical trials through MedDRA Low Level Terms (www.meddra.org), we have set up a panel of outcomes that encompassed several features, possibly connected to a treatment with amphetamines and/or methylphenidate and/or atomoxetine.

In essence, the results of this meta-analysis suggest that drug therapies for ADHD may have a neglected potential for interfering with mood and/or emotion symptoms in both desirable and adverse ways.

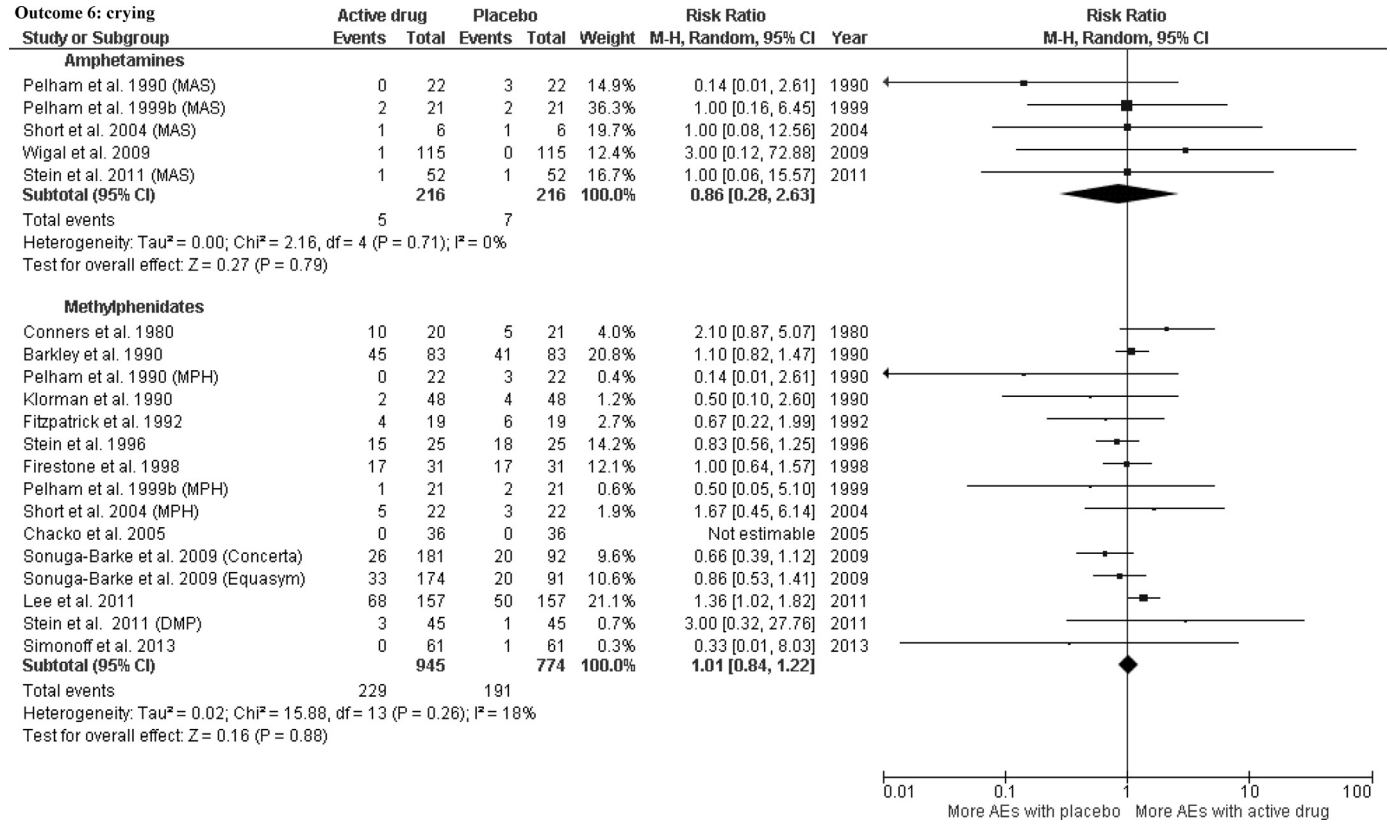

Fig. 7. Forest plots of adverse events for the outcome: crying. Active treatments vs. placebo.
Legend: The funnel plot is available in Supplemental Fig. 6.

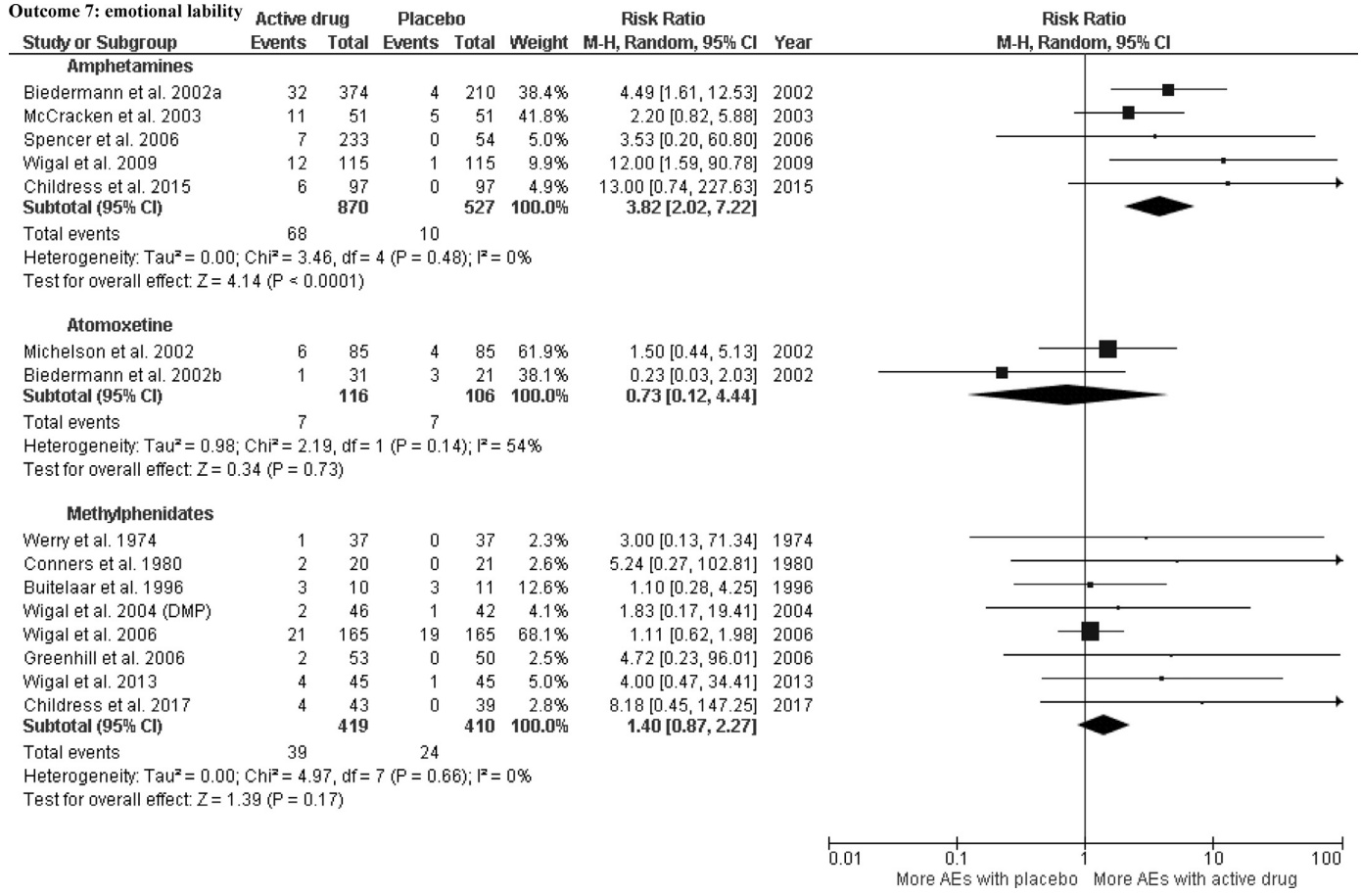

Fig. 8. Forest plots of adverse events for the outcome: emotional lability. Active treatments vs. placebo.
Legend: The funnel plot is available in Supplemental Fig. 7.

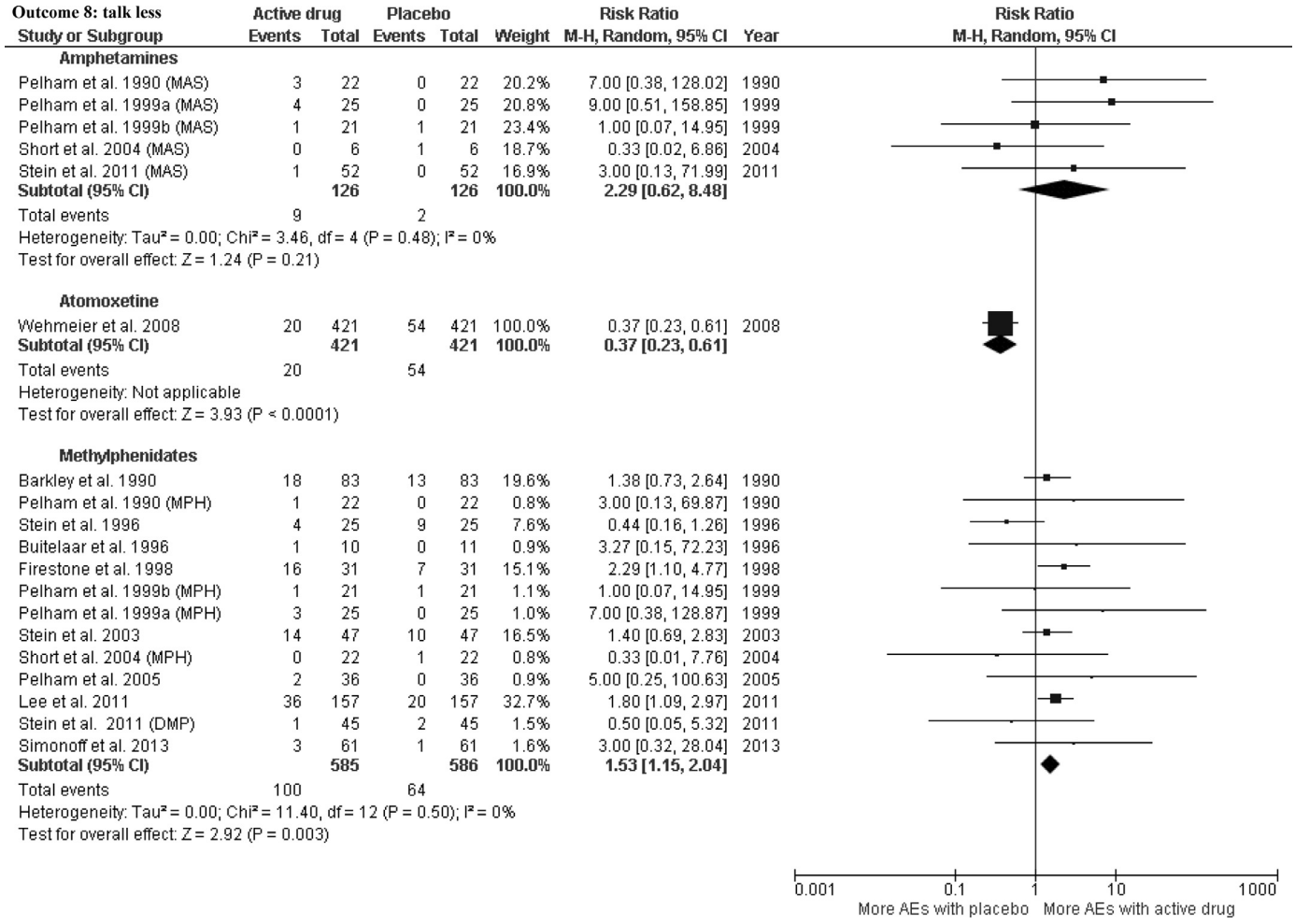

Fig. 9. Forest plots of adverse events for the outcome: talking less. Active treatments vs. placebo.
Legend: The funnel plots are available in Supplemental Fig. 8.

This issue may regard in particular amphetamine, widely used in the United States, and methylphenidate, which in Europe is the main or only approved pharmacological treatment for ADHD. Studies on atomoxetine were scant, and most outcomes reported data from one study only, which did not allow us to draw meaningful conclusions.

Atomoxetine was found to have no significant effect on irritability by three studies, nor on apathy by two studies; among those, only one study (Wehmeier et al., 2008) found beneficial effects on both outcomes. The same study found beneficial effects of atomoxetine also on anxiety, sadness, talking less, euphoria, and perseveration, possibly suggesting usefulness beyond the core symptoms of ADHD. These very positive results obtained from (for)seven out of 11 outcomes should, however, be considered with some scepticism, as they all come from one observation.

The adverse event investigated by the largest number of studies was irritability, which resulted in being reduced by treatment with methylphenidates. The result, in accordance with a previous meta-analysis (Stuckelman et al., 2017), is not surprising: it must be considered that irritability may comprise both a “true” adverse event of increased irritability and a lack of pharmacological efficacy resulting in the “non-reduction” of irritability, among the targets of pharmacotherapy for ADHD. This confusion is likely inevitable in clinical trials, since the Good Clinical Practices recommend to report all events that may be adverse and possibly related to drug therapy. One interesting consideration regarding irritability is that atomoxetine and amphetamines failed at reducing this adverse event, which may suggest they are less efficacious than methylphenidate at obtaining a complete therapeutic effect. Although amphetamines did not have a significant overall influence on irritability, the risk was found to be higher in parallel-group and more recent studies. This suggests that amphetamines may now be used as comparators for newer drugs, and thus be subject to a negative bias.

Similar to irritability, anxiety was found to be reduced by methylphenidates, consistent with a previous meta-analysis that found a positive effect of stimulants on the reduction of anxiety (Coughlin et al., 2015). This result may be expected because anxiety is a very frequent comorbidity of patients with ADHD (Anderson et al., 1987; Kessler et al., 2006; Kunwar et al., 2007; Tzang and Chang, 2009). Anxiety may thus be reduced by an efficacious treatment. Moreover, some aspects of hyperactivity can be mistaken for anxiety, such as being restless or always reactive to external stimuli. This outcome may have a bias in that its occurrence tended to be associated with the study year. Moreover, the funnel plot showed an asymmetry towards the right and sizable heterogeneity, indicating a possible conceptual issue. A possible explanation is that anxiety, initially reported in connection with inefficacy, was only later considered as a separate adverse effect and thus reported. This may also suggest that increasing attention has been drawn to this aspect in later and/or independent studies, after the issues of suicidality and mood disturbances in adolescents treated with psychoactive drugs came to the surface.

Methylphenidates increased the occurrence of apathy, with limited heterogeneity between studies. From a critical perspective, reporting an adverse event of apathy in a patient with ADHD may have two interpretations. Apathy may stem from pharmacological activity that

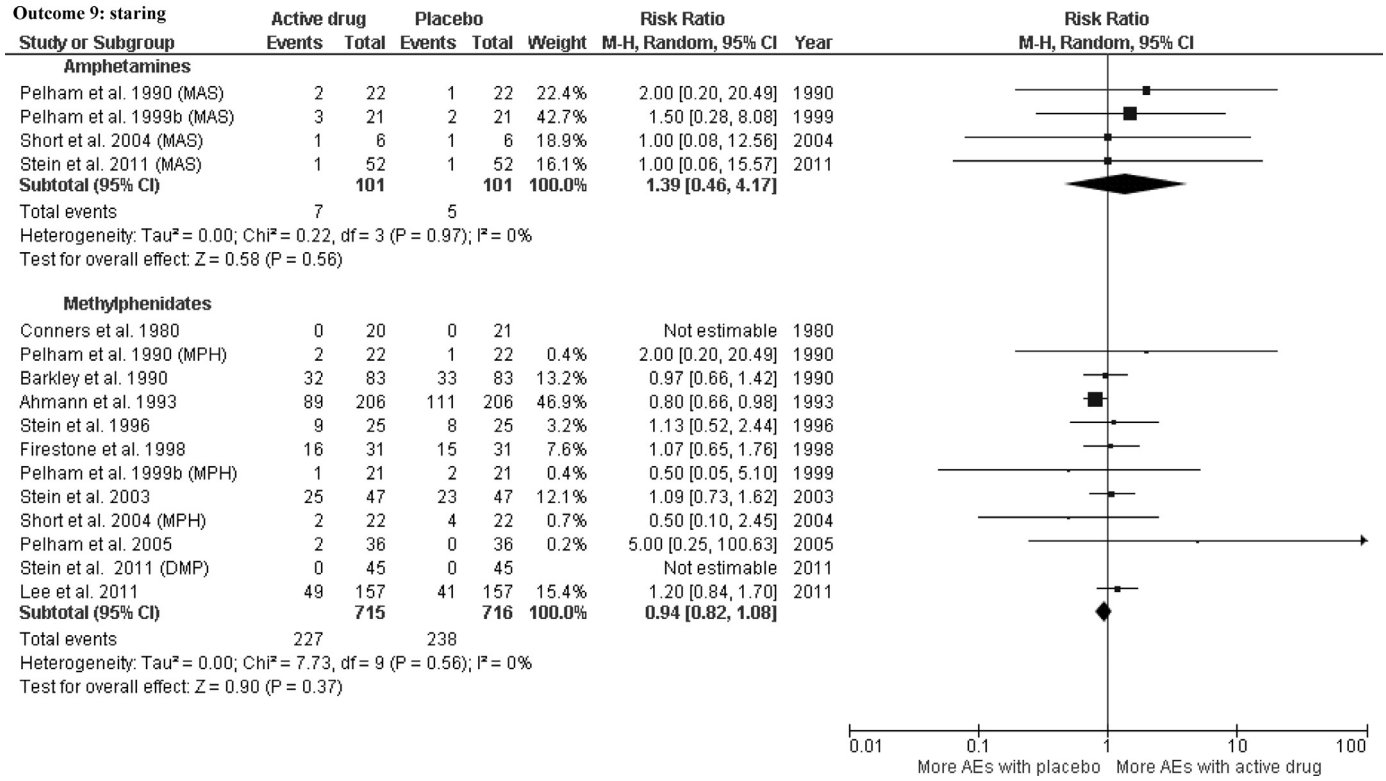

Fig. 10. Forest plots of adverse events for the outcome: staring. Active treatments vs. placebo.
Legend: The funnel plots are available in Supplemental Fig. 9.

switches a patient's behaviour from hyperactivity to a state of normal or reduced activity; therefore, raters who never saw the patient in a calm state may mistake a strong efficacy for an adverse effect. Conversely, apathy may also consist of a true adverse effect separate from therapeutic efficacy, where patients may lack the will to act. This possible duality cannot be disentangled by our methodological approach, by which we comprised within the outcome of apathy all adverse events that may have led to a reduction of patients' activity, including for instance also sedation and dullness. However, if we only considered reports of "apathy", then we would have found very few studies reporting on this outcome, leading to a potential underestimation.

Methylphenidates had a negative effect also on the disposition to talk by reducing it. The duality of this outcome may encompass both the excessive therapeutic effect of moderating excessive, inappropriate, or rushed speech, which can be found among patients with ADHD (Green et al., 2014), as well as a true adverse effect of communication reduction or loss.

Amphetamines resulted in promoting emotional lability. This may directly depend upon an excessive dopaminergic stimulation, which leads to manic and/or psychogenic effects, expectable from amphetamines (Ellinwood, 1967). In fact, we did not find a significant effect of methylphenidates on emotional lability.

Methylphenidates showed a protective effect against euphoria, without indications of bias, which may be interpreted alongside the reduction of irritability and anxiety as a global soothing, therapeutic effect; this may also support the absence of psychogenic effects with dopamine-enhancing (methylphenidate) versus dopamine-releasing (amphetamine) agents (Bisagno et al., 2016).

Although no significant effect of any treatment was found on sadness and crying, meta-regression results on methylphenidates demand discussion. The risk of sadness and crying with methylphenidates resulted in being higher in females, contrary to previous data (Cornforth et al., 2010), and it was higher in younger patients, in accordance with previous observations from single studies (Lee et al., 2015). Drug-related factors also emerged as important: immediate-release methylphenidates presented a higher risk of sadness and higher doses were connected to worsened risks of crying. Together, these results suggest moderation with the use of high dose methylphenidates, with particular respect to immediate-release formulations, when younger children and girls are involved. Therefore the methodological heterogeneity among studies may have masked, at meta-analyses, the findings that emerged from meta-regressions. Further investigations are warranted, which should address specifically the issues of sex, age, dose, and formulation of methylphenidate with respect to these two key symptoms such as crying and sadness.

Overall, based on our meta-analysis, we conclude that methylphenidates may reduce symptoms of irritability and anxiety, as well as euphoria, while worsening the symptoms of apathy and reducing talkativeness. Amphetamines worsened the symptoms of emotional lability, while providing no clear benefit on irritability, possibly as a consequence of suboptimal dosing. The potential usefulness of atomoxetine should be further examined, especially in view of the black box warning. There is a knowledge gap that highlights the need for studies addressing specifically mood/emotion symptoms associated with atomoxetine in patients with ADHD. This lack is especially important since we observed herein how stimulant medications seem to have a "not entirely safe" profile regarding mood and emotional symptoms.

4.1. Study limitations

The selective reporting of adverse events in trials is the major limitation of this type of analysis (selection bias); several studies did not report some classes of adverse events at all, and this does not allow to evaluate their contribution to the meta-analysis. Moreover, each study may have used a different checklist to monitor adverse events, introducing additional variability. There may also be an incomplete identity between what is meant as a specific adverse event in each trial

Table 1
Description of selected studies.

Study reference	Study ID in metanalysis	Experimental treatment	Study year	Study design	Male subjects (%)	Age of subjects (years)	Study duration (weeks)	N of subjects with placebo placebo treatment	N of subjects with experimental treatment	Minimum experimental dose (per day)	Maximum experimental treatment dose (per day)	Exclusion criteria
Michelson et al. (2002)	Michelson et al. (2002)	ATX	2002	RCT-DB-PG	70.6	10.3	6	85	85	1 mg/kg	1.5 mg/kg	Any N/P comorbidity
Biederman et al. (2002b)	Biederman et al. (2002b)	ATX	2002	RCT-DB-PG	0	9.7	9	21	31	0.5 mg/kg	2 mg/kg	Any N/P comorbidity
Newcorn et al. (2008)	Newcorn et al. (2008) (ATX)	ATX	2008	RCT-DB-PG	77.5	10.2	6	74	222	1 mg/kg	1.5 mg/kg	Any N/P comorbidity
Wehmeier et al., (2008)	Wehmeier et al., (2008)	ATX	2008	RCT-DB-XO	80.3	11.1	24	421	421	0.5 mg/kg	1.4 mg/kg	a
Greenberg et al. (1972)	Greenberg et al. (1972)	DxA	1972	RCT-DB-PG	100	8.7	8	10	17	5 mg	25 mg	n/a
Biederman et al. (2007)	Biederman et al. (2007)	LDX	2007	RCT-DB-PG	69.3	9	4	54	176	30 mg	70 mg	b
Wigal et al. (2009)	Wigal et al. (2009)	LDX	2009	RCT-DB-XO	76	10.1	6	115	115	30 mg	70 mg	Any N/P comorbidity
Findling et al. (2011)	Findling et al. (2011)	LDX	2011	RCT-DB-PG	70.3	14.6	4	79	235	30 mg	70 mg	c
Pelham et al. (1990)	Pelham et al. (1990) (MAS)	MAS	1990	RCT-DB-XO	100	10.4	1	22	22	10 mg	10 mg	n/a
Pelham et al. (1999a)	Pelham et al. (1999a) (MAS)	MAS	1999	RCT-DB-XO	84	9.6	3	25	25	15 mg	25 mg	n/a
Pelham et al. (1999b)	Pelham et al. (1999b) (MAS)	MAS	1999	RCT-DB-XO	90.5	10.3	2	21	21	0.3 mg/kg	0.6 mg/kg	n/a
Pliszka et al. (2000)	Pliszka et al. (2000) (MAS)	MAS	2000	RCT-DB-PG	n/a	8.1	3	18	20	10 mg	30 mg	Any N/P comorbidity
Biedermann et al. (2002a)	Biedermann et al. (2002a)	MAS	2002	RCT-DB-PG	77.1	8.6	3	210	374	10 mg	30 mg	Any N/P comorbidity
Short et al. (2004)	Short et al. (2004) (MAS)	MAS	2004	RCT-DB-XO	85	5.3	4	6	6	5 mg	15 mg	n/a
Spencer et al. (2006)	Spencer et al. (2006)	MAS	2006	RCT-DB-PG	65.5	14.2	4	54	233	10 mg	40 mg	Any N/P comorbidity
Stein et al.(2011)	Stein et al. (2011) (MAS)	MAS	2011	RCT-DB-XO	72.3	11.7	4	52	52	10 mg	30 mg	Any N/P comorbidity
Childress et al. (2015)	Childress et al. (2015)	MAS	2015	RCT-DB-XO	60.8	9.6	10	97	97	10 mg	n/a	e
McCracken et al. (2003)	McCracken et al. (2003)	MAS-Xr	2003	RCT-DB-XO	86.3	9.5	*	51	51	30 mg	30 mg	Any N/P comorbidity
Rapoport et al. (1974)	Rapoport et al. (1974)	MPH-Ir	1974	RCT-DB-PG	100	9	6	18	29	10 mg	30 mg	None
Werry and Sprague (1974)	Werry and Sprague (1974)	MPH-Ir	1974	RCT-DB-XO	87	8.9	4	37	37	0.1 mg/Kg	1 mg/Kg	Any N/P comorbidity
Conners et al. (1980)	Conners et al. (1980)	MPH-Ir	1980	RCT-DB-PG	95	7.9	8	21	20	10 mg	60 mg	Any N/P comorbidity
Klorman et al. (1990)	Klorman et al. (1990)	MPH-Ir	1990	RCT-DB-XO	87.5	14.1	3	48	48	15 mg	40 mg	ID, any P comorbidity
Barkley et al. (1990)	Barkley et al. (1990)	MPH-Ir	1990	RCT-DB-XO	85.5	8.2	1	83	83	1 mg/kg	1 mg/kg	Any N/P comorbidity
Pelham et al. (1990)	Pelham et al. (1990) (MPH)	MPH-Ir	1990	RCT-DB-XO	100	10.4	1	22	22	20 mg	20 mg	n/a
Ahmann et al. (1993)	Ahmann et al. (1993)	MPH-Ir	1993	RCT-DB-XO	78.2	9.1	1	206	206	1.5 mg/kg	1.5 mg/kg	ID, TD, Any N comorbidity
Buitelaar et al. (1996)	Buitelaar et al. (1996)	MPH-Ir	1996	RCT-DB-PG	98	9.2	4	11	10	10 mg	20 mg	ASDs
Stein et al. (1996)	Stein et al. (1996)	MPH-Ir	1996	RCT-DB-XO	100	8	1	25	25	15 mg	60 mg	Any P comorbidity
Firestone et al. (1998)	Firestone et al. (1998)	MPH-Ir	1998	RCT-DB-XO	84.4	4.8	3	31	31	0.5 mg/kg	0.5 mg/kg	Any N/P comorbidity
Pelham et al. (1999a)	Pelham et al. (1999a) (MPH)	MPH-Ir	1999	RCT-DB-XO	84	9.6	3	25	25	20 mg	35 mg	n/a
Pelham et al. (1999b)	Pelham et al. (1999b) (MPH)	MPH-Ir	1999	RCT-DB-XO	90.5	10.3	2	21	21	0.3 mg/kg	0.9 mg/kg	n/a
Pliszka et al. (2000)	Pliszka et al. (2000) (MPH)	MPH-Ir	2000	RCT-DB-PG	n/a	8.1	3	18	20	10 mg	50 mg	n/a
Short et al. (2004)	Short et al. (2004) (MPH)	MPH-Ir	2004	RCT-DB-XO	85	5.3	4	22	22	10 mg	30 mg	n/a
Chacko et al. (2005)	Chacko et al. (2005)	MPH-Ir	2005	RCT-DB-XO	89	6.1	6	36	36	1.2 mg/kg	1.2 mg/kg	n/a
Wigal et al. (2006)	Wigal et al. (2006)	MPH-Ir	2006	RCT-DB-XO	74	4.7	70	165	165	7.5 mg	22.5 mg	Any N/P comorbidity
Lee et al. (2011)	Lee et al.,(2011)	MPH-Ir	2011	RCT-DB-XO	n/a	9	1	157	157	0.5 mg/kg	0.5 mg/kg	ASDs, PSDs, TDs
Fitzpatrick et al. (1992)	Fitzpatrick et al. (1992)	MPH-Xr	1992	RCT-DB-XO	89.5	8.7	2	19	19	20 mg	20 mg	Any N/P comorbidity
Greenhill et al. (2002)	Greenhill et al. (2002)	MPH-Xr	2002	RCT-DB-PG	82	9	3	158	163	20 mg	60 mg	Any N/P comorbidity, g
Stein et al. (2003)	Stein et al. (2003)	MPH-Xr	2003	RCT-DB-XO	70.2	9	1	47	47	54 mg	54 mg	Any N/P comorbidity
Swanson et al. (2004)	Swanson et al. (2004)	MPH-Xr	2004	RCT-DB-XO	73.8	9.6	1	184	184	20 mg	60 mg	Any N/P comorbidity
Pelham et al. (2005)	Pelham et al. (2005)	MPH-Xr	2005	RCT-DB-XO	91.7	9.6	1	36	36	5 mg	22 mg	n/a
Findling et al. (2006)	Findling et al. (2006)	MPH-Xr	2006	RCT-DB-PG	79.2	9.5	3	46	139	20 mg	60 mg	Any N/P comorbidity, g
Newcorn et al. (2008)	Newcorn et al. (2008) (MPH)	MPH-Xr	2008	RCT-DB-PG	70.9	10.2	6	74	220	0.5 mg/kg	2.5 mg/kg	Any N/P comorbidity
Schachar et al. (2008)	Schachar et al. (2008)	MPH-Xr	2008	RCT-DB-XO	88.2	11.3	1	17	17	20 mg	60 mg	Any N/P comorbidity
Sonuga-Barke (2009)	Sonuga-Barke (2009) (Concerta)	MPH-Xr	2009	OLT-PG	73.9	9.6	1	183	181	10 mg	60 mg	Severe P comorbidity
Sonuga-Barke et al. (2009)	Sonuga-Barke et al. (2009) (Equasym)	MPH-Xr	2009	OLT-PG	73.9	9.6	1		174	10 mg	60 mg	Severe P comorbidity
Wigal et al. (2013)	Wigal et al. (2013)	MPH-Xr	2013	RCT-DB-XO	72.7	8.8	6	45	45	20 mg	60 mg	e
Simonoff et al. (2013)	Simonoff et al. (2013)	MPH-Xr	2013	RCT-DB-PG	74	10.8	16	61	61	0.5 mg/kg	1.5 mg/kg	Any P comorbidity
Childress et al. (2017)	Childress et al. (2017)	MPH-Xr	2017	RCT-DB-PG	69.8	9.1	4	39	43	20 mg	60 mg	f
Wigal et al. (2004)	Wigal et al. (2004) (DMP)	dMPH	2004	RCT-DB-PG	87	9.8	4	42	46	10 mg	40 mg	Any N/P comorbidity
Greenhill et al. (2006)	Greenhill et al. (2006)	dMPH	2006	RCT-DB-PG	64.1	10	7	50	53	10 mg	30 mg	Any N/P comorbidity
Silva et al. (2006)	Silva et al. (2006)	dMPH	2006	RCT-DB-XO	70.4	9.4	1	54	54	20 mg	20 mg	Any N/P comorbidity, d

(*continued on next page*)

Table 1 (*continued*)

Study reference	Study ID in metanalysis	Experimental treatment	Study year	Study design	Male subjects (%)	Age of subjects (years)	Study duration (weeks)	N of subjects with placebo placebo treatment	N of subjects with experimental treatment	Minimum experimental dose (per day)	Maximum experimental treatment dose (per day)	Exclusion criteria
Childress et al. (2009)	Childress et al. (2009)	dMPH	2009	RCT-DB-PG	64.4	8.7	5	63	182	10 mg	30 mg	Any N/P comorbidity
Stein et al. (2011)	Stein et al. (2011) (DMP)	dMPH	2011	RCT-DB-XO	72.3	11.7	4	45	45	10 mg	30 mg	Any N/P comorbidity

Table is ordered by active treatment and year of study. n/a = not available or not specified. Study type: RCT-DB = randomized controlled double-blind trial; OLT = open-label trial. Study design: PG = parallel groups; XO = cross-over. *single acute administrations. Exclusion criteria: N comorbidity = neurological comorbidity; P comorbidity = psychiatric comorbidity; ASDs = autism spectrum disorders; PSDs = psychosis spectrum disorders; TDs = tic disorders; a = any psychiatric comorbidity or subjects at risk of suicide; b = subjects with an emotional disregulation profile; c = subjects at risk of suicide; d = only enrolled responders from previous trial; e = DSM-IV axis I comorbidity except those typically connected with ADHD; f = poor responders to previous therapies; g = patients were previous responders to MPH-Ir. Treatments: ATX = atomoxetine; DxA = dextroamphetamine; LDX = lisdexamphetamine; MAS = mixed amphetamine salts, immediate release; MAS-Xr = mixed amphetamine salts, controlled release; MPH-Ir = methylphenidate, immediate release; MPH-Xr = methylphenidate, controlled release; dMPH = dexmethylphenidate.

and what we collected as symptoms for our study purposes. Similarly, we cannot guarantee that all studies applied the MedDRA terms consistently, which led us to use a random-effects meta-analysis model. The method of aggregating different adverse events should be clear of bias, since we only grouped similar terms and synonyms based on the MedDRA, with an exception made for the apathy outcome. In this case, we considered both apathy itself, together with other adverse events that, however, resulted in a reduction of activity. This decision was made since reduced activity, which is an objective element, could have been reported in one study as apathy and in another study as sedation, depending on the preference of researchers. Regarding drug groups, the choice of aggregating different drugs of the same therapeutic category appeared as a most convenient option so as not to waste data on infrequent treatments, such as the dextro- forms of amphetamine and methylphenidate; the duration of action and dose were still taken into account for post hoc analyses (meta-regressions). In order to account for all the above differences in study design and interpretation, we conducted our meta-analyses and meta-regressions by random-effects models: fixed effects models would have required much more homogeneity among included studies, which we acknowledged was lacking. This conservative approach may have expanded the confidence intervals of our risk ratios and prevented some results from reaching statistical significance. In addition, meta-regressions may have been affected by the low number of studies available for most outcomes; for the same reason, we did not explore all factors which resulted to be different in meta-regressions through subgroup analyses. This procedure would have required a stratified meta-analysis (by drug and factor), which was not feasible for most outcomes, due to the small dimension of the analysable sample sizes. We found indications of bias for several outcomes, potentially explainable by simple factors: this may not exclude, however, the presence of different sources of bias which we did not investigate. One further limitation consists of the method chosen to select treatment arms from studies reporting on multiple treatments: whenever possible we chose the highest dose and the controlled-release formulation, as they may better represent what is used for maintenance therapies; a different selection strategy (for instance, splitting all control arms) would have resulted in a different dataset and therefore different results. A final limitation of this work, directly dependent on limitations from the included studies, is a lack of observations regarding self-injurious thoughts and acts, an aspect almost never reported, and the dearth of data regarding atomoxetine.

4.2. Conclusion and future view

Results of this meta-analysis have to be considered with a critical and clinical approach in order to appraise them appropriately. Crude results present a possibly unsatisfying safety profile both for amphetamines, as their use may promote symptoms of apathy and emotional lability, and for methylphenidate, as its positive effects on irritability, anxiety, and euphoria seem to be counterbalanced by detrimental effects on apathy and reduced talkativeness.

First, it must be considered that, although mood and emotion symptoms may be caused by drug treatment, mood and emotion disorders are common among patients with ADHD. These comorbid disorders may be unmasked or worsened by treatment, meaning that a more appropriate patient selection may be required to ensure better treatment safety. Second, as indicated by heterogeneity and bias, some aspects of mood and emotion features are evolving concepts in the field of pharmacotherapy for ADHD and may be subject to interpretation issues.

Future clinical trials on the efficacy of drugs to treat ADHD should devote better efforts to quantify mood and emotional symptoms, as data from adverse event reports are sufficient to raise the suspicion of detrimental effects. The routine use of Child Behaviour CheckList (CBCL) scales at several time points during trials, for instance, could be advised, in order to draw out psychological profiles and changes therein

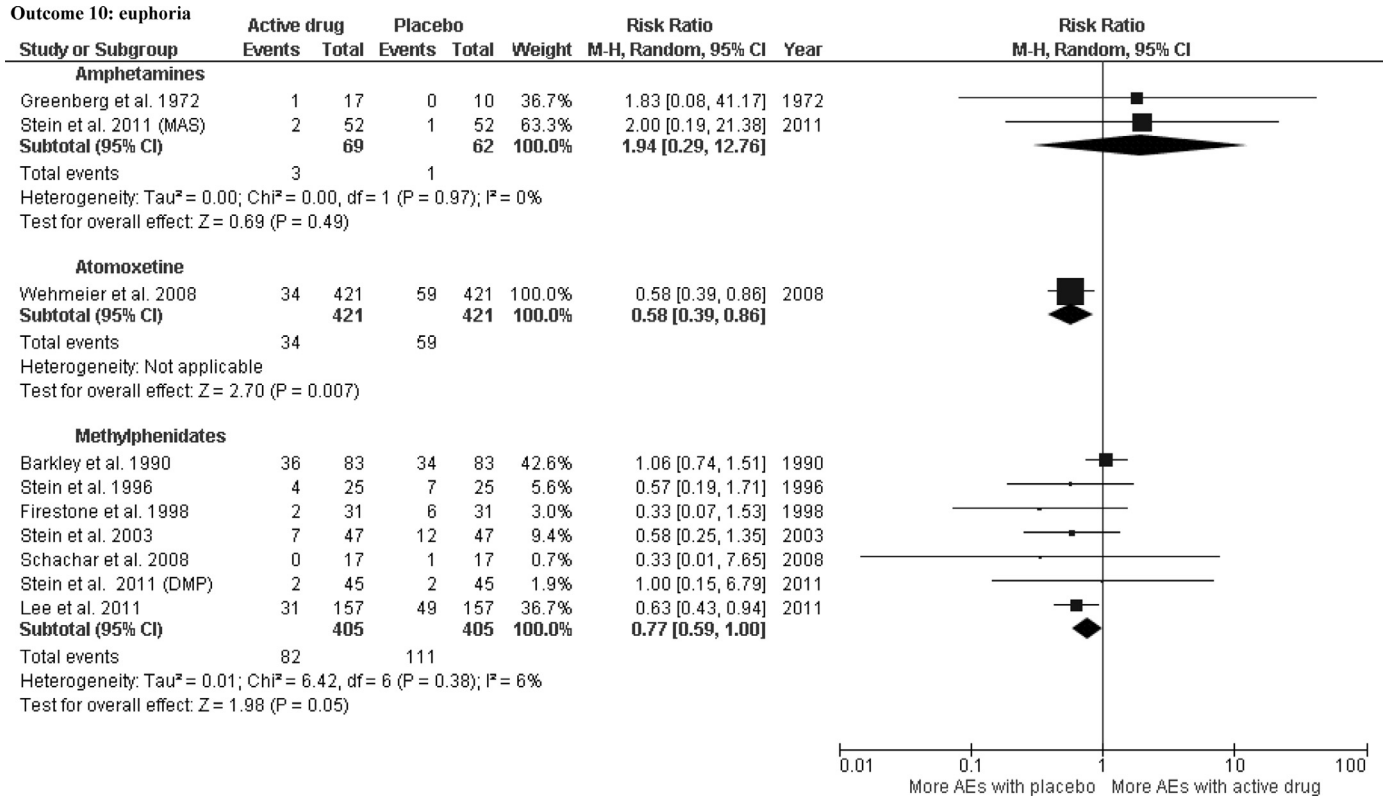

Fig. 11. Forest plots of adverse events for the outcome: euphoria. Active treatments vs. placebo.
Legend: The funnel plots are available in Supplemental Fig. 10.

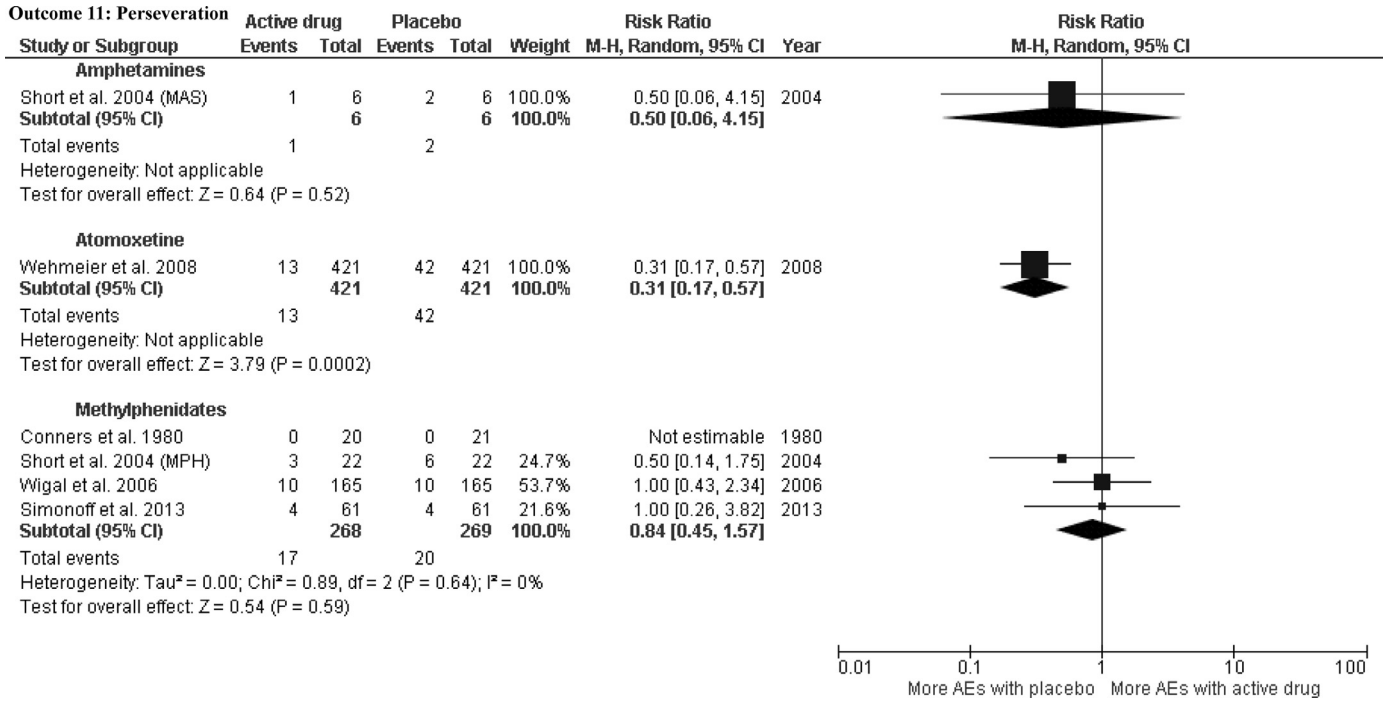

Fig. 12. Forest plots of adverse events for the outcome: perseveration. Active treatments vs. placebo.
Legend: The funnel plots are available in Supplemental Fig. 11.

(Bianchi et al., 2017). Current literature on this topic is scant and controversial, and the lack of information can have serious drawbacks on inappropriate limitations of use imposed on several drugs. Clear examples regard cautions in using stimulants, which may be unsupported (Cohen et al., 2015; Coughlin et al., 2015; Stuckelman et al., 2017), and even more atomoxetine, a drug that holds a black-box warning. Adverse events connected with mood or emotions should not be underestimated in the context of a drug therapy for ADHD. Tolerability is essential for the long-term viability of therapies and to allow an all-round beneficial effect of drugs within complex rehabilitation

courses that also include psychological therapies: these may be undermined by adverse drug effects on mood and emotions. Conclusive data are thus required to confirm or refute current security concerns. One easy way to obtain them could be to generate a consensus checklist of psychological adverse events, to be used in future clinical trials on ADHD. From a perspective of patient growth, better knowledge of the mix of comorbid mood and emotional disorders with iatrogenic mood and emotional symptoms in ADHD will help to prevent the development of more serious psychiatric disturbances in adulthood.

Conflicts of interest

None.

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Author statement

MP, CC, GP, EC, MN conceived the research and wrote the manuscript. MP, CC, GP, MG, SA performed data collection and analysis. SR, EC, MN critically reviewed the manuscript. All authors have approved the final version of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.05.021.

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SUICIDE RISK IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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SUMMARY

***Background**: ADHD (Attention-deficit/hyperactivity disorder) is a common neurodevelopmental disorder that manifests itself during childhood with various combinations of symptoms, including inattention, hyperactivity and impulsivity. Research has shown that psychiatric comorbidities play an important role in the development of suicidal behavior and, recently, there has been a growing interest in a possible association between ADHD and suicide during both childhood and adulthood. Furthermore, some authors have shown a relationship between pharmacological treatments and suicide in patients affected by ADHD.*

***Aims**: We conducted a selective review of current literature to explore the factors which contribute to suicidal behavior and self-harm in those with ADHD.*

***Methods**: We performed a PubMed/MEDLINE, Scopus, PsycLit, and PsycINFO search to identify all articles and book chapters on the topic up to 2017.*

***Results**: Several studies have showed that ADHD may be correlated with an increased suicide ideation and attempts.*

***Conclusions**: Although differences in studies design and samples made the results difficult to compare and interpret, many studies indicate an association between ADHD and suicidal behavior. It remains controversial whether there is a direct relationship or whether the association depends on the increased prevalence of pre-existing comorbid conditions and individual and family dysfunctional factors.*

***Key words:** ADHD - suicide risk - suicide ideation - suicide attempt – adolescence - adulthood*

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INTRODUCTION

Suicide is one of the most serious public health problems and represents a frequent cause of medical emergencies with high medical costs (WHO 2014). Suicide is the second leading cause of death among young people aged 15-29 years and the fourth leading cause of death among children aged 5-14 (Hauser et al. 2013, WHO 2014). Several studies have confirmed that self-destruction and suicidal ideation are present in about 10% of the medical records of adolescent psychiatric inpatients (De Leo et al. 2004, Hargus et al. 2009, Hawton et al. 2002, Hawton et al. 2003, Madge et al. 2008, Moran et al. 2012). Other studies have demonstrated that about 10-15% of children who present with self-destructive behaviors have a very high risk of completed suicide (Cooper et al. 2005, Hawton et al. 1996, Owens et al. 2002, Spirito et al. 1992). A recent study showed an increasing suicide rate over age in America, going from 0.03 per 100.000 per year among children aged 5-9 and 1.29 among children aged 10-14, to 7.53 among 15- to 19-year-old adolescents and 13.92 among young adults aged 20-29, with the highest rate (16.69) among 40- to 49-year-old adults (Hauser et al. 2013).

ADHD (attention-deficit/hyperactivity disorder) is a common neurodevelopmental disorder characterized by a variable combination of symptoms, including inattention, hyperactivity and impulsivity (Biederman 2005, Biederman et al. 2010, Greydanus et al. 2007, Polanczyk et al. 2007). ADHD symptoms arise during childhood, but can often persist into adulthood in 10-79% of child patients (Biederman et al. 1996, Cantwell 1996, Mannuzza et al. 1991, Shaffer 1994, Spencer et al. 1998, Caye et al. 2016). The prevalence of ADHD during childhood is 5-10% (Faraone et al. 2003), while during adulthood the prevalence is 1-6% (Wender et al. 2001). Several authors have studied the correlates of ADHD symptoms in adulthood (Greydanus et al. 2007, Lundervold et al. 2011, Sorensen et al. 2011, Yazgan 2007), and it has been found that adult ADHD increases the risk of antisocial behavior, substance abuse, aggressive behavior, social exclusion, social impairment, and low self-esteem (Babinski et al. 2011, Barkley 2008, Biederman et al. 2012, Brook et al. 2013, Lichtenstein et al. 2012, Rasmussen et al. 2000). To confirm these results, a recent trial (Chaim-Avancini et al. 2017) reported the first neurobiological evidence supporting the individual diagnosis of ADHD in adulthood, based on a sample of stimulant-naıve patients.

Previous research has also demonstrated an association between ADHD and suicide in male adolescents and in male young adults (Gould et al. 1998, Impey 2011, Kelly et al. 2004, James et al. 2004, Lam 2002, Miller et al. 1982, Murphy 2002) and, in addition, an association between ADHD and self-injurious acts and suicidal ideation in female adolescents (Cho et al. 2008, Manor et al. 2010).

This article will focus on the relationship between ADHD and suicidal/parasuicidal events. We conducted a selective review of the medical literature in order to highlight factors which contribute to suicidal behavior and self-harm in those with ADHD.

METHODS

To provide a comprehensive review of ADHD and suicidal risk, we performed a PubMed/MEDLINE, Scopus, PsycLit, and PsycINFO search to identify all articles and book chapters on the topic up to 2015. We used the following search terms: suicide* AND ADHD, suicide* AND "attention deficit disorder with hyperactivity", suicide* AND "attention deficit", suicide* AND hyperactivity, parasuicide* AND ADHD, parasuicide* AND "attention deficit disorder with hyperactivity", parasuicide* AND "attention deficit", parasuicide* AND hyperactivity, self-harm AND ADHD", self-harm AND "attention deficit disorder with hyperactivity", self-harm AND "attention deficit", self-harm AND hyperactivity. The reference lists of the articles included in the review were manually checked for relevant studies. All included articles were in English or German.

RESULTS

ADHD cohort studies have shown that ADHD patients have a higher risk of suicidal ideation, self-inflicted wounds and suicide (Hurtig et al. 2012, James et al. 2004). Two studies have demonstrated that 10% of adult subjects with ADHD have attempted suicide in the past and that 5% of them died by suicide or accidents (Goldstein 2002, Schmidt & Freidson 1990).

In a large longitudinal sample of Swedish families (Ljung et al. 2014), 51,707 individuals met the criteria for ADHD and were studied 23 years later. Among all the probands, 17,349 (33.6%) had a comorbid disorder. ADHD patients had an increased rate of attempted and completed suicide compared with matched control (OR=8.46 and OR=12.22, respectively), even after adjusting for comorbid psychiatric disorders (OR=3.62 and OR=5.91), in both males and females. The same study showed an increased rate of suicidal behavior also among relatives of ADHD individuals, with an OR of 2.42 for attempted suicide among parents of ADHD probands and 2.28 among the full siblings of probands with ADHD. First-degree relatives of individuals with ADHD reported a higher risk of completed suicide (OR 2.23-2.24) than second-degree relatives (OR=1.51-2.02) and third-degree relatives (OR=1.51).

Several studies have shown ADHD patients to have several psychiatric comorbidities (Duran et al. 2014, Goldstein 2002, James et al. 2004, Schmidt & Freidson 1990). A meta-analysis of 6 prospective studies on suicide (James et al. 2004) suggested that ADHD may increase the severity of other psychiatric comorbidities, such as behavior disorders and depression, and may increase the rate of subsequent completed suicide, albeit modestly.

ADHD patients with a combination of major depressive disorder, behavior disorder and substance abuse have a very high rate of subsequent suicidal behavior (attempted and completed), with major depression disorder being the most frequent diagnosis found among ADHD patients with previous suicide attempts (50.7%), followed by substance abuse (47.4%), borderline personality disorder (19.2%), bipolar disorder (15.6%), and behavior disorders (8.9%) (Chen et al. 2014). Duran and colleagues (2014) investigated comorbid psychiatric disorders in adult ADHD outpatients and reported major depressive disorder to be the most frequent diagnosis (43%), followed by generalized anxiety disorder (23%), and obsessive- compulsive disorder (17%). The most common behavior problems in these ADHD patients were substance abuse (58.9%) and attempted suicide (38.5%). Ruchkin et colleagues (2017) confirmed that comorbidity of ADHD and drug dependence increased risk for suicidal ideation and comorbidity of ADHD and alcohol dependence increased the risk for suicide attempts.

Several studies have reported cognitive impairment (impaired executive functions) in patients with ADHD (Berlin et al. 2003, Scheres et al. 2004, Thorell 2007), and this is associated with non-suicidal self-injurious behavior (Fikke et al. 2010). In a sample of 59 adult patients with ADHD, Dowson et al. (2007) found that patients with a positive clinical history for previous self-injurious behavior showed a deficit in spatial working memory. Since several executive functions are involved in the regulation of impulse control and emotions, it has been proposed that deficits of executive functions may predict suicide attempts (Barkley et al. 2001, Zelazo et al. 2007).

Suicidal behavior in children and adolescents with ADHD

Observational studies have indicated an increased suicide risk among young patients with ADHD compared to the general population (Manor et al. 2010, McCarthy et al. 2009), with male gender and the presence of psychiatric comorbidities (especially behavior disorders and depression) being major suicide risk factors (James et al. 2004). Kelly and colleagues (2004) studied 503 adolescents aged 12 to 19 years with alcohol use disorder, and found that the presence of a mood disorder was the strongest predictor of attempted

suicide, in both boys and girls, and that ADHD increased the risk for attempted suicide for boys. In a sample of female adolescents, Biederman and colleagues (2008) found that a combination of ADHD and depression was associated with an increased the incidence of suicidal ideation in adolescent and young adult females. Plattner et al. (2007) studied a sample of 319 young prisoners and found that individuals non-lethal suicidal behavior was associated depression, ADHD and social phobia in the boys, but not in the girls. Rucklidge and colleagues (2001) reported higher rate of self-injurious behavior in a sample of 59 ADHD adolescents (24 girls and 35 boys), compared to 48 healthy controls (28 girls and 20 boys).

In order to identify potential predictors of lifetime suicidal behavior (suicidal ideation, suicide gestures, suicide attempts and self-injurious behaviors), Daviss & Diler (2014) examined a sample of 101 individuals aged 11-18 years and found lifetime trauma exposure, parent-child conflict, ADHD symptoms, psychiatric comorbidities and social impairment played an important role in the development of suicide behaviors in these adolescents.

Manor et al. (2010) gave 23 adolescents admitted to the emergency room for attempted suicide the Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL), the Strengths and Difficulties Questionnaire (SDQ), the Conners' Rating Scale (CRS) and the Test of Variables of Attention (TOVA). The authors found that 65% of the sample was diagnosed with ADHD, 43.5% with depressive disorders and 39% with cluster B personality disorders.

In a longitudinal study, Chronis-Toscano and colleagues (2010) showed that children (n=125) diagnosed with ADHD between 4 and 6 years of age, had an increased risk of major depression or dysthymia (hazard ratio or HR, 4.32) and suicide attempt (HR, 3.60) up to the age of 18 years, compared to controls. There were marked variations in risk for this outcome among children with ADHD. Only girls were at greater risk for depression and suicide attempts. Maternal depression and concomitant child emotional and behavior problems from 4 to 6 years of age predicted depression and suicidal behavior.

Hurtig et al. (2012), analyzed data from a sample of 457 adolescents included in the Northern Finland Birth Cohort 1986 to which the K-SADS-PL was administered. The authors found that participants with ADHD (n=104) showed a higher incidence of suicidal ideation (57% versus 28%, P<0.001) and deliberate self-harm (DSH) (69% versus 32%, P<0.001), compared to adolescent probands without ADHD (n=169). The association between ADHD-suicidal ideation remained strong after controlling for other several variables. Other contributing factors to suicidal behavior included female gender, childhood emotional and behavioral problems, depression and anxiety, and, specifically for DSH, behavioral disorder and substance abuse.

Early childhood "suicidal cognition and behavior", defined as persistent suicidal thoughts, suicidal plans and suicidal attempts, was associated with ADHD in a recent prospective longitudinal study of 306 children aged 7-12 years (Whalen et al. 2015). In a sample of adolescent patients hospitalized as a result of injuries, Lam (2002, 2005) found that a diagnosis of ADHD was associated with younger age, male gender and low socioeconomic status, as well as injuries resulting from assault and suicidal behavior.

In an Irish study analyzing the prevalence of psychiatric disorders, suicidal ideation and intent and parasuicide in a population of 723 adolescents (aged 12-15 years), in the community Lynch et al. (2006) found that 15.6% of the total study population met the criteria for a current psychiatric disorder; 3.7% of the adolescents received a diagnosis of ADHD, while 19.4% of the sample were judged to be "at risk" for mental health difficulties and 2.4% presented possible suicidal intent, based on CDI (Children's Depression Inventory) and SDQ (The Strengths and Difficulties Questionnaire) scores. Significant past suicidal ideation was experienced by 1.9% of the total sample, and 1.5% of participants had a history of parasuicide. Donath and colleagues (2014) studied a sample of 44,134 students (15 years of age) in order to analyze the role of parenting behavior and parenting styles in the adolescents' suicide attempts. The overall lifetime prevalence of suicide attempt was 9.0%, and the prevalence of suicidal ideation was 39.4%. Donath, et al. reported that authoritative parenting was a protective factor (OR: 0.79) while rejecting-neglecting parenting was a risk factor (OR: 1.63) for suicidal attempts (p<0.001). ADHD, female gender, smoking, binge drinking, absenteeism/truancy, migration background, and parental separation were also found to be significantly related to suicide attempts, with ADHD showing the highest OR after female gender. In a sample of 349 urban children aged 6-9 years with aggressive behaviors, Wyman et al. (2009) found that 10% of the children with suicidal ideation met the criteria for ADHD versus 5.6% of the children with no suicidal ideation. A longitudinal study by Hinshaw (2012) analyzed a population of 140 females aged 6 to 12 years with ADHD (93 with a combined type and 47 with the inattentive type), compared to 88 healthy controls. The suicide attempt rate was 22% for the combined type and 8% for the inattentive type, whereas the control group had a 6% rate. In a 13-year longitudinal study, Goldston et al. (2009), analyzing the relationship between suicide attempts and psychiatric comorbidities in a sample of 180 adolescent inpatients, found that 14.3% of patients at first suicide attempt and 25% of participants with several suicide attempts met the criteria for ADHD (OR=2.41).

Dickerson Mayes and colleagues (2015) analyzed suicide ideation and attempts in 1,706 children and adolescents (6-18 years of age) with psychiatric disorders and found an overall incidence of suicidal behavior

(ideation and non-lethal attempts) of 24%. The incidences by diagnosis were bulimia 48%, major depression or anxiety disorder 34%, oppositional defiant disorder 33%, ADHD-combined type 22%, anorexia nervosa 22%, autism 18%, intellectual disability 17%, and ADHD-inattentive type 8%), compared to an incidence of 0.5% in the healthy control group. In a study of 500 adolescents and young adults aged 15-24 years with bipolar disorder and ADHD, Lan et al. (2015) reported that comorbidity with ADHD to increase the likelihood of attempting suicide in patients aged between 15 and 24 years affected by bipolar disorder.

In a study of 29,737 young subjects aged 0 to 21 years, Sheikh and colleagues (2015) found that 14% of the sample used ADHD medications to attempt suicide and suggested that undiagnosed ADHD may be a potential cause for self-harming behaviors in very young subjects.

Suicidal behavior in ADHD adults

Huntley and colleagues (2012) studied a sample of 226 psychiatric patients with substance dependence and found that the ADHD incidence was 12.2%. The presence of an ADHD diagnosis was associated with worse social functioning, abuse of alcohol and substances, depression and suicide attempts, with suicide attempts present in 54.5% in the ADHD group (likelihood ratio of 4.675). Using the MINI (Mini International Neuropsychiatric Interview), Grall-Bronnec et al. (2011) reported a 25% prevalence of ADHD in patients affected by gambling addiction, with 62.5% of the comorbid group (ADHD+gambling) showing "suicide risk (the report did not specify how this was assessed) compared to 34.5% of participants with gambling addiction only. Arias and colleagues (2008) studied the prevalence and the course of psychiatric comorbidities in a population of 1,761 individuals with substance use disorder and found the incidence of ADHD to be 5.22%. Suicidal ideation was present in 66.30% of the ADHD group, vs. 42.32% in the non-ADHD group (OR=1.57). The suicide attempt rate was 40.66% in the ADHD group vs. 17.50% in the non-ADHD group (OR=2.32). The self-injury rate was 20.88% in the ADHD group vs. 6.31% in the non-ADHD group (OR=3.31). Swanson et al. (2014) found that young adult women with a childhood diagnosis of ADHD-combined type, especially if childhood impulsivity was also present, had a higher incidence of prior suicide attempts than did women with ADHD-inattentive type and those in the control group. Furthermore, chronic ADHD was related to a higher incidence of suicidal behavior (self-harm or suicide attempts) compared to transient diagnosis and non-ADHD. Semiz and colleagues (2008) studied a sample of 105 male prisoners with antisocial personality disorder to evaluate the relationship between ADHD and psychopathy using the Hare Psychopathy Checklist-Revised and the Structured Clinical Interview for Axis II Disorders (DSM-III-R), and noting suicidal behavior and a history of social and familiar adversities. An ADHD diagnosis was present in the 65% of the sample with an overall self-injury behavior rate of 92% (average onset at age 14.8±3.5). The ADHD group had a rate of self-injury behavior of 94% and a rate of attempted suicide of 70% versus rates of 89% and 43%, respectively, in the non-ADHD group (OR=1.06). In a multicenter study in 21 countries, Nock et al. (2009) analyzed suicidal behavior among 108,664 adults in the community with ADHD. He calculated the lifetime odds rations for the incidence of suicidal ideation and attempted suicide to be 1.4-1.9 and 1.7, respectively, in developed countries compared to 1.5-2.8 and 2.2 in developing countries. Tai et al. (2017) in 1,047 military recruits highlighting that depression and quality of life were mediator in the association between ADHD and suicidality.

The Effects of Medications

In a Swedish register-based cohort study, Chen et al. (2014) found that a total of 7,019 suicide related events (SRE, defined as lifetime suicide attempt and completed suicide) occurred in 37,936 patients with a diagnosis of ADHD followed for 150,721 person years. The study focused on three stimulants (methylphenidate (N06BA04), amphetamine (N06BA01), and dexamphetamine (N06BA02)) and one non-stimulant (atomoxetine (N06BA09)). Among subjects of the sample, 93.9% received at least one prescription for methylphenidate and 26.1% received at least one prescription for atomoxetine. The other two stimulants, amphetamine and dexamphetamine, were rarely prescribed. The authors found that drug treatment of ADHD was associated with an increased rate of SRE (hazard ratio 1.31, 95% confidence interval 1.19 to 1.44). Nevertheless, the within-patient analysis demonstrated a inverse association between ADHD drug treatment and the rate of SRE (0.89, 0.79 to 1.00). Among stimulant users, a reduced within-patient rate of SRE was observed during the treatment periods (0.81, 0.70 to 0.94). Among non-stimulant/mixed users, no significantly increased within-patient rate of SRE was observed during non-stimulant treatment periods (0.96, 0.72 to 1.30).

Atomoxetine

Atomoxetine is a norepinephrine reuptake inhibitor approved for the treatment of ADHD, with some studies reporting increased suicidality in ADHD patients treated with atomoxetine (Reed et al. 2016). In particular, Wooltorton et al. (2005) found an increased rate of suicidal ideation in children treated with atomoxetine, as confirmed by two meta-analyses (by Bangs et al. (2008) and FDA (2005)) of 14 and 12 pediatric clinical trials, demonstrating a statistically significant association between atomoxetine and suicidal ideation and behavior.

A British cohort study of 2,544 patients treated with atomoxetine reported rates of 1% and 0.9% for lifetime self-harm behavior and suicidal ideation, respectively,

and 0.3% for both suicide attempt and overdose (Davies et al. 2009). Donnelly and colleagues (2009) studied 714 patients treated with atomoxetine for 3 years, and found a suicidal ideation incidence of 1.5%, a suicide attempt incidence of 0.3% and completed suicide incidence of 0.1%. A retrospective cohort study, (Linden et al. 2016) was conducted to evaluate suicide events in pediatric patients in treatment with atomoxetine compared with stimulants; however, the authors didn't observe a statistically increase in the risk of suicidal events in both groups of patients.

Future studies will also be needed to investigate the possible role of atomoxetine as a kappa-opioid receptor (KOR) partial agonist and subsequent mediator of e hypothalamic pituitary adrenal (HPA) axis hyperactivity as suggested by some previous studies (Fluegge et al. 2016).

Methylphenidate

Methylphenidate increases dopamine levels by inhibiting the dopamine transporter (DAT) and adenosine monofosfatase c (Kuczenski et al. 1997). Treatment with methylphenidate has been associated with violent behavior, agitation, and depression with suicidal ideation (Hesapcioglu et al. 2013, Ruggiero et al. 2012). More than 30 years ago, Gualtieri et al. (1985) reported a suicide attempt by methylphenidate ingestion by a patient included in a sample of 8 male adults with ADHD (average age 27.3 years) treated with methylphenidate for 3-6 months.

In 2009 a retrospective cohort study of 5,351 children and adolescents treated with methylphenidate or amphetamine (McCarthy et al. 2009) found an increased standardized mortality ratio (SMR) for complete suicide compared to general population (for 11-14 years old subjects 161.91 and for 15-20 years old subjects 1.84).

On the other hand, in the above-mentioned Swedish study (Chen et al. 2014), the use of drug treatment at the population level was associated with a decreased rate (not statistically significant) of SRE among stimulant users (HR 1.02, 95% CI 0.90 to 1.16). A statistically significant protective effect of stimulants on suicidal behavior (HR 0.81) has also been reported (Chen et al. 2014). The protective effect is probably mediated by the improvement in impulsivity. After the exclusion of any comorbid condition, the association between the rate of SRE and the use of ADHD drug treatment at the population level (hazard ratio 1.24) was largely attenuated. A recent cohort study (Liang et al. 2017) on 84,898 youths less than 18 years old with ADHD diagnosis evaluated if methylphenidate treatment reduces the risk of suicide attempts and if this effect depended by duration of exposure to treatment. The authors found a 59% suicide attempt risk reduction among ADHD youths prescribed MPH between 90 days to 180 days and a 72% risk reduction for those with more than 180 days of MPH. In contrast, Man et al. (2017) observed that, in the period immediately before the start of methylphenidate treatment suicide attempts were more frequent and returned to baseline levels during continuation of the treatment.

The efficacy of methylphenidate hydrochloride extended-release chewable tablets (MPH ERCT) was compared with placebo in children with ADHD in a study composed by 6-week, open-label, dose-optimization treatment period followed by a 1-week, randomized, double-blind, placebo-controlled period (Wigal et al. 2017). Treatment with MPH ERCT showed a safety and tolerability profile similar to that of other MPH ER formulations and the use of MPH ERCT 20-60mg significantly improved ADHD symptoms compared with placebo.

Amphetamines

Amphetamines are some of the most powerful central nervous system stimulant substances as capable of increasing synaptic amine levels (Madras et al. 2005). They were initially synthesized in Berlin in 1887 (Fleckenstein et al. 2007), and research showed their affinity to all monoaminergic transporters. In particular, the behavioral stimulant effect has been found to be mediated by increasing dopamine levels through the inhibition of the dopamine active transporter (DAT) and Monoamine Oxidase-A and B (Boutrel et al. 2004)

Some studies have suggested that some methylphenidate-resistant individuals may benefit from amphetamines and vice versa (Elia et al. 1990). The only study on this is a retrospective study (McCarthy et al. 2009), based on the UK GPRD (General Practice Research Database) database. In a sample of 5,351 children and adolescents, those who took amphetamines or methylphenidate showed an increased standardized mortality ratio (SMR) for complete suicide compared to the general population. The standardized mortality ratio (SMR) was 161.91 in those 11-14 years old and 1.84 in those 15-20 years old.

CONCLUSIONS

In this paper, we have reviewed research about the relationship between ADHD and suicidal behavior in children, adolescents and adults. Differences in study design (cross-sectional vs. longitudinal, population-based vs. case-control) and samples made the results difficult to compare and interpret. Nevertheless, many studies indicate an association between ADHD and suicidal behavior, but it is still controversial whether there is a direct relationship or whether the association depends on the increased prevalence of pre-existing comorbid conditions and individual and family dysfunctional factors. Regardless, patients with ADHD should be routinely screened for suicidal behavior, and early intervention protocols should be established in order to detect and reduce suicidal ideation and behavior and to improve the quality of life. Clinician should pay attention if, apart from the features of the primary disorder, symptoms ascribed to mixed states, especially when depression escalates into mania and when volatile and

erratic moods are associated with dysphoria and agitation, are detectable in patients. Doctors and caretakers should also bear in mind characteristics of the "Is Path Warm?" indicating warning signs for suicide such as Ideation – threatened or communicated; Substance abuse – excessive or increased; Purposeless – no reasons for living; anhedonia; Anxiety – agitation/insomnia; Trapped – feeling no way out; perceived burdensomeness; Hopelessness; Withdrawal – from friends, family, society; Anger (uncontrolled)/rage/seeking revenge; Recklessness – risky acts; unthinking; Mood changes (dramatic).

In conclusion, more research is needed to better understand the role of ADHD in suicidal behavior during childhood, adolescence and adulthood and to identify risk factors for future suicidal behavior in this population in order to develop prevention programs and improve treatment approaches. Furthermore, more research is needed on whether the medication prescribed for ADHD patients are effective in reducing the incidence of suicidal behavior.

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Contribution of individual authors:

Giancarlo Giupponi designed the study;

Giancarlo Giupponi, Gloria Giordano & Ignazio Maniscalco reviewed the study;

Denise Erbuto, *Isabella* Berardelli & *Andreas* Conca supervised the study;

David Lester contributed in drafting the paper and in providing consultancy for pending papers to be included;

Paolo Girardi & *Maurizio* Pompili provided the scientific impetuous for the study. All authors contributed in drafting the paper.

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ADHD: e dopo la diagnosi?!

Interventi efficaci dall'infanzia all'adolescenza

Sabato 15 dicembre 2018

INGRESSO GRATUITO

L'Equipe del Centro per l'Età Evolutiva di Bergamo propone un incontro di approfondimento e confronto sulle difficoltà di attenzione e iperattività in età evolutiva. L'incontro è rivolto soprattutto a **genitori**, ma aperto anche ad altre figure interessate a questa tematica.

9.15 - 9.45 Quali sono gli interventi efficaci
Prof. Gian Marco Marzocchi - Docente Università Milano-Bicocca

9.45 - 10.15 Prima è meglio: cosa si può fare in età prescolare
Dott.ssa Paola Zanchi - Psicologa

10.15 - 10.30 *Pausa caffè*

10.30 - 11.00 Adesso è ora! I percorsi in età scolare
Dott.ssa Ilaria Rota - Psicologa, Psicoterapeuta

11.00 - 11.30 Non è mai troppo tardi!! Gli interventi con l'adolescente
Dott.ssa Elisa Tomasoni - Psicologa

11.30 - 12.30 Dibattito con il pubblico

Sede dell'incontro:
Sala Nembrini - Casa del Giovane
Via Gavazzeni, 13 - Bergamo

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ADHD: E DOPO LA DIAGNOSI?!

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POSTI LIMITATI - prenotazione obbligatoria compilando il form sottostante
(compilare un form per ogni partecipante)

P.S....se cambiate idea o siete impossibilitati a partecipare per cortesia comunicatecelo così lasciate il posto ad altri :)

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Il Progetto è realizzato con il contributo, parziale, della Regione Lombardia
(in attuazione della D.G. sanità n. 3798 del 08/05/2014, n. 778 del 05/02/2015, n. 5954 del 05/12/2016 e N. 1077 del 02/02/2017) Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia" "*Percorsi diagnostico-terapeutici per l'ADHD*".

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