NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD OTTOBRE 2017

Acad Pediatr. 2017.

REASONS WHY CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER STOP AND RESTART TAKING MEDICINE.

Brinkman WB, Simon JO, Epstein JN.

Objective: To describe the prevalence of reasons why children and adolescents stop and restart attention-deficit/hyperactivity disorder (ADHD) medicine and whether functional impairment is present after stopping medicine.

Methods: We used the prospective longitudinal cohort from the Multimodal Treatment of Study of Children With ADHD. At the 12-year follow-up, when participants were a mean of 21.1 years old, 372 participants (76% male, 64% white) reported ever taking ADHD medicine. Participants reported the age when they last stopped and/or restarted ADHD medicine and also endorsed reasons for stopping and restarting.

Results: Seventy-seven percent (286 of 372) reported stopping medicine for a month or longer at some time during childhood or adolescence. Participants were a mean of 13.3 years old when they last stopped medicine. The most commonly endorsed reasons for stopping medication related to 1) medicine not needed/helping, 2) adverse effects, 3) logistical barriers of getting or taking medication, and 4) social concerns or stigma. Seventeen percent (64 of 372) reported restarting medicine after stopping for a month or longer. Commonly endorsed reasons for restarting related to medicine being needed or medicine helping; and resolution of logistical barriers to getting or taking medicine. For both stopping and restarting, the proportion endorsing some reasons differed by age range, with the overall pattern suggesting that parental involvement in decisions decreased with age. Nearly all participants had impairment at the assessment after stopping, regardless of whether medication was resumed.

Conclusions: Different reasons for stopping and/or restarting medicine are relevant at different times for different teens. Tailored strategies may help engage adolescents as full partners in their treatment plan

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Acta Dermatovenerologica Croatica. 2017;25:210-14.

RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN WITH ATOPIC DERMATITIS.

Horev A, Freud T, Manor I, et al.

Atopic dermatitis (AD) is a common, chronic, inflammatory, pruritic skin disorder that affects up to 20% of the children in Western countries. Attention-Deficit/Hyperactivity disorder (ADHD) has been reported to be more frequent in children with AD. The purpose of this study was to explore the risk for ADHD in our population of patients with AD. A population-based case-control study, using the medical database of Clalit Health Services (CHS), the largest healthcare provider organization in Israel. The study included 840 patients with AD between the age of 0-18 years and 900 age and gender frequency-matched patients without AD. The proportion of ADHD in patients with AD was 7.1% as compared to 4.1% in controls. ADHD was more frequent in boys with AD (9.6% vs. 5.2%, odds ratio (OR) 1.9, 95% confidence interval (CI) 1.1-3.2) but not in girls with AD (4.6% vs. 2.9% OR 1.5). In multivariate analyses, AD was associated with ADHD (OR 2.1, 95% CI 1.3-3.4). The current study demonstrated an association between AD and ADHD. This report and earlier observations emphasize the need for detection and treatment of ADHD in atopic patients

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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.

Acta Medica Mediterranea. 2017;33:1197-203.

REVIEW ABOUT COMORBIDITIES OF BEHAVIOURAL DISORDERS IN CHILDREN AND ADOLESCENTS: THE FOCUS ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Gallai B, Valentini V, Barbanera F, et al.

Disruptive behavior disorders (DBD) present high comorbidity rate mainly for opposite-defiant disorders that are frequent among children, adolescents and adults affected by with attention deficit and hyperactivity disorder (ADHD), probably as result of common temperamental risk factors such as attention, distraction, impulsivity. ADHD tend to manifest in about 50% of individuals diagnosed as disruptive behavioral disorders

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Acta Paediatr Int J Paediatr. 2017.

ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER REQUIRE SPECIFIC SUPPORT FROM HEALTHCARE PROFESSIONALS.

Lindblad I, et al.

Aim: Managing type 1 diabetes mellitus requires efficient cognitive and executive skills, and adolescents who have attention-deficit/hyperactivity disorder (ADHD) may face specific challenges. This study explored young people's experiences of diabetes treatment and care.

Method: In a population-based study, comprising 175 patients aged 5-16 years with type 1 diabetes mellitus in two Swedish counties, we found that eight also met criteria for ADHD. Six of these, aged 14.5-16 years, participated 2013-2014 in interviews that targeted aspects of their diabetes treatment. Conducted by two psychologists, these used the inductive qualitative, semi-structured interview format.

Results: The two boys and four girls all reported difficulties in creating routines for their diabetes treatment and that problems were aggravated during stress. They had been criticised by their parents and the diabetes team when their blood levels indicated inadequate diabetes control. They requested ongoing information, involvement of their friends, group meetings and easy access to the healthcare system during difficult times.

Conclusion: Patients with type 1 diabetes mellitus and concomitant ADHD faced problems with their diabetes management, especially during stressful situations. Diabetes care provision should pay particular attention to patients with co-existing neuropsychiatric and neurodevelopmental disorders such as ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;1-5.

A CASE SERIES ON THE POTENTIAL EFFECT OF OMEGA-3-FATTY ACID SUPPLEMENTATION ON 24-H HEART RATE VARIABILITY AND ITS CIRCADIAN VARIATION IN CHILDREN WITH ATTENTION DEFICIT (HYPERACTIVITY) DISORDER.

Buchhorn R, Koenig J, Jarczok MN, et al.

Attention deficit disorder with and without hyperactivity (ADHD) in children is associated with decreased 24-h heart rate variability (HRV). Previous research has shown that supplementation of omega-3-fatty acid increases HRV. Here, we aimed to investigate whether the supplementation of omega-3-fatty acids would increase 24-h HRV in an uncontrolled case series of children with ADHD. HRV was recorded in 18 children and adolescents (age 13.35 -¦ 2.8 years) before and after omega-3 supplementation. Preliminary results indicate that omega-3 supplementation in children with AD(H)D may reduce mean heart rate and increase its variability. Future studies would do well to implement randomized, placebo-controlled designs with greater methodological rigor

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Am J Med Genet A. 2017 Apr;173:1009-16.

EXOME SEQUENCING IDENTIFIES NOVEL NTRK1 MUTATIONS IN PATIENTS WITH HSAN-IV PHENOTYPE.

Altassan R, Saud HA, Masoodi TA, et al.

Hereditary sensory autonomic neuropathy type IV (HSAN-IV) is a rare autosomal recessive disorder that usually begins in infancy and is characterized by anhidrosis, insensitivity to noxious stimuli leading to self-mutilating behavior, and intellectual disability. HSAN-IV is caused by mutations in the neurotrophic tyrosine

kinase receptor type 1 gene, NTRK1, encoding the high-affinity receptor of nerve growth factor (NGF) which maps to chromosome 1q21-q22. Patients with HSAN-IV lack all NGF-dependent neurons, the primary afferents and sympathetic postganglionic neurons leading to lack of pain sensation and the presence of anhidrosis, respectively. Herein, we report nine patients from nine unrelated families with HSAN-IV due to various mutations in NTRK1, five of which are novel. These are three missense and two nonsense mutations distributed in various domains of NTRK1 involved in binding of NGF. The affected patients had variable intellectual deficits, and some had delayed diagnosis of HSAN-IV. In addition to being the first report of HSAN-IV from the Arabian Peninsula, this report expands the mutational spectrum of patients with NTRK1 mutations and provides further insights for molecular and clinical diagnosis

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Behav Brain Funct. 2017;13.

BEHAVIORAL SENSITIVITY OF JAPANESE CHILDREN WITH AND WITHOUT ADHD TO CHANGING REINFORCER AVAILABILITY: AN EXPERIMENTAL STUDY USING SIGNAL DETECTION METHODOLOGY.

Furukawa E, Shimabukuro S, Alsop B, et al.

Background: Most research on motivational processes in attention deficit hyperactivity disorder (ADHD) has been undertaken in Western Europe and North America. The extent to which these findings apply to other cultural groups is unclear. The current study evaluated the behavioral sensitivity of Japanese children with and without ADHD to changing reward availability. Forty-one school-aged children, 19 diagnosed with DSM-IV ADHD, completed a signal-detection task in which correct discriminations between two stimuli were associated with different reinforcement frequencies. The response alternative associated with the higher rate of reinforcement switched twice during the task without warning. Findings: Both groups of children developed an initial bias toward the more frequently reinforced response alternative. When the reward contingencies switched the response allocation (bias) of the control group children followed suit. The response bias scores of the children with ADHD did not, suggesting impaired tracking of reward availability over time. Conclusions: Japanese children with ADHD adjust their behavioral responses to changing reinforcer availability less than their typically developing peers. This is not explained by poor attention to task or a lack of sensitivity to reward. The current results are consistent with altered sensitivity to changing reward contingencies identified in non-Japanese samples of children with ADHD. Irrespective of their country of origin, children with ADHD will likely benefit from behavioral expectations and reinforcement contingencies being made explicit together with high rates of reinforcement for appropriate behaviors

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Biol Psychiatry. 2017;81:S135.

TESTING THE SPECIFICITY OF EXECUTIVE FUNCTIONING IMPAIRMENTS IN ADOLESCENTS WITH ADHD, ODD/CD AND ASD.

Leno VC, Rubia K, Hobson C, et al .

Background: Attention-deficit hyperactivity disorder (ADHD), oppositional defiant/conduct disorder (ODD/CD) and autism spectrum disorder (ASD) are separate psychiatric conditions, yet they often co-occur. They are all associated with impairments in executive functions (EF). The specificity of impairments in EF to each condition remains relatively unexplored. Methods: Four groups of 10-16 year olds; typically developing (TD; N543), patients clinically diagnosed with ADHD (N524), ODD/CD (N526) and ASD (N541) completed a GoNoGo and a Switch task, giving indices of inhibition, intra-subject response variability, response time, and flexibility. Parent-reported psychiatric symptom severity was measured using the Strengths and Difficulties Questionnaire (SDQ). Analysis of variance (ANOVA) explored group differences; co-variates included age, IQ, sex, SDQ conduct and hyperactive symptoms. Sensitivity analyses excluded a) those with IQ,70 (N59) and b) ASD participants scoring above SDQ hyperactivity threshold (N510). Results: All clinical groups demonstrated worse inhibitory performance, and increased response variability compared to the TD group. The ADHD group had significantly longer response times than all other groups. Results remained significant with inclusion of co-variates and in sensitivity analyses, except for response variability, which was no longer significant after inclusion of co-variates. No group differences were found in flexibility. Conclusions: A more

impulsive response style was present across all clinical groups. A similar pattern was found for response variability, although co-variates may have contributed to group differences. Disorder-specific impairment was found for ADHD, which was characterised by longer reaction times. Results suggest impairment in inhibition and increased response variability may represent trans-diagnostic deficits that are associated with a number of diagnoses

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Biol Psychiatry. 2017;81:S102.

NEURAL CORRELATES OF FRUSTRATION IN CHILDREN WITH ADHD COMPARED TO TYPICALLY-DEVELOPING CHILDREN.

Seymour K, Rosch K, Martinelli M, et al.

Background: Frustration tolerance is noted to be poor in children with ADHD compared to typically-developing controls (TDC). However, little is known about the neural correlates underlying poor frustration tolerance in children with ADHD. This study examined the neural correlates of frustration in children with ADHD compared to TDCs using an adapted version of the Mirror Tracing Persistence Task (MTPT). Methods: Participants included 52 children with DSM-5 ADHD and 33 TDCs (ages 8-17 years) who completed the MTPT in which participants trace the outline of a star using the computer mouse, but to elicit frustration, the controls are reversed and the task restarts if the participant makes an error. Participants can quit the task at any time, but are told their prize depends on task performance. Dependent variables include: latency to quit and quit/no quit. High resolution MPRAGE images were acquired. Subcortical (caudate, putamen, globus pallidus, thalamus) and cortical (dlPFC, OFC, mPFC, and ACC) volumes of interest were extracted. Results: Results showed children with ADHD (controlling for age) had a shorter latency to quit than TD children, F(2,82)5 5.25, p,.05, suggesting poorer frustration tolerance. Smaller putamen volumes were associated with quitting the task among children with ADHD (n536; right: r52.450, p,.01; left: r52.291, p=.08), whereas smaller mPFC volumes (left: r5 2.382, p,.05; right: r52361, p=.06) and right dlPFC volume (r5 2.390, p,.05) were associated with quitting the task among TDCs (n525). Conclusions: Results suggest distinct neural correlates of frustration in children with ADHD compared to TDCs

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Biol Psychiatry. 2017;81:S41-S42.

A LARGE SCALE STUDY OF CORTICAL AND CEREBELLAR MORPHOLOGY IN ADHD ACROSS THE LIFE SPAN: AN ENIGMA-ADHD COLLABORATION.

Shaw P, Hoogman M, Bratlen J, et al.

Background: While structural alterations of various brain regions in ADHD are often reported, studies are often underpowered and use heterogeneous methods. After studying subcortical structures (1), the ENIGMA-ADHD working group now aims to study cortical and cerebellar measures across the life-span. Methods: Thirty four sites currently participate (2197 cases, 1926 controls). All sites have used automated, validated segmentation softwares (FreeSurfer to measure thickness and surface area of 34 cortical regions; MAGeT to measure 21 cerebellar regional volumes). Meta-and mega regressions have combined site-specific case-control differences. Developmental trajectories were modelled through age stratification, fractured polynomials (cortex) and piecewise linear mixed model regression (cerebellum). Effects of medication, symptom severity and comorbidity are considered. Results: Subtle but significant reductions in cortical thickness localized to temporal (temporal pole, fusiform gyrus, entorhinal cortex) and frontal regions (pre/paracentral gyrus). The largest effect size was for total surface area: d 5-0.21. Differences were larger in children than adults. Cerebellar analyses found significant baseline volume reductions in ADHD (effect sizes around 0.2). Trajectory analyses showed that diagnosis differed in its impact on the growth of cerebellar grey and white matter. Conclusions: We find reduced fronto-temporal cortical and cerebellar regions in ADHD. The most compromised cortical regions-fusiform gyrus and temporal pole- are connected to the amygdala, which showed the largest case-control difference in our subcortical study, highlighting the role of emotional processing in ADHD. Cortical age analyses show delayed maturation and lower peak volumes in

ADHD. Preliminary cerebellar analyses also find baseline reductions in ADHD, along with altered developmental trajectories

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Biol Psychiatry. 2017;81:S346.

RESPONSE TO METHYLPHENIDATE AND ATOMOXETINE IN CHILDREN WITH ADHD: PHARMACOGENETIC PREDICTORS.

Stein M, Bishop J, Cook E, et al.

Background: Despite inconsistent findings from studies using diverse methodologies and populations, commercial genotyping services have been marketed which recommend specific ADHD treatments. We sought to examine the relationship between several candidate and metabolism genes (DAT1,Drd4, ADRA1, COMT, CYP2D6) and response in children who are treated with OROS methylphenidate (MPH) and atomoxetine (ATX) in a crossover study. Methods: Children (n = 191) with ADHD, ages 6-17 (mean 10.5), participated in a double blind, double-dummy, crossover study comparing MPH (mean dose 54 mg) and ATX (mean dose 1.35 mg/kg). Medication was titrated using a flexible, stepped dose optimization for 3-7 weeks with 2 weeks on optimal dose. Primary outcome was ADHD RS and CGI completed by blind raters. Results: The largest number of youth responded to both medications (49%), with a mean reduction in ADHD RS of 15.5 to ATX and 19.1 to MPH. None of the genetic markers were associated with an excellent response to MPH or ATX (i.e., 50% reduction in ADHD symptoms). However, significant associations between nonresponse (< 30 reduction in ADHD symptoms) to ATX and CYP2d6 were detected. Specifically, odds of non-responding to ATX is 2.4 times higher for CPY2D6 poor metabolizers compared to a non-poor metabolizer. Conclusions: In a crossover study of children with ADHD treated for several weeks, dopaminergic and adrenergic genes were not associated with response to either stimulant or non-stimulant medication, although genetic variation in cytochrome P-450 2d6 pathway was associated with non-response to ATX

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Biol Psychiatry. 2017;81:S17.

NEURAL CORRELATES OF ADOLESCENT IRRITABILITY AND ITS COMORBIDITY.

Althoff R, Chaarani B, Kan K-J, et al.

Background: We examined irritability (IRR) in IMAGEN, a sample of 2024 14-year-youth from five European countries. Irritable mood is a very common and often impairing symptom of psychopathology and is defined by temper outbursts and proneness to anger. It has been associated with a host of psychiatric and nonpsychiatric conditions including suicide, violence, and cardiovascular disease. Relatively little is known about the neural mechanisms of irritability in childhood and adolescence. Methods: The Development and Well-Being Assessment (DAWBA) was used to assess ADHD, MDD, ODD, and GAD. Three items from the DAWBA, selected as close matches to the Affective Reactivity Index, were used to assess irritability. Structural MRI (sMRI) was examined using whole brain Voxel Based Morphometry analysis and functional MRI (fMRI) was examined during a stop signal task of inhibitory control. sMRI and fMRI data for these regions were included in structural equation models to examine the direct and indirect associations between IRR and comorbid DSM diagnoses. Results: A voxelwise regression analysis between GMV and irritability showed, after correcting for multiple comparisons ($p<0.05$), a significant negative correlation in two bilateral clusters and included the bilateral frontal gyrus and the left insula. The seven regions showing GMV reductions revealed significantly decreased activity in irritable subjects vs controls, in the bilateral superior temporal gyrus (STG), the right insula, and the right ventral pre-and postcentral gyrus (VPPG) ($p<0.05$), after controlling for other diagnoses. Conclusions: Decreased GMV and less response inhibition activity was observed within the right VPPG and the bilateral STG for individuals with high IRR

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Biol Psychiatry. 2017;81:S376.

SHARED AND DISORDER-SPECIFIC NEURAL DYSFUNCTION DURING SUSTAINED ATTENTION IN ADOLESCENT ATTENTION-DEFI-CIT/HYPERACTIVITY DISORDER AND OBSESSIVE/COMPULSIVE DISORDER.

Norman L, Carlisi C, Christakou A, et al.

Background: Patients with Attention-Deficit/Hyperactivity Disorder (ADHD) and obsessive/compulsive disorder (OCD) share deficits in attention. The aim was examine whether brain activation abnormalities underlying sustained attention in the two disorders were shared or disorder-specific. Methods: Twenty boys with ADHD, 20 boys with OCD and 20 healthy controls aged between 12-18 years completed a functional magnetic resonance imaging (fMRI) version of a sustained attention task with a progressively increasing attention load. Performance and brain activation were compared between groups. Results: A group by delay interaction analysis showed that OCD patients had disorder-specific underactivation in middle anterior cingulate, while ADHD patients showed disorder-specific underactivation in left dorsolateral prefrontal cortex/dorsal inferior frontal gyrus relative to controls and each other. ADHD and OCD patients shared left insula/ventral IFG underactivation and increased activation in posterior default mode network (DMN) regions, but had disorder-specific overactivation within anterior DMN regions, in dorsal anterior cingulate for ADHD and in anterior ventromedial prefrontal cortex for OCD. Only ADHD patients were impaired in performance. Conclusions: Findings suggest that sustained attention in both disorders relative to controls is associated with decreased recruitment of regions of task-positive salience and attention networks, as well as increased activation in DMN regions. However, the specific regions showing abnormalities in each disorder were disorder-specific, with disorder-specific underactivation in ADHD in task-relevant lateral prefrontal cortex and in OCD in medial frontal cortex, and hyperactivation in both disorders in different frontal parts of the DMN

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Biol Psychiatry. 2017;81:S209-S210.

OMEGA-3 FATTY ACIDS LEVELS AND ADHD SYMPTOMS, MOOD STATES, AND DEPRESSION.

Haven S, Gow R, Majchrzak-Hong S, et al.

Background: Meta-analyses of randomized controlled trials (RCTs) report omega-3 fatty acids can reduce symptoms of attention deficit hyperactivity disorder (ADHD) in children. Here we present baseline data from a currently un-blinded RCT designed to evaluate efficacy in adults; the Neuroimaging, Omega-3 and Reward in Adults with ADHD trial (NCT02156089). Methods: Thirty participants with ADHD aged 18-55 (M 5 32.87, SD 5 10.97, Female 5 30%) were assessed using the Conner's Adult ADHD Rating Scales (CAARS) Self Report Long Version, the Profile of Mood States-Bipolar (POMS-Bi), and the Beck Depression Inventory (BDI). Concurrently, red blood cells were obtained to quantify fatty acid levels. Results: Higher 22:6 n-3 (DHA) was associated with higher CAARS scores (r5 0.49, p, 0.006) and higher 22:5 n-6 was associated with lower CAARS scores (r5 20.42, p, 0.03). Higher 22:5 n-3 was associated with fewer depression symptoms (r5 20.41, p, 0.03) and higher levels of 20:2 n-6 (Eicosadienoic acid) was associated with greater depression symptoms (r5 0.51, p, 0.004). Higher 20:2 n-6 was positively associated with unsure (r5 20.49, p, 0.006), confused (r5 20.57, p, 0.001), depressed (r5 20.37, p, 0.05), and anxious symptoms (r5 20.52, p, 0.003). Conclusions: The relationships between higher omega-3 and lower scores on the BDI at baseline are concordant with current literature on omega-3 and depression. Contrary to predictions, a positive association of DHA, and a negative association of 22:5n-6, with CAARS scores were found. Findings regarding 20:2n-6 are curious because this metabolic intermediate is not directly related to dietary intakes

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Biol Psychiatry. 2017;81:S167.

EMPIRICAL CATEGORIES OF COMMON DIMENSIONS OF PSYCHOPATHOLOGY IN YOUTH AND THEIR NEUROCORRELATES.

Stoddard J, Kircanski K, Haller S, et al.

Background: Common dimensions of psychopathology often co-occur, and such co-occurrence may have a neural basis. Recently, we determined broad categories of co-occurring dimensions of psychopathology in youth (Kircanski et al., 2016). Here, in a subsample, we explore the associations of such categories to neural

activation during implicit face-emotion processing. Methods: Participants were 201 youth, 8-18 years (165 psychiatric outpatients and 36 healthy volunteers). During fMRI, they labelled the gender of Ekman faces with 3 Emotions (angry, happy, fearful) at 3 Intensities of expression (50%, 100%, and 150%). Agreement between latent profile analysis and singular value decomposition categorized the youth by parent-and self-report measures of anxiety, depression, inattention/hyperactivity, and irritability. BOLD fMRI data for correct trials were analyzed by multivariate modeling with Category, Emotion, and Intensity as predictors. Results were whole brain, cluster corrected at $p<0.05$. Results: Four Categories emerged: (1) low levels of all symptoms (LOW); (2) high levels of all symptoms (HIGH); (3) predominant irritability and inattention/hyperactivity (IRR/ADHD); and (4) predominant anxiety and depression (ANX/DEP). Category by Emotion activation was significant in the right dorsolateral prefrontal cortex (dlPFC) (xyz5 46.2,18.8,31.2, $F(6,389.8)55.17$, $p<0.001$) and right fusiform gyrus (xyz541.2,56.2,-16.2, $F(5.9,383.4)55.11$, $p<0.001$). In the dlPFC, ANX/DEP and IRR/ADHD youth exhibited opposing patterns of activation to fearful faces. In the right fusiform gyrus, HIGH youth exhibited hypoactivation to fearful faces relative to LOW and ANX/DEP youth. Conclusions: Four categories of co-occurring dimensions of psychopathology emerge in the current and parent sample. These categories have distinct neural responses to fearful faces, adding to their discriminant validity

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Biol Psychiatry. 2017;81:S101-S102.

STRUCTURAL NETWORKS CHARACTERISE METHYLPHENI-DATE TREATMENT RESPONSE IN ADHD.

Griffiths K, Kohn M, Clarke S, et al.

Background: While methylphenidate (MPH) is largely successful in treating the symptoms and cognitive impairments associated with ADHD, in approximately 30% of cases it is either ineffective or causes intolerable side-effects. The exact biological reasons for this individual variability in MPH response are unclear. We used graph theory to determine whether whole-brain white matter connectivity differed in MPH responders versus non-responders. Methods: Thirty-six children and adolescents with ADHD completed a 6 week MPH trial (international Study to Predict Optimized Treatment Response in ADHD; iSPOT-A). Treatment response was defined as.25% improvement from baseline on the ADHD-Rating Scale. Structural connectivity matrices were constructed using DTI probabilistic tractography between 84 parcellated whole-brain regions. Graph theory was applied to quantify global network characteristics (characteristic path length, clustering coefficient and global efficiency) and the connectivity of local nodes within the network. Results: MPH responders (R, n520) exhibited increased pre-treatment global efficiency relative to non-responders (NR, n516). Locally, NR had higher connectivity of the right superior temporal (p=.04) and supramarginal (p=.04) regions, while R had greater connectivity of the left caudate (p=.02) and amygdala (p=.02). Lower right supramarginal and higher left caudate connectivity were associated with greater reduction of inattentive symptoms (r5.45, p=.006; r52.42, p=.01), while higher amygdala connectivity was associated with greater hyperactivity symptom reduction (r52.574, p,.001). Conclusions: Favorable clinical response to MPH may rely upon efficient network organization and heightened baseline connectivity within striatal and limbic networks. Structural connectomics provides new insights into the inter-individual variability in MPH response in child and adolescent ADHD

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Biol Psychiatry. 2017;81:S129.

HEDONIC CAPACITY AS A PREDICTOR OF ADHD AND TREATMENT RESPONSE IN DEPRESSED PATIENTS.

Sternat T, Fotinos K, Fine A, et al.

Background: Depression has become a major public health concern as rates continue to increase and has become among the leading cause of disability and subsequent death. Research suggests that more than 11% of adolescents experience depression and that depressed adolescents are 6-times more likely to attempt suicide compared to non-depressed individuals. A core symptom of depression, anhedonia, is associated with poorer treatment response in patients treated with traditional antidepressants. Thus, the aim of this study is to determine predictive factors and clinical features associated with the development of

treatment-resistant depression (TRD). Methods: Data is being collected from consecutive referrals to a tertiary-care mood and anxiety clinic 160 subjects have been enrolled in the study to date. Diagnosis was established by using the Mini International Neuropsychiatric Interview Plus 5.0.0 and a semi-structured interview by the treating physician. Oneway analysis of variance and t-tests were undertaken to examine predictive factors related to the development of TRD. Results: Preliminary results suggest that 34% of patients referred for TRD had untreated ADHD of which 48% suffered with chronic anhedonia. The number of failed psychiatric medications ($p<0.001$), and past SSRI failures ($p<0.032$) were predictive of ADHD in patients with TRD, with SSRI failure predicting chronic anhedonia ($p<0.002$). Conclusions: These results support ADHD as a significant risk factor for the development of TRD, with chronic (trait) anhedonia or low hedonic tone providing a link between TRD and ADHD, which may predict poorer treatment outcomes in a subset of patients treated with SSRIs

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Biol Psychiatry. 2017;81:S374.

GLOBAL PROBABILISTIC TRACTOGRAPHY AND SYMPTOM DIMENSIONS IN A PROSPECTIVELY CHARACTERIZED SAMPLE OF ADULTS WITH A CHILDHOOD DIAGNOSIS OF ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Versace A, Allen B, Pelham W, et al.

Background: White matter abnormalities have been shown to play an important role in the pathophysiology of Attention Deficit-Hyperactivity Disorder (ADHD). However, little is known about the extent to which ADHD symptom severity is associated with abnormalities in white matter tracts known to be involved in attention and emotional control processes Methods: We aimed to determine if abnormalities in fronto-temporal white matter tracts involved in attention (superior longitudinal fasciculus, SLF) and emotional control processes (uncinate fasciculus, UF) relate to clinically relevant symptom-dimensions in 46 adults with or without ADHD (32 ADHD, 14 non-ADHD; mean age[SD]533[3] years, 44males), recruited from an ongoing longitudinal study in 347 children with ADHD prospectively characterized from-youth-to-adulthood. Symptom-dimensions of inattention, hyperactivity/impulsivity (H/I), and anger-irritability (A/I) were used. Global probabilistic tractography was used to reconstruct SLF and UF. Volume, length, and diffusivity metrics were extracted for each participant. Results: ADHD, vs non-ADHD, adults showed smaller volume in the right UF ($p=.05$) and right SLF ($p=.06$). In ADHD adults, H/I symptoms were negatively correlated with length in the SLF (left: r5-.40, p50.01; right: r5-.40, p50.03) and A/I symptoms were positively correlated with volume of the right UF (r50.40,p50.04). Conclusions: Findings suggest that higher volumes in fibers connecting medial-temporal and orbitofrontal regions might be associated with higher severity of A/I symptoms. Abnormal reorganization of the fibers connecting DLPFC and temporo-parietal regions, as evidenced by a shorter length in the SLF, may represent a neurobiological substrate of higher levels of H/I symptoms, possibly associated with inability of modulating thoughts and actions in goal-directed behaviors reported in ADHD

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Biol Psychiatry. 2017;81:S259.

A NOVEL FNIRS-BASED NEUROCOGNITIVE INTERVENTION FOR TARGETED ENHANCEMENT OF EXECUTIVE FUNCTION NETWORK IN ADHD.

Hosseini H, Tam G, Gosse L, et al.

Background: Executive function (EF) deficit is associated with a host of serious brain disorders including ADHD, depression and autism. Current treatments for EF deficits do not account for differences in brain networks across multiple disorders and thus lack specificity. We propose a novel intervention that is based upon rehabilitation of individualized neural systems underlying EF. Methods: The proposed intervention is the first that combines real-time functional near-infrared spectroscopy (fNIRS) and multivariate pattern analysis, in conjunction with computerized cognitive rehabilitation for targeted enhancement of EF network. Here, we discuss the innovative aspects of the proposed approach along with the preliminary results of validating this technique in children with ADHD. Results: We argue that the proposed approach expands current cognitive intervention techniques in two ways: (1) The proposed intervention integrates real-time fNIRS imaging and computational techniques for accurate detection of the target network, thus accounting

for individual variability in neuropathology. (2) It integrates neurofeedback with active cognitive training exercises, and thus is more engaging for children (and patients). We recently validated the proposed intervention in young healthy adults (N 5 20), who showed enhancement in their executive function networks and performance after four weeks of intervention relative to active controls. Further, our preliminary data on children with ADHD (N 5 5) suggest reliable detection of an affected EF network in the right prefrontal cortex in these patients that is consistent with previous meta-analysis reports. Conclusions: The proposed approach provides a foundation for developing efficient, pathology-focused interventions for a variety of patients with significant EF deficits

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Biol Psychiatry. 2017;81:S189.

LONGITUDINAL TRAJECTORIES OF PSYCHIATRIC DIAGNOSES AND PREDICTORS OF PERSISTENCE IN YOUTH WITH 22Q11.2 DELETION SYNDROME.

Mariano M, Fremont W, Antshel KM, et al.

Background: Youth with 22q11.2 deletion syndrome (22q11DS) display a high incidence of psychiatric disorders. While several cross-sectional studies have reported the prevalence of psychopathology across age groups, few studies have reported on the longitudinal trajectories of psychiatric disorders within the same cohort of youth. Methods: Eighty-seven youths with 22q11DS were assessed for psychopathology, IQ, global functioning, family relationship status, and pharmacotherapy at four timepoints over a period of 10 years (initial mean age 5 11.87). Descriptive statistics and logistic regression methods provided information on longitudinal trajectories of psychiatric diagnoses and factors predicting persistence of a diagnosis. Results: Rates of attention deficit hyperactivity disorder (ADHD) decreased from 52% to 15%, with 31% of participants persisting in ADHD from their initial to final assessment. Baseline age and pharmacotherapy (p 5.002 2.006) predicted ADHD persistence. Participants exhibiting prodromal/overt psychosis increased (5% to 31%) with 39% persisting. Predictors of prodromal/overt psychosis at the final timepoint included decreased global functioning, decreased IQ, and the presence of multiple diagnoses including anxiety (p 5.011-.041). Anxiety diagnoses increased slightly (30% to 36%) with 50% of participants persisting. Increased family conflict and pharmacotherapy (p 5.005-.008) predicted anxiety persistence. Prevalence of mood disorders was stable (17% to 15%) with 32% of persisters characterized by decreased baseline global functioning (p 5.031). Conclusions: This longitudinal study validates previous findings regarding the prevalence of psychopathology in 22q11DS youth and highlights valuable information on the risk factors differentiating persisters from youth without a corresponding psychiatric diagnosis

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Biol Psychiatry. 2017;81:S86.

THE CONTRIBUTION OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER COMMON GENETIC RISK VARIANTS TO CHILDHOOD IRRITABILITY: EVIDENCE FROM CLINICAL AND POPULATION COHORTS.

Eyre O, Riglin L, Cooper M, et al.

Background: Severe, childhood irritability is a common feature of neurodevelopmental disorders including Attention-Deficit/Hyperactivity Disorder (ADHD). Twin studies suggest that ADHD and irritability share genetic aetiology. However, other studies have highlighted genetic and longitudinal links between childhood irritability and later depression. This study aimed to test whether common genetic variants associated with ADHD diagnosis, indexed by polygenic risk scores (PRS), were associated with childhood irritability. Methods: Three UK samples were utilised: two population-based (n= 14,701 and Γêé+ 17,000) and one clinical ADHD sample (n=696). ADHD polygenic risk scores were derived from the largest published ADHD genome-wide association data-set (5,621 cases and 13,589 controls) and generated in each sample. Associations between ADHD PRS and parent rated presence/absence of childhood irritability were examined. Results: In both population-based samples the prevalence of irritability decreased from childhood (age 7) to adolescence (age 15/16) in males, and increased in females; childhood irritability was more likely to be present in males than females. ADHD PRS were associated with presence of childhood irritability in all three samples (population based samples: OR51.08, 95% CI51.01-1.14, p50.018 and OR51.13, 95% CI51.02-1.25,

p50.025, clinical sample: OR51.38, 95% CI51.31-1.85, p50.030). The associations were no longer significant on reaching adolescence in the population based-samples. Conclusions: ADHD genetic risk may have pleiotropic effects on childhood irritability. Further work is needed to better understand the nature of the relationship between irritability and ADHD, including the possibility that, in childhood, irritability is a neurodevelopmental difficulty

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Biomedical Signal Processing and Control. 2018;40:351-58.

INVESTIGATION OF BRAIN NETWORKS IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER USING A GRAPH THEORETICAL APPROACH.

Cao J, Li Y, Yu H, et al.

In this study, brain networks in children with attention-deficit/hyperactivity disorder (ADHD) were investigated. Electroencephalogram (EEG) data were collected from 16 children with ADHD (ADHD group) and 16 healthy children (control group) while they performed an improved visual continuous performance test. A combination coherence and graph theory method was used to construct each subject's nerve conduction network using EEG signal data. Differences in brain network topology parameters between the two groups were then compared (two-sample t test). Results revealed the following: when performing functional tasks, alpha bands can be used as an important parameter in ADHD research; the shortest path length can be used as a reference to assess ADHD; and ADHD brains exhibit significant defects in left lateralization of neural networks. These results support the conclusions of the cognitive-energetic model

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BJOG Int J Obstet Gynaecol. 2017.

COGNITIVE, MOTOR, BEHAVIOURAL AND ACADEMIC PERFORMANCES OF CHILDREN BORN PRETERM: A META-ANALYSIS AND SYSTEMATIC REVIEW INVOLVING 64 061 CHILDREN.

Allotey J, Zamora J, Cheong-See F, et al.

Background: Preterm birth may leave the brain vulnerable to dysfunction. Knowledge of future neurodevelopmental delay in children born with various degrees of prematurity is needed to inform practice and policy. Objective: To quantify the long-term cognitive, motor, behavioural and academic performance of children born with different degrees of prematurity compared with term-born children. Search strategy: PubMed and Embase were searched from January 1980 to December 2016 without language restrictions. Selection criteria: Observational studies that reported neurodevelopmental outcomes from 2 years of age in children born preterm compared with a term-born cohort. Data collection and analysis: We pooled individual estimates of standardised mean differences (SMD) and odds ratios (OR) with 95% confidence intervals using a random effects model. Main results: We included 74 studies (64 061 children). Preterm children had lower cognitive scores for FSIQ (SMD: -0.70; 95% CI: -0.73 to -0.66), PIQ (SMD: -0.67; 95% CI: -0.73 to -0.60) and VIQ (SMD: -0.53; 95% CI: -0.60 to -0.47). Lower scores for preterm children in motor skills, behaviour, reading, mathematics and spelling were observed at primary school age, and this persisted to secondary school age, except for mathematics. Gestational age at birth accounted for 38-48% of the observed IQ variance. ADHD was diagnosed twice as often in preterm children (OR: 1.6; 95% CI: 1.3-1.8), with a differential effect observed according to the severity of prematurity (I2 = 49.4%, P = 0.03). Conclusions: Prematurity of any degree affects the cognitive performance of children born preterm. The poor neurodevelopment persists at various ages of follow up. Parents, educators, healthcare professionals and policy makers need to take into account the additional academic, emotional and behavioural needs of these children. Tweetable abstract: Adverse effect of preterm birth on a child's neurodevelopment persists up to adulthood

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BMC Psychiatry. 2017;17.

PREVALENCE AND CORRELATES FOR ADHD AND RELATION WITH SOCIAL AND ACADEMIC FUNCTIONING AMONG CHILDREN AND ADOLESCENTS WITH HIV/AIDS IN UGANDA.

Mpango RS, Kinyanda E, Rukundo GZ, et al.

Background: Aim of this study was to determine the prevalence of attention-deficit/hyperactivity disorder (ADHD), its associated correlates and relations with clinical and behavioural problems among children and adolescents with HIV/AIDS (CA-HIV) attending five HIV clinics in central and South Western Uganda. Methods: This study used a quantitative design that involved a random sample of 1339 children and adolescents with HIV and their caregivers. The Participants completed an extensive battery of measures including a standardized DSM-5 referenced rating scale, the parent version (5-18 years) of the Child and Adolescent Symptom Inventory-5 (CASI-5). Using logistic regression, we estimated the prevalence of ADHD and presentations, correlates and its impact on negative clinical and behavioural factors. Results: The overall prevalence of ADHD was 6% (n = 81; 95%CI, 4.8-7.5%). The predominantly inattentive presentation was the most common (3.7%) whereas the combined presentation was the least prevalent (0.7%). Several correlates were associated with ADHD: socio-demographic (age, sex and socio-economic status); caregiver (caregiver psychological distress and marginally, caregiver educational attainment); child's psychosocial environment (quality of child-caregiver relationship, history of physical abuse and marginally, orphanhood); and HIV illness parameters (marginally, CD4 counts). ADHD was associated with poor academic performance, school disciplinary problems and early onset of sexual intercourse. Conclusions: ADHD impacts the lives of many CA-HIV and is associated with poorer academic performance and earlier onset of sexual intercourse. There is an urgent need to integrate the delivery of mental health services into routine clinical care for CA-HIV in Sub-Saharan Africa

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BMJ Case Rep. 2017;2017.

DOES QUALITY OF LIFE OUTWEIGH THE CARDIOVASCULAR RISKS OF STIMULANT MEDICATION IN A CHILD WITH ADHD AND HYPERTROPHIC CARDIOMYOPATHY?

Senderey E, Sousa J, Stavitsky M.

A 10-year-old girl with attention-deficit hyperactivity disorder (ADHD) is diagnosed with hypertrophic cardiomyopathy. The stimulant medications used to control her ADHD pose possibly fatal risks to her cardiovascular health, so stimulant medication is stopped. Due to very poor quality of life off of medication, alternative therapies are used without improvement. The patient's caretakers decide that the benefits of stimulant medication outweigh the risks to the patient. The healthcare team clears the patient to be put back on stimulant medication with a signed waiver of liability by her caretakers

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BMJ Open. 2017;7.

RISK OF UNINTENTIONAL INJURIES IN CHILDREN AND ADOLESCENTS WITH ADHD AND THE IMPACT OF ADHD MEDICATIONS: PROTOCOL FOR A SYSTEMATIC REVIEW AND META-ANALYSIS.

Ruiz-Goikoetxea M, Cortese S, Aznarez-Sanado M, et al.

Introduction Attention-deficit hyperactivity disorder (ADHD) has been related to increased rates of unintentional injuries. However, the magnitude of the effect and to which extent variables such as sex, age or comorbidity can influence this relationship is unknown. Additionally, and importantly, it is unclear if, and to which degree, ADHD medications can decrease the number of unintentional injuries. Due to the amount of economic and social resources invested in the treatment of injuries, filling these gaps in the literature is highly relevant from a public health standpoint. Here, we present a protocol for a systematic review and meta-analysis to estimate the relationship between ADHD and unintentional injuries and assess the impact of pharmacological treatment for ADHD Methods and analysis We will combine results from 114 bibliographic databases for studies relating ADHD and risk of injuries. Bibliographic searches and data extraction will be carried out independently by two researchers. The studies' risk of bias will be assessed using the Newcastle-Ottawa Scale. Articles reporting ORs or HRs of suffering an injury in ADHD compared with controls (or

enough data to calculate them) will be combined using Robust Variance Estimation, a method that permits to include multiple non-independent outcomes in the analysis. All analyses will be carried out in Stata. Age, sex and comorbid conduct disorders will be considered as potential causes of variance and their effect analysed through meta-regression and subgroup analysis. Sensitivity analyses will exclude articles with longer follow-ups, non-stringent definitions of ADHD or controls and statistically uncontrolled/controlled outcomes. Studies implementing a self-controlled case series methodology to investigate if ADHD drugs reduce the risk of injuries will be combined with a generalised linear mixed model using the Poisson distribution and a log link function. Registration details PROSPERO - Prospective Register of Systematic Reviews (CRD42017064967)

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Br J Educ Psychol. 2017 Jun;87:127-45.

EARLY HIGH SCHOOL ENGAGEMENT IN STUDENTS WITH ATTENTION/DEFICIT HYPERACTIVITY DISORDER.

Zendarski N, Sciberras E, Mensah F, et al.

BACKGROUND: Students with attention/deficit hyperactivity disorder (ADHD) continue to languish behind their peers with regard to academic achievement and education attainment. School engagement is potentially modifiable, and targeting engagement may be a means to improve education outcomes. AIMS: To investigate school engagement for students with ADHD during the crucial high school transition period and to identify factors associated with low school engagement. SAMPLE: Participants are adolescents (12-15 years) in the first and third year of high school with diagnosed ADHD (n = 130). Participants were recruited from 21 paediatric practices. METHODS: Cross-sectional study assessing school engagement. Data were collected through direct assessment and child, parent, and teacher surveys. School engagement is measured as student attitudes to school (cognitive and emotional) and suspension rates (behavioural). Multivariable regression analyses examined student, family, and school factors affecting engagement. RESULTS: In comparison with state data, students with ADHD in the first year of high school were less motivated ($p < .01$) and less connected to peers ($p < .01$). Overall, there was no discordance in third year attitudes. There were high rates of suspension in both years in comparison to state-wide suspensions (21% vs. 6%, $p < .01$). Explanatory factors for poor attitudes include adolescent depression, poor adolescent supervision, and devaluing education. Conduct problems and increased hyperactivity were related to increased likelihood of being suspended, whilst higher cognitive ability, family socio-economic status, and independent schools reduced risk. CONCLUSIONS: Potentially modifiable individual and family factors including adolescent depression, behavioural problems, education values, and family supervision could be targeted to better manage the high school transition for students with ADHD

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Brain Behav. 2017;7.

INTERACTION EFFECTS OF GIT1 AND DRD4 GENE VARIANTS ON CONTINUOUS PERFORMANCE TEST VARIABLES IN PATIENTS WITH ADHD.

Kim H, Kim JI, Kim H, et al.

Introduction The G protein-coupled receptor kinase interacting protein 1 gene (GIT1) has been proposed to be a risk gene for attention deficit hyperactivity disorder (ADHD), and it regulates the endocytosis of G protein-coupled receptors like dopamine receptors. The purpose of this study was to investigate the interaction effects of GIT1 and dopamine receptor D4 (DRD4) gene variants on variables of the continuous performance test (CPT).

Methods This study recruited 255 ADHD patients and 98 healthy controls (HC) who underwent CPT and genetic analyses. The genotypes were classified into two groups (the C/C and C/T genotype groups for GIT1, 4R homozygotes and others for DRD4) and the genotype × genotype effects were examined using hierarchical multivariable linear regression analyses.

Results There were significant GIT1 × DRD4 effects for commission errors on the CPT in the ADHD group ($p = .006$). In contrast, there were no significant GIT1 × DRD4 effects on any CPT variables in the HC.

Conclusions The present findings demonstrated that there were significant interaction effects of the GIT1 and DRD4 gene variants on impulsivity in ADHD. Replication studies with larger sample sizes that include patients from various ethnic backgrounds are warranted to confirm these findings.

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Brain Dev. 2017.

ATTENTION PROFILES IN CHILDHOOD ABSENCE EPILEPSY COMPARED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lee H-J, Kim E-H, Yum M-S, et al.

Objective: This study aimed to compare the attention profiles of subjects with childhood absence epilepsy (CAE) to those of children with attention-deficit/hyperactivity disorder (ADHD) and controls. Method: We retrospectively reviewed the medical records of 20 children (age 7.2[U+202F]-¦[U+202F]1.6[U+202F]years, 5 boys) in whom CAE was diagnosed at the Department of Pediatric Neurology of Asan Medical Center, Seoul, Korea. ADHD and control subjects were selected from children who visited the Department of Pediatric Psychiatry and were confirmed as having or not having ADHD based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL). The 20 children with CAE, 20 with ADHD and 20 controls completed the Advanced Test of Attention (ATA), which is a computerized continuous performance task. Results: The CAE subjects without ADHD showed increased Omission errors (p = .013) on the visual ATA and Response time (p = 0.044) on the auditory ATA than the controls, although these differences did not remain significant after multiple comparison correction. The CAE subjects without ADHD had significantly decreased Response time variability on the visual ATA than the ADHD group (p <. 0.001). The CAE subjects with comorbid ADHD showed increased Commission errors (p = 0.020) and Response time variability (p = 0.016) on the visual ATA and increased Commission errors (p = 0.022) on the auditory ATA than the CAE subjects without ADHD, although statistical significance disappeared after multiple comparison adjustments. Conclusion: These findings suggest that selective attention is impaired in children with CAE and comorbid ADHD contributes to further impairment of sustained attention and response inhibition

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Brain Injury. 2017;1-7.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IS ASSOCIATED WITH BASELINE CHILD SPORT CONCUSSION ASSESSMENT TOOL THIRD EDITION SCORES IN CHILD HOCKEY PLAYERS.

***Collings LJ, Cook NE, Porter S, et al*.**

OBJECTIVES: The objectives of this study were to report baseline, preseason data for the Child-SCAT3, stratified by attention deficit hyperactivity disorder (ADHD) status, and examine group differences in Child-SCAT3 performance between children with and without ADHD.

DESIGN: Cross-sectional study.

METHODS: Young male hockey players (n = 304), aged 8-12 years, were administered the Child-SCAT3 during pre-season. Child-SCAT3 measures included a 20-item symptom scale, a Standardised Assessment of Concussion Child Version (SAC-C), a modified Balance Error Scoring System (m-BESS), a tandem gait task, and a coordination test.

RESULTS: Children with ADHD (n = 20) endorsed significantly more symptoms (d = 0.95) and greater symptom severity (d = 1.13) compared to children without ADHD. No statistically significant differences were found between groups on Child-SCAT3 measures of cognitive or physical functioning (e.g. balance and coordination).

CONCLUSIONS: ADHD should be considered when interpreting Child-SCAT3 scores, especially symptom reporting, in the context of concussion assessment. Better understanding of symptom reporting in uninjured child athletes with ADHD can inform the clinical interpretation of symptoms at baseline and following an

actual or suspected concussion. Normative data for the Child-SCAT3 that is not stratified by or otherwise accounts for ADHD status should be used with caution when appraising performance of children with ADHD.

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Child Neuropsychol. 2017;1-14.

NAMING SPEED AS A PREDICTIVE DIAGNOSTIC MEASURE IN READING AND ATTENTIONAL PROBLEMS.

Areces D, et al.

This study aimed to describe and compare naming speed abilities in children diagnosed with either Reading Learning Difficulties (RLD) or Attention Deficit/Hyperactivity Disorder (ADHD), or comorbidity for both (ADHD+RLD). To examine the explanatory power of naming speed and ADHD symptomatology in predicting group associations (while controlling for gender and age), the "Rapid Automatized Naming and Rapid Alternating Stimulus Tests" (RAN/RAS) were utilized. A sample of 101 children (age range = 5-16 years) was divided into four groups: RLD (n = 14), ADHD (n = 28), comorbid (n = 19), and control (n = 40). There were statistically significant differences in RAN/RAS results among the diagnostic groups. Moreover, discriminant analysis revealed that naming speed tasks significantly predicted reading and attentional problems, especially at earlier ages. These results demonstrate the potential usefulness of RAN/RAS in the diagnosis of reading and attentional problems, particularly if the children are aged from 5 to 9.

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Child Neuropsychol. 2017;1-19.

MULTIPLE CAUSAL PATHWAYS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER - DO EMERGING EXECUTIVE AND MOTIVATIONAL DEVIATIONS PRECEDE SYMPTOM DEVELOPMENT?

Pauli-Pott U, et al.

The multiple causal pathways model on the etiology of attention-deficit/hyperactivity disorder (ADHD) is well established. However, developmental implications of the model are not yet sufficiently analyzed. The model implies that critical neural and neuropsychological deviations from normative development precede secondarily developing ADHD symptoms. Cognitive, "cool" inhibitory control (CIC) and reward-related, "hot" functions (RRF) are regarded as neuropsychological basic deficits that indicate independent causal pathways. Both functions involve top-down control networks that undergo major normative developmental changes in the preschool period. We formalized the following assumptions in a path model: (a) CIC and RRF predict change in ADHD symptoms in the preschool period, (b) the reverse is not true, and (c) CIC and RRF independently contribute to this prediction. A community-based sample of 125 (71 boys) preschoolers was assessed at at age 4 and 5 years. At each assessment wave, CIC and RRF were measured by a battery of age-appropriate valid tasks. ADHD symptoms were measured by a clinical parent interview. Evaluation of model fit using manifest maximum likelihood parameter estimation clearly supported the hypothesized path model while controlling for gender of child and maternal education level. Thus, regarding the basic deficits of CIC and RRF, the results add evidence on the developmental implications of the multiple causal pathways

model. Our findings point to the potential significance of these early emerging characteristics as indicators of risk and as targets for preventive interventions

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Child Neuropsychol. 2017;1-25.

ASSESSMENT OF EXECUTIVE FUNCTION IN ADHD ADOLESCENTS: CONTRIBUTION OF PERFORMANCE TESTS AND RATING SCALES.

Krieger V, Amador-Campos JA.

This study aimed to analyze performance on measures of neuropsychological and behavioral executive functions (EF) in adolescents with attention deficit hyperactivity disorder (ADHD), and to evaluate the utility of performance-based tests for predicting scores on behavioral EF ratings. One hundred eighteen adolescents (75 ADHD and 43 controls) aged 12ΓÇô16-áyears performed neuropsychological tests and

completed a behavior rating scale of EF. The ADHD group presented significantly lower scores than controls on Full Scale IQ (FSIQ) and all indexes of the WISC-IV, except the verbal comprehension index (VCI). The ADHD group had significantly lower scores on performance-based tests of working memory, planning and inhibition, and on EF rating scales. Scores on the cognitive EF working memory, planning and flexibility modestly predicted performance on behavioral EF. The results suggest that the combined use of performance-based tests and rating scales provides valuable complementary information that can improve the assessment of executive domains in ADHD

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Child Psychiatry Hum Dev. 2017 Oct;48:691-98.

SUICIDAL BEHAVIOR IN JUVENILE DELINQUENTS: THE ROLE OF ADHD AND OTHER COMORBID PSYCHIATRIC DISORDERS.

Ruchkin V, Koposov RA, Koyanagi A, et al.

This study evaluated the role of psychiatric morbidity in relation to a history of suicidal behavior, with a particular focus on attention-deficit/hyperactivity disorder (ADHD). Suicidality and psychiatric diagnoses were assessed in 370 incarcerated male juvenile delinquents from Northern Russia using the semi-structured K-SADS-PL psychiatric interview. A lifetime history of suicidal ideation only (24.7 %) and suicidal ideation with suicide attempts (15.7 %) was common. Binary logistic regression analysis was used to assess the role of ADHD and other psychiatric disorders in suicidal ideation and suicide attempts. A history of suicidal ideation and of suicide attempts were associated with higher rates of psychiatric morbidity and with the number of comorbid psychiatric disorders. An ADHD diagnosis was associated with an increased risk for both suicidal ideation and for suicide attempts. The comorbidity of ADHD with drug dependence further increased the risk for suicidal ideation, while ADHD and alcohol dependence comorbidity increased the risk for suicide attempts. Our findings highlight the importance of adequately detecting and treating psychiatric disorders in vulnerable youths, especially when they are comorbid with ADHD

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Clin Pediatr (Phila). 2017 Nov;56:1219-26.

ON-SITE MENTAL HEALTH PROFESSIONALS AND PEDIATRIC RESIDENTS IN CONTINUITY CLINIC.

Ragunanthan B, Frosch EJ, Solomon BS.

The objective of the study was to examine differences in pediatric resident perceptions and practices related to child mental health conditions in continuity clinic settings with versus without on-site mental health professionals (MHPs). A 20-item questionnaire, based on the American Academy of Pediatrics Periodic Survey Number 59, was administered to pediatric residents in a medium-sized program from 2008 to 2011. Of 130 residents surveyed, compared with their peers, those practicing with the on-site MHPs were more likely to report mental health services as very available in their clinic (odds ratio [OR] = 39.7; P = .000). Residents with on-site MHPs inquired more frequently about attention-deficit/hyperactivity disorder (ADHD; OR = 2.96; P = .029) and referred more frequently for ADHD (OR = 3.68; P = .006), depression (OR = 2.82; P = .030), and behavioral problems (OR = 3.04; P = .012). On-site MHPs in continuity clinics offer great potential to improve resident education and patient care. Additional research is necessary to further understand their impact

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Clinical Drug Investigation. 2017;1-8.

THE CHALLENGE OF PHARMACOTHERAPY IN CHILDREN AND ADOLESCENTS WITH EPILEPSY-ADHD COMORBIDITY.

Verrotti A, Moavero R, Panzarino G, et al.

Epilepsy is common in children and adolescents where its prevalence is 3.2ΓÇô5.5/1000. About one-third of patients also have attention deficit hyperactivity/impulsivity disorder (ADHD). The possible relationship between epilepsy and ADHD is still unclear, and ADHD symptoms (such as inattention, hyperactivity, behavioral disturbances) are frequently considered as adverse effects of antiepileptic drugs (AEDs). The

literature was searched for data on the behavioral effects of AEDs. Phenobarbital is the most frequently reported medication to induce symptoms of ADHD, followed by topiramate and valproic acid. Phenytoin seems to exert modest effects, while for levetiracetam there are contrasting data. Lacosamide induces some beneficial effects on behavior; carbamazepine and lamotrigine exert favorable effects on attention and behavior. Gabapentin and vigabatrin have limited adverse effects on cognition. Oxcarbazepine, rufinamide, and eslicarbazepine do not seem to aggravate or induce ADHD symptoms, whereas perampanel can lead to a high incidence of hostile/aggressive behavior, which increases with higher dosages. Information about the behavioral effects of ethosuximide, zonisamide, tiagabine, pregabalin, stiripentol, and retigabine is still limited. Because ADHD significantly affects the quality of life of epilepsy patients, the clinical management of this neuropsychiatric disorder should be a priority. Methylphenidate is effective most children and adolescents with ADHD symptoms and comorbid epilepsy, without a significant increase of seizure risk, although data are still limited with few controlled trials

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Clin Neurophysiol. 2017;128:2258-67.

NEURAL NETWORK TOPOLOGY IN ADHD; EVIDENCE FOR MATURATIONAL DELAY AND DEFAULT-MODE NETWORK ALTERATIONS.

Janssen TWP, Hillebrand A, Gouw A, et al.

OBJECTIVE: Attention-deficit/hyperactivity disorder (ADHD) has been associated with widespread brain abnormalities in white and grey matter, affecting not only local, but global functional networks as well. In this study, we explored these functional networks using source-reconstructed electroencephalography in ADHD and typically developing (TD) children. We expected evidence for maturational delay, with underlying abnormalities in the default mode network.

METHODS: Electroencephalograms were recorded in ADHD (n=42) and TD (n=43) during rest, and functional connectivity (phase lag index) and graph (minimum spanning tree) parameters were derived. Dependent variables were global and local network metrics in theta, alpha and beta bands.

RESULTS: We found evidence for a more centralized functional network in ADHD compared to TD children, with decreased diameter in the alpha band (ηp2=0.06) and increased leaf fraction (ηp2=0.11 and 0.08) in the alpha and beta bands, with underlying abnormalities in hub regions of the brain, including default mode network.

CONCLUSIONS: The finding of a more centralized network is in line with maturational delay models of ADHD and should be replicated in longitudinal designs.

SIGNIFICANCE: This study contributes to the literature by combining high temporal and spatial resolution to construct EEG network topology, and associates maturational-delay and default-mode interference hypotheses of ADHD

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CNS Drugs. 2017;1-16.

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED ACUTE COMPARATOR TRIALS OF LISDEXAMFETAMINE AND EXTENDED-RELEASE METHYLPHENIDATE IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Newcorn JH, Nagy P, Childress AC, et al.

BACKGROUND: Psychostimulants are considered first-line pharmacotherapy for youth with attention-deficit/hyperactivity disorder (ADHD), but questions remain regarding the comparative efficacy of amphetamine- and methylphenidate-based agents.

OBJECTIVE: Our objective was to describe two acute randomized, double-blind, placebo-controlled, head-to-head studies of lisdexamfetamine dimesylate (LDX) and osmotic-release oral system methylphenidate (OROS-MPH) in adolescents with ADHD.

METHODS: Adolescents (13-17 years) diagnosed with ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria were enrolled in an 8-week flexible-dose study [LDX 30-70 mg/day (n = 186 randomized); OROS-MPH 18-72 mg/day (n = 185 randomized); placebo (n = 93 randomized)] or a 6-week forced-dose study [LDX 70 mg/day (n = 219 randomized); OROS-

MPH 72 mg/day (n = 220 randomized); placebo (n = 110 randomized)]. Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) total score changes from baseline (primary endpoint) at week 8 (flexible-dose study) or week 6 (forced-dose study) were assessed with mixed-effects models for repeated measures. Secondary endpoints included improvement on the dichotomized Clinical Global Impressions-Improvement scale (CGI-I; key secondary endpoint) and changes from baseline on the ADHD-RS-IV subscales. Safety assessments included treatment-emergent adverse events (TEAEs) and vital signs.
RESULTS: Least squares (LS) mean ± standard error of the mean (SEM) ADHD-RS-IV total score changes from baseline to end of treatment were -17.0 ± 1.03 with placebo, -25.4 ± 0.74 with LDX, and -22.1 ± 0.73 with OROS-MPH in the forced-dose study and -13.4 ± 1.19 with placebo, -25.6 ± 0.82 with LDX, and -23.5 ± 0.80 with OROS-MPH in the flexible-dose study. LS mean ± SEM treatment difference for the change from baseline significantly favored LDX over OROS-MPH in the forced-dose [-3.4 ± 1.04, p = 0.0013, effect size (ES) -0.33] but not the flexible-dose (-2.1 ± 1.15, p = 0.0717, ES -0.20) study. The percentage of improved participants on the dichotomized CGI-I at end of treatment was significantly greater with LDX than with OROS-MPH in the forced-dose study (81.4 vs. 71.3%, p = 0.0188) but not the flexible-dose study (LDX 83.1%, OROS-MPH 81.0%, p = 0.6165). The LS mean ± SEM treatment differences for change from baseline on the ADHD-RS-IV hyperactivity/impulsivity and inattentiveness subscales nominally favored LDX in the forced-dose study (hyperactivity/impulsivity subscale -1.3 ± 0.49, nominal p = 0.0081, ES -0.27; inattentiveness subscale -2.0 ± 0.63, nominal p = 0.0013, ES -0.33), but there were no significant differences between active treatments in the flexible-dose study. In both studies, LDX and OROS-MPH were superior to placebo for all efficacy-related endpoints (all nominal p < 0.0001; ES range -0.43 to -1.16). The overall frequency of TEAEs for LDX and OROS-MPH, respectively, were 66.5 and 58.9% in the forced-dose study and 83.2 and 82.1% in the flexible-dose study. TEAEs occurring in ≥ 5% of participants that were also reported at two or more times the rate of placebo were decreased appetite, decreased weight, insomnia, initial insomnia, dry mouth, and nasopharyngitis (LDX and OROS-MPH), irritability and dizziness (LDX only), and increased heart rate (OROS-MPH only) in the forced-dose study and decreased appetite, decreased weight, insomnia, and dizziness (LDX and OROS-MPH) and dry mouth and upper abdominal pain (LDX only) in the flexible-dose study. Mean ± standard deviation (SD) increases from baseline in vital signs (systolic and diastolic blood pressure, pulse) were observed in the forced-dose study [LDX 1.6 ± 9.65 and 3.3 ± 8.11 mmHg, 6.7 ± 12.78 beats per minute (bpm); OROS-MPH 2.6 ± 10.15 and 3.3 ± 9.13 mmHg, 7.6 ± 12.47 bpm] and the flexible-dose study (LDX 2.4 ± 9.46 and 2.8 ± 8.41 mmHg, 4.7 ± 11.82 bpm; OROS-MPH 0.4 ± 9.90 and 2.2 ± 8.64 mmHg, 6.0 ± 10.52 bpm) at the last on-treatment assessment.
CONCLUSIONS: LDX was superior to OROS-MPH in adolescents with ADHD in the forced-dose but not the flexible-dose study. Safety and tolerability for both medications was consistent with previous studies. These findings underscore the robust acute efficacy of both psychostimulant classes in treating adolescents with ADHD.
CLINICALTRIALS

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Dev Med Child Neurol. 2017 Nov;59:1112-16.

NEURODEVELOPMENTAL DISORDERS IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1.

Vogel AC, Gutmann DH, Morris SM.

Over the past several decades, neurofibromatosis type 1 (NF1) has become increasingly recognized as a neurodevelopmental disorder conferring increased risk for several important neurodevelopmental problems. In this review, we summarize the specific neurodevelopmental problems encountered in the context of NF1. These include impairments in general cognitive function, deficits in specific cognitive domains such as executive function and visuospatial processing and risk for specific learning disorders, impairments in attention and social skills and the overlap with attention-deficit-hyperactivity disorder and autism spectrum disorder, and the risk of developing other psychiatric conditions including anxiety and depression. Early recognition of these developmental impairments is important for the effective treatment of children with NF1, and further characterization is essential to improve our understanding of how mutations in the NF1 gene create the diversity of clinical neuropsychiatric symptomatology observed in this at-risk population

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Drug Alcohol Depend. 2017 Oct;179:167-73.

SOCIAL CONTEXTUAL RISK FACTORS FOR STIMULANT USE AMONG ADOLESCENT AMERICAN INDIANS.

Spillane NS, Weyandt L, Oster D, et al.

Objective: Stimulants are the most common and efficacious treatment for Attention-Deficit Hyperactivity Disorder (ADHD). We examined the relationship between stimulant misuse and social factors that could be malleable to prevention among American Indian (AI) adolescents.

Method: Participants were AI students (N = 3498) sampled from 33 schools in 11 states. Participants completed the American Drug and Alcohol Survey. A multilevel analytic approach was used to evaluate the effects of participant-level (level 1) variables (i.e., gender, grade, peer, school, family, stimulant prescribed by doctor) on lifetime and current simulant use to 'get high.'

Results: Nearly 7% of our sample had been prescribed stimulants and nearly 6% of the sample reported using stimulants to get high. Age [OR = 1.22; 95% CI = 1.09, 1.36, p < 0.001], perception of peer substance use [OR = 1.19; 95% CI = 1.14, 1.23, p < 0.001], parental monitoring [OR = 0.96; 95% CI = 0.92, 1.99, p = 0.04], and stimulants prescribed by a doctor [OR = 8.79, 95% CI = 5.86, 13.18, p < 0.001] were associated with ever using stimulants to get high. Perception of peer substance use, [b = 0.09, SE = 0.02, p < 0.001, 95%CI [0.05, 0.13], and having stimulants prescribed by a doctor, [b = 0.58, SE= 0.21, p = 0.006, 95%CI [0.17, 0.99], were associated with frequency of past month use to get high. There was also a significant quadratic effect for parental monitoring, suggesting that low and high levels were associated with increased stimulant use.

Conclusions: Our results suggest a need for prevention efforts to be directed to AI youth who are prescribed stimulants

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Drug Alcohol Depend. 2017;171:e73-e74.

ASSOCIATIONS BETWEEN NON-TRADITIONAL TOBACCO PRODUCT USE AND ADHD SYMPTOMS IN ADOLESCENTS.

Goldenson N, Khoddam R, Leventhal A.

Aims: While cigarette smoking is declining among U.S. adolescents, there has been a dramatic increase in the initiation and continued use of new and non-traditional tobacco products such as electronic cigarettes (e-cigarettes) and hookah (water pipe). Previous research has shown that attention-deficit hyperactivity disorder (ADHD) is an important risk factor for combustible cigarette use among adolescents, yet there is little data assessing possible associations between ADHD symptoms and nontraditional tobacco products.

Methods: High school students in the Los Angeles area (N= 3383) completed longitudinal surveys assessing lifetime and current use of e-cigarettes and hookah and ADHD symptoms at 2 time points. Logistic regression in repeated-measures, generalized linear mixed models assessed relations between standardized scores of ADHD symptoms and measures of tobacco product use after controlling for pertinent demographic, interpersonal and substance-related covariates.

Results: Among teens who never used e-cigarettes, the odds of reporting e-cigarette initiation increased by 23% with each 1 SD increase in ADHD score (odds ratio [OR], 1.23 [95% CI, 1.0-1.5]; p = .04). Among teens who never used hookah, the odds of reporting hookah initiation increased by 30% with each 1 SD increase in ADHD score (OR, 1.30 [95% CI, 1.1-1.6]; p < .001). Among current users, the odds of reporting continued use increased by 18% (OR, 1.18 [1.0-1.4]; p = .02) and 26% (OR, 1.26 [1.1-1.4]; p < .001) with each 1 SD increase in ADHD score for e-cigarettes and hookah, respectively.

Conclusions: These results indicate that ADHD symptomology may be a risk factor for both the initiation and maintenance of nontraditional tobacco products. Understanding the relations between ADHD symptomology and alternative tobacco products could play a key role in developing effective programs for preventing and/or reducing use of these products among adolescent populations

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Drug Alcohol Depend. 2017;171:e26.

THE PREVALENCE OF ADULT ATTENTION DEFICIT/HYPERACTIVITY DISORDER AMONG TREATMENT-SEEKING PROBLEM GAMBLERS.

Brandt L, Fischer G.

Aims: (1) Examining the frequency of childhood ADHD and ADHD persistent in adulthood as well as other psychiatric comorbidities in problem gamblers [3 DSM-IV criteria for pathological gambling (PG)]; (2) providing detailed characteristics of the association between PG and ADHD; (3) identifying risk factors for a history of ADHD.

Methods: 80 treatment-seeking problem gamblers (20% female) were examined using a structured and standardized interview [PG: DSM-IV criteria for PG, Gambling Attitudes and Beliefs Survey; ADHD: Wender Utah Rating Scale (childhood), Adult ADHD selfreport scale; comorbidities: Mini International Neuropsychiatric Interview].

Results: 43% of the subjects screened positive for ADHD in childhood and in 11% ADHD persisted in adulthood. Patients with adult ADHD were characterized as having more severe gambling problems compared to those without a history of ADHD ($p = .009$, $d = 1.03$). Moreover, they had a significantly higher number of psychiatric comorbidities (mean: 3.8) compared to subjects with ADHD in childhood only ($p = .043$, $d = 0.82$) and those without a history of ADHD ($p < .001$, $d = 1.62$). Substance abuse/dependence constituted a significant predictor for the likelihood of having a history of ADHD (OR: 4.07, $p = .025$); anxiety (OR: 3.07, $p = .053$) and mood disorders (OR: 3.56, $p = .051$) were predictors with a trend towards significance. Regarding gender differences, women had a significantly lower number of years from first gambling experience to developing problems compared to men (3.5 vs. 9.4 years, $p = .003$).

Conclusions: ADHD-PG comorbidity is linked to factors that worsen the prognosis, which highlights the clinical importance of screening for ADHD and verifying persistence in adulthood in the treatment of problem/pathological gamblers. A standardized diagnostic assessment and adequate treatment of ADHD and other psychiatric comorbidities is an inevitable (pre)condition to achieve a stabilisation of PG and increase the quality of life of these patients

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Emot Behav Difficulties. 2017;1-16.

EXTERNALIZING BEHAVIOUR AND ACADEMIC PERFORMANCE □ÇÔ THE CROSS-LAGGED RELATIONSHIP DURING SCHOOL TRANSITION.

Palmu IR, N+ñrhi VM, Savolainen HK.

The current study examined the over-time association between externalizing behaviour problems and academic performance during school transition in a cross-lagged design. The main focus was to reveal whether the externalizing behaviour composite and its components separately, including symptoms of CD and ADHD, differ in their relationship with academic performance; and if controlling child- or family-related covariates altered the strength or direction of the relationship. Externalizing behaviour composite was associated with a decrease in academic performance over a 1-year time lag. Academic performance at Grade 6 was associated with low CD symptoms at Grade 7. The effect remained significant when child-related covariates were controlled, but not after controlling family-related covariates. ADHD symptoms systematically had a negative effect on grade 7 GPA, even after child- and family-related covariates were controlled. The results indicate that during early adolescence and school transition, CD and ADHD symptoms differ in their association with academic performance

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Emot Behav Difficulties. 2017;1-14.

DIAGNOSING ADHD IN DANISH PRIMARY SCHOOL CHILDREN: A CASE STUDY OF THE INSTITUTIONAL CATEGORIZATION OF EMOTIONAL AND BEHAVIOURAL DIFFICULTIES.

Tegtmejer T, Hj+Ârne E, S+ñlj+Â R.

This study of institutional categorization reports an investigation of the practices, procedures and assumptions of psychiatric staff members when diagnosing ADHD. The main data upon which the study is

based consist of transcribed audio recordings of meetings in the psychiatric clinic. Here children referred from primary schools on the suspicion of ADHD are attended to. The tools and procedures for gathering information are shown to produce decontextualized and individualizing representations of children's conduct. The evaluation against a number of norms is found to be central. Finally, the discussions at the central team conferences are shown to reveal the use of hypothesis testing structured around a number of dichotomies, where isolated aspects of the child's life are considered against each other as the source of the difficulties. Together, these practices have cumulative and profound consequences for how children's problems come to be understood as caused by a neurological condition

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Environ Res. 2017.

COMBINED EFFECTS OF PRENATAL EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS AND MATERIAL HARDSHIP ON CHILD ADHD BEHAVIOR PROBLEMS.

Perera FP, Wheelock K, Wang Y, et al.

Importance: Polycyclic aromatic hydrocarbons (PAH) are carcinogenic and neurotoxic combustion by-products commonly found in urban air. Exposure to PAH is disproportionately high in low income communities of color who also experience chronic economic stress.

Objective: In a prospective cohort study in New York City (NYC) we previously found a significant association between prenatal PAH exposure and Attention Deficit Hyperactivity Disorder (ADHD) behavior problems at age 9. Here, we have evaluated the joint effects of prenatal exposure to PAH and prenatal/childhood material hardship on ADHD behavior problems.

Materials and Methods: We enrolled nonsmoking African-American and Dominican pregnant women in New York City between 1998 and 2006 and followed their children through 9 years of age. As a biomarker of prenatal PAH exposure, PAH-DNA adducts were measured in maternal blood at delivery and were dichotomized at the limit of detection (to indicate high vs. low exposure). Maternal material hardship (lack of adequate food, housing, utilities, and clothing) was self-reported prenatally and at multiple time points through child age 9. Latent variable analysis identified four distinct patterns of hardship. ADHD behavior problems were assessed using the Conners Parent Rating Scale- Revised. Analyses adjusted for relevant covariates.

Results: Among 351 children in our sample, across all hardship groups, children with high prenatal PAH exposure (high adducts) generally had more symptoms of ADHD (higher scores) compared to those with low PAH exposure. The greatest difference was seen among the children with hardship persisting from pregnancy through childhood. Although the interactions between high PAH exposure and hardship experienced at either period ("persistent" hardship or "any" hardship) were not significant, we observed significant differences in the number of ADHD symptoms between children with high prenatal PAH exposure and either persistent hardship or any hardship compared to the others. These differences were most significant for combined high PAH and persistent hardship: ADHD Index ($p < 0.008$), DSM-IV Inattentive ($p = 0.006$), DSM-IV Hyperactive Impulsive problems ($p = 0.033$), and DSM-IV Index Total ($p = 0.009$).

Conclusion: The present findings add to existing evidence that co-exposure to socioeconomic disadvantage and air pollution in early life significantly increases the risk of adverse neurodevelopmental outcomes. They suggest the need for multifaceted interventions to protect pregnant mothers and their children

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Environ Res. 2018;160:339-46.

THE INTERACTIONS AMONG ORGANOPHOSPHATE PESTICIDE EXPOSURE, OXIDATIVE STRESS, AND GENETIC POLYMORPHISMS OF DOPAMINE RECEPTOR D4 INCREASE THE RISK OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN.

Chang C-H, Yu C-J, Du J-C, et al.

Objective The aim of this study was to clarify the association between organophosphate pesticides (OPs) and attention-deficit/hyperactivity disorder (ADHD) related to oxidative stress and genetic polymorphisms.

Methods This case-control study enrolled 93 children with ADHD and 112 control children in north Taiwan. Six dialkyl phosphate (DAP) metabolites of OPs and oxidative stress biomarkers were analyzed. Polymorphisms of the dopamine receptor D4 gene (DRD4) were identified.
Results Children with ADHD had significantly higher dimethylphosphate (DMP, 236.69 nmol/g cre. vs. 186.84 nmol/g cre., p value = 0.01) and 4-hydroxy-2-nonenal-mercapturic acid (HNE-MA, 28.95 -Ág/g cre. vs. 16.55 -Ág/g cre., p value<0.01) concentrations than control children. Children who carried DRD4 GA/AA genotypes (rs752306) were less likely than those who carried the DRD4 GG genotype to have ADHD (odds ratio [OR]: 0.45, 95% CI: 0.24-0.84). The estimated value of the AP (attributable proportion due to interaction) was 0.59 (95% CI: 0.13-1.05), indicating that 59% of ADHD cases in DMP-exposed children with the DRD4 GG genotype were due to the gene-environment interaction. After adjustment for other covariates, children who carried the DRD4 GG genotype, had been exposed to high DMP levels (more than the median), and had high HNE-MA levels had a significantly increased risk for developing ADHD (OR = 11.74, 95% CI: 2.12-65.04).
Conclusion This study indicated a gene-environment interaction in the risk of ADHD in children. The association between DMP and ADHD in children might relate to the mechanism of lipid peroxidation. Dose-response relationships and the combined effects of OPs, oxidative stress, and genetic polymorphism on ADHD should not be neglected

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Eur J Endocrinol. 2017 Nov;177:R261-R273.
MECHANISMS IN ENDOCRINOLOGY: MATERNAL THYROID DYSFUNCTION DURING PREGNANCY AND BEHAVIOURAL AND PSYCHIATRIC DISORDERS OF CHILDREN: A SYSTEMATIC REVIEW.
Fetene DM, Betts KS, Alati R.
BACKGROUND: Maternal thyroid dysfunction during pregnancy may lead to persistent neurodevelopmental disorders in the offspring appearing in later life. This study aimed to review the available evidence concerning the relationship between maternal thyroid status during pregnancy and offspring behavioural and psychiatric disorders.
METHODS: Systematic electronic database searches were conducted using PubMed, Embase, PsycNET, Scopus, Google Scholar and Cochrane library. Studies including gestational thyroid dysfunction as the exposure and offspring behavioural and psychiatric disorders as the outcome were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed and, after thorough screening by two independent reviewers, 13 articles remained eligible for inclusion in this study.
RESULTS: Indicators of maternal thyroid dysfunction, including low and high thyroid hormone level and autoimmune thyroiditis, during early pregnancy, were found to be associated with several offspring behavioural and psychiatric disorders such as attention deficit hyperactivity disorder (ADHD), autism, pervasive developmental problems, externalising behaviour, in addition to epilepsy and seizure. The majority of associations were found with low maternal thyroid hormone level.
CONCLUSION: Maternal thyroid function during pregnancy, particularly hypothyroidism, is associated with behavioural and psychiatric disorders in children. Further studies are needed with a capacity to adjust for a fuller range of confounding factors

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Eur J Med Genet. 2017 Jul;60:374-79.
A CASE OF SPLENOMEGALY IN CBL SYNDROME.
Coe RR, McKinnon ML, Tarailo-Graovac M, et al.
INTRODUCTION: We present a child with unexplained splenomegaly to highlight this feature as a presenting sign of the RASopathy CBL syndrome and to draw attention to the power and utility of next generation genomic sequencing for providing rapid diagnosis and critical information to guide care in the pediatric clinical setting.
CLINICAL REPORT: A 7-year-old boy presented with unexplained splenomegaly, attention deficit hyperactivity disorder, mild learning difficulties, easy bruising, mild thrombocytopenia, and subtle dysmorphic

features. Extensive haematological testing including a bone marrow biopsy showed mild megaloblastoid erythropoiesis and borderline fibrosis. There were no haematological cytogenetic anomalies or other haematological pathology to explain the splenomegaly. Metabolic testing and chromosomal microarray were unremarkable. Trio whole-exome sequencing (WES) identified a pathogenic de novo heterozygous germline CBL variant (c.1111T > C, p.Y371H), previously reported to cause CBL syndrome and implicated in development of juvenile myelomonocytic leukemia (JMML).
DISCUSSION: CBL syndrome (more formally known as "Noonan-syndrome-like disorder with or without juvenile myelomonocytic leukemia") has overlapping features to Noonan syndrome with significant variability. CBL syndrome and other RASopathy disorders-including Noonan syndrome, neurofibromatosis 1, and Costello syndrome-are important to recognize as these are associated with a cancer-predisposition. CBL syndrome carries a very high risk for JMML, thus accurate diagnosis is of utmost importance. The diagnosis of CBL syndrome in this patient would not have been possible based on clinical features alone. Through WES, a specific genetic diagnosis was made, allowing for an optimized management and surveillance plan, illustrating the power of genomics in clinical practice

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Eur Child Adolesc Psychiatry. 2017;26:1155-64.

RISK FACTORS FOR COMORBID OPPOSITIONAL DEFIANT DISORDER IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Noordermeer SDS, Luman M, Weeda WD, et al.

Oppositional defiant disorder (ODD) is highly prevalent in attention-deficit/hyperactivity disorder (ADHD). Individuals with both ADHD and ODD (ADHD + ODD) show a considerably worse prognosis compared with individuals with either ADHD or ODD. Therefore, identification of risk factors for ADHD + ODD is essential and may contribute to the development of (early) preventive interventions. Participants were matched for age, gender, and ADHD-subtype (diagnostic groups), and did not differ in IQ. Predictors included pre- and perinatal risk factors (pregnancy duration, birth weight, maternal smoking during pregnancy), transgenerational factors (parental ADHD; parental warmth and criticism in diagnostic groups), and postnatal risk factors (parental socioeconomic status [SES], adverse life events, deviant peer affiliation). Three models were assessed, investigating risk factors for ADHD-only versus controls (N = 86), ADHD + ODD versus controls (N = 86), and ADHD + ODD versus ADHD-only (N = 90). Adverse life events and parental ADHD were risk factors for both ADHD + ODD and ADHD-only, and more adverse life events were an even stronger risk factor for comorbid ODD compared with ADHD-only. For ADHD + ODD, but not ADHD-only, parental criticism, deviant peer affiliation, and parental SES acted as risk factors. Maternal smoking during pregnancy acted as minor risk factor for ADHD-only, while higher birth weight acted as minor risk factor for ADHD + ODD. No effects of age were present. Findings emphasise the importance of these factors in the development of comorbid ODD. The identified risk factors may prove to be essential in preventive interventions for comorbid ODD in ADHD, highlighting the need for parent-focused interventions to take these factors into account

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Eur Child Adolesc Psychiatry. 2017;1-8.

PREDICTIVE VALUE OF DYSREGULATION PROFILE TRAJECTORIES IN CHILDHOOD FOR SYMPTOMS OF ADHD, ANXIETY AND DEPRESSION IN LATE ADOLESCENCE.

Wang B, Brueni LG, Isensee C, et al.

We examined whether there are certain dysregulation profile trajectories in childhood that may predict an elevated risk for mental disorders in later adolescence. Participants (N = 554) were drawn from a representative community sample of German children, 7ΓÇô11 years old, who were followed over four measurement points (baseline, 1, 2 and 6 years later). Dysregulation profile, derived from the parent report of the Strengths and Difficulties Questionnaire, was measured at the first three measurement points, while symptoms of attention deficit hyperactivity disorder (ADHD), anxiety and depression were assessed at the fourth measurement point. We used latent class growth analysis to investigate developmental trajectories in the development of the dysregulation profile. The predictive value of dysregulation profile trajectories for later

ADHD, anxiety and depression was examined by linear regression. For descriptive comparison, the predictive value of a single measurement (baseline) was calculated. Dysregulation profile was a stable trait during childhood. Boys and girls had similar levels of dysregulation profile over time. Two developmental subgroups were identified, namely the low dysregulation profile and the high dysregulation profile trajectory. The group membership in the high dysregulation profile trajectory (n = 102) was best predictive of later ADHD, regardless of an individualΓÇÖs gender and age. It explained 11% of the behavioural variance. For anxiety this was 8.7% and for depression 5.6%, including some gender effects. The single-point measurement was less predictive. An enduring high dysregulation profile in childhood showed some predictive value for psychological functioning 4 years later. Hence, it might be helpful in the preventive monitoring of children at risk

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Eur Child Adolesc Psychiatry. 2017;1-8.

A DOUBLE-BLIND PLACEBO-CONTROLLED RANDOMISED TRIAL OF OMEGA-3 SUPPLEMENTATION IN CHILDREN WITH MODERATE ADHD SYMPTOMS.

Cornu C, Mercier C, Ginhoux T, et al.

OBJECTIVE: Clinical trials and inconclusive meta-analyses have investigated the effects of omega-3 supplements in children with Attention-Deficit Hyperactivity Disorder (ADHD). We performed a randomised placebo-controlled trial to evaluate the efficacy of omega-3 fatty acids.

METHODS: Children aged 6-15 years with established diagnosis of ADHD were randomised 1:1 to receive either supplements containing docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) or a placebo for 3 months. Psychotropic or omega-3-containing treatments were not authorised during the study. The primary outcome was the change in the Attention-Deficit Hyperactivity Disorder Rating Scale version 4 (ADHD-RS-IV). Other outcomes included safety, lexical level (Alouette test), attention (Test of Attentional Performance for Children-KiTAP), anxiety (48-item Conners Parent Rating Scale-Revised-CPRS-R), and depression (Children's Depression Inventory-CDI).

RESULTS: Between 2009 and 2011, 162 children were included in five French child psychiatry centres. The mean age was 9.90 (SD 2.62) years and 78.4% were boys. The inclusion ADHD-RS-IV at was 37.31 (SD 8.40). The total ADHD-RS-IV score reduction was greater in the placebo group than in the DHA-EPA group: -19 (-26, -12) % and -9.7 (-16.6, -2.9) %, respectively, p = 0.039. The other components of the Conners score had a similar variation but the differences between groups were not significant. Two patients in the DHA-EPA group and none in the placebo group experienced a severe adverse event (hospitalisation for worsening ADHD symptoms).

CONCLUSION: This study did not show any beneficial effect of omega-3 supplement in children with mild ADHD symptoms.

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Eur Child Adolesc Psychiatry. 2017;1-14.

EFFECTIVENESS OF TIME-RELATED INTERVENTIONS IN CHILDREN WITH ADHD AGED 9□ÇÔ15 YEARS: A RANDOMIZED CONTROLLED STUDY.

Wennberg B, et al.

Specific problems with time and timing that affect daily routines, homework, school work, and social relations have been recognized in children with ADHD. The primary treatments for children with ADHD do not specifically focus on time-related difficulties. The aim of this randomized controlled study (RCT) was to investigate how multimodal interventions, consisting of training in time-processing ability (TPA) and compensation with time-assistive devices (TAD), affect TPA and daily time management (DTM) in children with ADHD and time difficulties, compared with only educational intervention. Thirty-eight children on stable medication for ADHD in the 9ΓÇô15-year age range were randomly allocated to an intervention or a control group. The children’s TPA was measured with a structured assessment (KaTid), and the children’s DTM was rated by a parent questionnaire (Time-Parent scale) and by children’s self-reporting (Time-Self-rating). The intervention consisted of time-skill training and compensation with TAD. Data were analysed for differences

in TPA and in DTM between the control and intervention groups in the 24-week follow-up. Children in the intervention group increased their TPA significantly (p = 0.019) more compared to the control group. The largest increase was in orientation to time. In addition, the parents in the intervention group rated their childrenΓÇÖs DTM as significantly (p = 0.01) improved compared with the parents in the control group. According to the children, their DTM was not significantly changed. In conclusion, a multimodal intervention consisting of time-skill training and TAD improved TPA and DTM in children with ADHD aged 9-15 years

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Eur J Paediatr Neurol. 2017.

MOTOR DYSFUNCTION IN NF1: MEDIATED BY ATTENTION DEFICIT OR INHERENT TO THE DISORDER?

Haas-Lude K, Heimg+ñrtner M, Winter S, et al.

Aim: Attention deficit and compromised motor skills are both prevalent in Neurofibromatosis type 1 (NF1), but the relationship is unclear. We investigated motor function in children with NF1 and in children with Attention Deficit/Hyperactivity Disorder (ADHD), and explored if, in patients with NF1, attention deficit influences motor performance.

Methods: Motor performance was measured using the Movement Assessment Battery for Children (M-ABC) in 71 children (26 with NF1 plus ADHD, 14 with NF1 without ADHD, and 31 with ADHD without NF1) aged 6-12 years.

Results: There was a significant effect of group on motor performance. Both NF1 groups scored below children with ADHD without NF1. Attention performance mediated motor performance in children with ADHD without NF1, but not in children with NF1.

Conclusions: Motor function is not mediated by attention performance in children with NF1. While in ADHD, attention deficit influences motor performance, motor problems in NF1 seem to be independent from attention deficit. This argues for different pathomechanisms in these two groups of developmental disorders

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Genet Epidemiol. 2016;40:636.

STRUCTURAL BRAIN IMAGING (MRI) CASE-CONTROL STUDY OF CORTICAL THICKNESS AND SURFACE AREA IN CHILDREN AFFECTED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Fotopoulos N, Devenyi GA, Chakravarty MM, et al.

MRI studies have attempted to elucidate the structural brain differences between children with and without ADHD. Findings in the literature are conflicting; some studies report morphological differences although others do not. Evidence has emerged that motion artifacts present on images can underestimate measurements. Hyperactivity is one of the main symptoms of ADHD; therefore, positive results must be interpreted with caution. Moreover, an unexplored venue of imaging is studying effects of environmental risk factors on brain morphology in children with ADHD. Our primary objective was to conduct a structural MRI study that compares the cortical thickness and surface area in children with ADHD and controls. A second objective was to explore the effect of maternal smoking during pregnancy on brain morphology in children with ADHD. A third objec-tive is to investigate the effect of polygenic risk scores of candidate ADHD genes on brain morphology. ADHD cases were recruited from a double-blind placebo control clinical trial from the ADHD clinic. All subjects were scanned with a 3T MRI scanner at the CIC at the Douglas Institute. General linear modeling was performed using CIVET 1.1.12. Cortical thickness and surface area were used as key outcome measures. Analysis showed that age and gender had significant effects on cortical thickness and surface area in both groups (n=103). Secondary analysis revealed no statistically significant difference in cortical thickness or surface area between children with ADHD and controls. However, a significant increase in surface area was observed in children with ADHD who were exposed to maternal smoking during pregnancy

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Genet Epidemiol. 2016;40:634.

SNAP-25 (RS1051312) GENE MIGHT BE ASSOCIATED WITH PLACEBO RESPONSE IN CHILDREN WITH ADHD.

Fageera W, Grizenko N, Sengupta SM, et al.

The idea that Placebo Response (PR) is not necessarily in an individual's head, but rather genes, has recently received more attention in the scientific community. Different neurotrans-mitters have been associated with PR and genetic variations in the brain's neurotransmitter pathways could modify placebo effects. Synaptosomal-associated protein 25 (SNAP25) is an essential component for synaptic vesicle mediated release of neurotransmitters. Therefore, genetic variations that might affect SNAP25 function have been suspected in the patho-physiology of ADHD. Making SNAP25 a good candidate for study its effect on PR. Here, we tested the association of rs1051312, a polymorphism in the 3ΓÇ¦ UTR of SNAP25, with response to placebo in children with ADHD. 378 children with ADHD (6-12 years) participated in a randomized, double-blind, placebo-controlled crossover trial and geno-typed for rs1051312 polymorphism. PR was calculated as the difference in Conners' (parents and teachers) scores at baseline and during placebo week. Repeated measures analysis of variance revealed a significant interaction between rs1051312 and response to placebo (p=0.022) according to teachers' assessments. Patients with C/C genotype were significantly more responsive to placebo. Patients with C/T and T/T genotypes barely showed any improvement after giving placebo. However, after administering MPH, all genotype groups tend to similarly respond to active medication. These findings provide evidence for the implication SNAP25 in placebo response. To the best of our knowledge, this is the first study to report an association between SNAP25 and placebo response

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Genet Epidemiol. 2016;40:634-35.

USING BEHAVIORAL DYNAMIC APPROACHES TO TEST FOR GENE-BY-GENE INTERACTION IN MODULATING ADHD BEHAVIORS.

Fageera W, Grizenko N, Sengupta SM, et al.

Dopamine (DA) plays an important role in the pathogene-sis of ADHD. Genes that regulate DA at consecutive junctures of its synaptic activity, such as COMT and DRD3 may interact to modulate ADHD behaviors. Using pharmacological probes that affect synaptic DA concentration (such as methylphenidate and placebo) may increase our capacity to reveal the effect of these genes on ADHD behaviors. We aim to test for DRD3 (ser-9-gly) by COMT (Val158Met) gene/gene interaction in modulating ADHD behaviors using a pharmacological challenge with methylphenidate and placebo. 391 children with ADHD were included in this study. Parents and teachers were asked to evaluate child's behavior at baseline, placebo, and MPH weeks using the Conners' scale. Association between genotypes and ADHD behavior was tested using repeated measure ANOVA, the two genes were the between-subject factors and the behaviors under the three Experimental Conditions (EC), were the within-subject factor. A 3-way interaction (DRD3 COMT EC) was revealed with teachers assessment (p=0.001). COM EC two-way interaction (but not DRD3ΓêùEC) was also significant; with the Met/Met genotype group having lower scores at baseline and on placebo, but the difference between groups disappeared on MPH. Remarkably, when children where stratified according to their COMT genotypes, statistically significant and biologically meaningful effects of the DRD3 genotypes were detected. In conclusion, using a combination of methodological tools (pharmacological probes, large sample size, and selecting genes consecutively implicated in synaptic DA activity) might be essential to better understand the role of candidate genes in complex behaviors

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Int J Neuropsychopharmacol. 2017;20:219-27.

DOES METHYLPHENIDATE REDUCE TESTOSTERONE LEVELS IN HUMANS? A PROSPECTIVE STUDY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang L-J, Chou M-C, Chou W-J, et al.

Background: Animal studies and case reports have suggested that methylphenidate exerts adverse effects on gonadal hormones. This study aimed to determine whether methylphenidate alters testosterone levels in

children with attention-deficit/hyperactivity disorder through comparison of those with or without methylphenidate treatment.
Methods: This 4-week, nonrandomized, prospective study conducted in Taiwan included 203 attention-deficit/hyperactivity disorder patients with a mean age of 8.7 years (boys: 75.8%). After the initial recruitment, 137 received daily methylphenidate treatment (medicated group) and 66 were assessed through naturalistic observation (nonmedicated group). The saliva samples of attention-deficit/hyperactivity disorder patients were used to quantify testosterone levels at baseline and the endpoint by using the chemiluminescence immunoassay. At the 4th week, 86 patients in the medicated group and 46 patients in the nonmedicated group were eligible for statistical analyses.
Results: During the study period, salivary testosterone levels did not significantly change in the medicated group (P=.389) or in the nonmedicated group (P=.488). After correction for the potential confounding effects of age and sex, salivary testosterone levels still remained unchanged in the medicated and nonmedicated groups during the 4-week follow-up. In the medicated group, changes in salivary testosterone levels over 4 weeks were not significantly correlated with the methylphenidate daily dose (mean daily dose: 18.1 mg).
Conclusions: Findings suggest that short-term treatment with methylphenidate at usual doses does not significantly alter salivary testosterone levels in attention-deficit/hyperactivity disorder patients. Future studies should clarify whether long-term methylphenidate treatment disrupts testosterone production as well as the function of the reproductive system

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Int J Psychiatry Clin Pract. 2017;1-6.
THE EFFECT OF METHYLPHENIDATE TREATMENT ON SUSPICIOUSNESS IN CHILDREN WITH ADHD ALONE OR COMORBID WITH ODD.
Golubchik P, Weizman A.
Objective: To assess the level of the suspiciousness in children with attention deficit/hyperactivity disorder (ADHD) and comorbid oppositional defiant disorder (ODD) in comparison to ADHD alone and the response of suspiciousness symptoms to methylphenidate (MPH) treatment.
Methods: In this open-label comparative study, children with DSM-IV-TR ADHD, aged 8-18 years, with (N=30) or without (N=30) ODD received MPH treatment for 12 weeks. The severity of ODD symptoms was assessed by the Kiddie Schedule for Affective Disorders and Schizophrenia. The severity of ADHD symptoms was assessed by the ADHD-Rating-Scale-IV and suspiciousness was assessed at baseline and at endpoint by a scale designed especially for assessment of suspiciousness and named Suspiciousness Rating Scale (SRS).
Results: Significant reductions in SRS scores were detected in both groups following MPH treatment (before and after: p= .0012 and p=.0273, respectively). Only in the ADHD/ODD group a significant correlation was found between the rate of improvement in ADHD, as assessed by the ADHD-RS, and the reduction in suspiciousness, as assessed by the SRS (Spearman r=0.48, p=.0066).
Conclusions: In addition to the beneficial effect of MPH treatment on ADHD and ODD symptoms it also diminishes suspiciousness. However, due to the small sample size further studies are needed to confirm the present results

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International Journal of Research in Ayurveda and Pharmacy. 2017;8:82-86.
EFFECTIVENESS OF INTERVENTION PACKAGE ON BEHAVIOUR OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN NORTH TAMILNADU, INDIA.
Srignanasoundari E, Vijayalakshmi S, Vijayaraghavan R, et al.
Attention Deficit hyperactivity disorder is a common childhood disorder characterized by inattention, hyperactivity and impulsivity. The average age of ADHD has generally been diagnosed in children between 6-12 years. Aim of the study is to evaluate the effectiveness of intervention package among ADHD children. A Quasi experimental pre-test and post-test research design had been used. 100 ADHD children had been selected from two special schools with total enumerative sampling technique. Pre-test and post-test

behaviour of ADHD children had been assessed by Modified Conner's parent and teacher rating scale. The comparison of pre-test and post-test was calculated by Wilcoxon singed rank test. The post-test mean score was 65.98 and 't' test 20.175 which was highly significant at $p < 0.005$. The study reported that the intervention package was highly effective and improved their attention span, concentration and resulting in reduced hyperactivity level among ADHD children

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J Pediatr Hematol Oncol. 2017 Apr;39:174-78.

THE BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION (BRIEF) TO IDENTIFY PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) SURVIVORS AT RISK FOR NEUROCOGNITIVE IMPAIRMENT.

Viola A, Balsamo L, Neglia JP, et al .

Neurocognitive problems, including executive dysfunction, are potential late effects of pediatric acute lymphoblastic leukemia treatment. Surveillance for neurocognitive impairment in a timely and efficient manner is imperative to ongoing clinical care. We sought to determine if the Behavior Rating Inventory of Executive Function (BRIEF) Parent Form identified leukemia survivors with cognitive impairment. In this 28-site cross-sectional study, parents of 256 children, a mean of 8.9+/-2.2 years after treatment for standard-risk precursor-B acute lymphoblastic leukemia and in first remission, completed the BRIEF. We used a multivariate logistic regression to calculate the association between elevated scores on 3 composite BRIEF indices (Behavioral Regulation Index, Metacognition Index, Global Executive Composite [GEC]) and special education and attention-deficit/hyperactivity disorder (ADHD) outcomes. All BRIEF index scores were significantly associated with receipt of special education services or ADHD. The BRI was most strongly associated with ADHD (odds ratios=4.33; 95% confidence interval, 1.72-10.9). The GEC was most strongly associated with ADHD (odds ratios=4.46; 95% confidence interval, 1.77-11.22). Elevated scores on the BRIEF GEC were associated with low sensitivity (24.1 to 39.1) for detecting the outcomes but better specificity (range, 87.7 to 89.3). These results suggest that the parent-completed BRIEF is associated with clinical outcomes but is not a sensitive tool to identify leukemia survivors that require a comprehensive neuropsychological assessment

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J Policy Anal Manage. 2017;36:790-827.

CHILD HEALTH IN ELEMENTARY SCHOOL FOLLOWING CALIFORNIA'S PAID FAMILY LEAVE PROGRAM.

Lichtman-Sadot S, Bell NP.

We evaluate changes in elementary school children health outcomes following the introduction of California's Paid Family Leave (PFL) program, which provided parents with paid time off following the birth of a child. Our health outcomes--overweight, ADHD, and hearing-related problems--are characterized by diagnosis rates that only pick up during early elementary school. Moreover, our health outcomes have been found to be negatively linked with many potential implications of extended maternity leave--increased breastfeeding, prompt medical checkups at infancy, reduced prenatal stress, and reduced non-parental care during infancy. Using the Early Childhood Longitudinal Studies (ECLS) within a difference-in-differences framework, our results suggest improvements in health outcomes among California elementary school children following PFL's introduction. Furthermore, the improvements are driven by children from less advantaged backgrounds, which is consistent with the notion that California's PFL had the greatest effect on leave-taking duration after childbirth mostly for less advantaged mothers who previously could not afford to take unpaid leave

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JAMA Psychiatry. 2017 Oct;74:1048-55.

ASSOCIATION OF RISK OF SUICIDE ATTEMPTS WITH METHYLPHENIDATE TREATMENT.

Man KKC, Coghill D, Chan EW, et al.

Importance: Patients with attention-deficit/hyperactivity disorder (ADHD) are at an increased risk of attempting suicide. Stimulants, such as methylphenidate hydrochloride, are the most common treatment for ADHD, but the association between their therapeutic use and suicide is unclear.

Objective: To investigate the association between methylphenidate and the risk of suicide attempts.

Design, Setting, and Participants: A population-based, electronic medical records database from the Hong Kong Clinical Data Analysis & Reporting System was used to identify 25 629 individuals aged 6 to 25 years who were treated with methylphenidate between January 1, 2001, and December 31, 2015. Those who had attempted suicide were included in the analysis. A self-controlled case series design was used to control for time-invariant characteristics of the patients.

Main Outcomes and Measures: Relative incidence of suicide attempt during periods when patients were exposed to methylphenidate compared with nonexposed periods.

Results: Among 25 629 patients with methylphenidate prescriptions, 154 had their first recorded suicide attempt within the study period; of these individuals, 111 (72.1%) were male; mean (SD) age at baseline was 7.15 (2.19) years. The overall incidence of suicide attempts during methylphenidate treatment was 9.27 per 10 000 patient-years. An increased risk of suicide attempts was detected during the 90-day period before methylphenidate was initiated, with an incidence rate ratio (IRR) of 6.55 (95% CI, 3.37-12.72). The IRR remained elevated during the first 90 days of treatment (IRR, 3.91; 95% CI, 1.62-9.42) before returning to baseline levels during ongoing treatment (IRR, 1.35; 95% CI, 0.77-2.38). When the risk during the first 90 days of treatment was compared with the 90 days preceding first treatment, the incidence of suicide attempts was not elevated (IRR, 0.78; 95% CI, 0.26-2.35).

Conclusions and Relevance: The incidence of suicide attempts was higher in the period immediately before the start of methylphenidate treatment. The risk remained elevated immediately after the start of methylphenidate treatment and returned to baseline levels during continuation of methylphenidate treatment. The observed higher risk of suicide attempts before treatment may reflect emerging psychiatric symptoms that trigger medical consultations that result in a decision to begin ADHD treatment. Therefore, this study's results do not support a causal association between methylphenidate treatment and suicide attempts

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JBI Database of Systematic Reviews and Implementation Reports. 2017;15:2265-69.

NUTRITIONAL INTERVENTIONS TO REDUCE SYMPTOMS IN CHILDREN AND ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SCOPING REVIEW PROTOCOL.

Pedersen P, Bjerrum M, Larsen P, et al.

Review question/objective: The objective of this scoping review is to examine and map reported nutritional interventions and their outcomes in relieving symptoms of attention deficit hyperactivity disorder (ADHD) in the daily lives of children and adults. A further objective is to determine if experiences of people diagnosed with ADHD, their relatives or staff in being on a diet or having to eat or avoid eating specific food items have been reported in the existing literature. Specifically the scoping review questions are:1. What nutritional interventions have been tested in children or adults with ADHD in order to reduce ADHD symptoms? 2. Have any experiences of people with ADHD, their relatives and/or staff in changing or sticking to a strict diet been reported?

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J Abnorm Child Psychol. 2017 Oct;45:1311-24.

NEURAL CORRELATES OF EMOTION REACTIVITY AND REGULATION IN YOUNG CHILDREN WITH ADHD SYMPTOMS.

Lugo-Candelas C, Flegenheimer C, Harvey E, et al.

Emotion reactivity and regulation are frequently impaired in individuals with attention-deficit/hyperactivity disorder (ADHD), yet few studies have examined these factors in young children with ADHD, and none have explored the neural correlates of emotion reactivity and regulation in this group through event-related

potentials (ERPs). Children aged 4 to 7 with (n = 25; 18 boys) and without (n = 29; 20 boys) ADHD symptoms completed an attention task composed of four blocks: baseline, frustration, suppression, and recovery. In the frustration and suppression blocks, negative affect was induced by false negative feedback. During the suppression block, children were asked to suppress emotional expressions. Neural reactivity, assessed via the N2 and P3 components, suggests that children with ADHD symptoms processed the emotional induction differently than typically developing (TD) children. TD children demonstrated decreased N2 and increased P3 amplitudes at frontal and frontocentral regions across task conditions whereas children with ADHD symptoms showed relatively stable N2 and P3 amplitudes. This pattern suggests that young children with ADHD symptoms are not as effective as their TD peers in modulating attention allocation and cognitive control in emotionally laden situations. The present study underscores that emotional contexts may exacerbate attentional control deficits in young children with ADHD symptoms

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J Abnorm Child Psychol. 2017 Oct;45:1325-37.

CORRESPONDENCE BETWEEN HEART RATE VARIABILITY AND EMOTION DYSREGULATION IN CHILDREN, INCLUDING CHILDREN WITH ADHD.

Bunford N, Evans SW, Zoccola PM, et al.

Youth and adults with Attention-Deficit/Hyperactivity Disorder (ADHD) experience academic and social impairment and engage in risky behaviors. Emotion dysregulation (ED) is associated with ADHD and may contribute to these impairments and behaviors. Although many measures of ED exist, little is known about the physiological bases of ED, in the context of ADHD. In a large sample of children (Mage = 9.01 years; 62% male) with (n = 48) and without (n = 56) ADHD, we examined (1) the correspondence between parent-reported ED and heart rate variability (HRV) – a psychophysiological marker of parasympathetic engagement and (2) whether parent-reported ED is predicted by HRV above and beyond ADHD. For both aims, we tested both dichotomous and continuous indices of parent-reported ED. Results indicated (1) a dichotomous index of parent-reported emotion regulation was associated with HRV and (2) this index was predicted by HRV above and beyond ADHD. Together, findings indicate that the correspondence between ED and HRV depends on the specific manifestation of ED that is considered (emotion regulation vs. lability/negativity) and the way in which ED is conceptualized (dichotomous vs. continuous)

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J Abnorm Child Psychol. 2017 Oct;45:1297-310.

EMOTIONAL UNDERSTANDING, REACTIVITY, AND REGULATION IN YOUNG CHILDREN WITH ADHD SYMPTOMS.

Lugo-Candelas C, Flegenheimer C, McDermott JM, et al.

The goal of the present study was to examine whether young children with attention-deficit/hyperactivity disorder (ADHD) symptoms experience difficulties with emotional understanding, reactivity, and regulation. Participants were 64 children, 4 to 7 years of age (43 boys, 20 girls), 29 with ADHD symptoms and 34 typically developing children. Children completed an emotion matching task and parents reported on child lability and emotional regulation. Children also completed a frustrating computer task. Facial expressions of emotions were coded and children self reported affect during the task. Parent reports indicated heightened lability and impaired emotional regulation abilities in children with ADHD symptoms. Compared to typically developing children, children with ADHD symptoms demonstrated emotional understanding impairments in matching similar expressions and matching expressions to situations, but not in producing expression labels or matching expression labels to images. Self-reports of negative affect during the frustration task indicated that children with ADHD symptoms experienced more difficulty with emotional regulation than typically developing children. Behavioral observations during the frustration task indicated that the two groups demonstrated a similar increase in expressed negative affect during frustration; however, children with ADHD symptoms showed higher levels of negative affect across all four conditions of the task. This study suggests that the

deficits documented in older children with ADHD are already evident during the preschool years, and distinct from the developmentally appropriate emotional dysregulation seen in typically developing preschoolers

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J Abnorm Child Psychol. 2017 Oct;45:1355-67.

PARASYMPATHETIC NERVOUS SYSTEM REACTIVITY MODERATES ASSOCIATIONS BETWEEN CHILDREN'S EXECUTIVE FUNCTIONING AND SOCIAL AND ACADEMIC COMPETENCE.

McQuade JD, Penzel TE, Silk JS, et al.

This study examined whether children with poor executive functioning (EF) evidenced less social and academic impairments, compared to other children, if they demonstrated adaptive parasympathetic nervous system (PNS) regulation during experiences of failure. Participants with and without clinical elevations in ADHD symptoms (N = 61; 9–13 years; 48% male; 85% Caucasian) were administered a battery of EF tests and completed manipulated social and cognitive failure tasks. While participants completed failure tasks, respiratory sinus arrhythmia reactivity (RSA-R) was measured as an indicator of PNS reactivity. Children's social and academic impairment in daily life was assessed based on parent and teacher report on multiple measures. RSA-R during social failure moderated the association between poor EF and adult-rated social impairment and RSA-R during cognitive failure moderated the association between poor EF and adult-rated academic impairment. Simple effects indicated that poor EF was significantly associated with impairment when children demonstrated RSA activation (increased PNS activity) but not when children demonstrated RSA withdrawal (decreases in PNS activity). Domain-crossed models (e.g., reactivity to social failure predicting academic impairment) were not significant, suggesting that the moderating effect of RSA-R was domain-specific. Results suggest that not all children with poor EF evidence social and academic impairment; RSA withdrawal during experiences of failure may be protective specifically for children with impaired EF skills

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J Abnorm Child Psychol. 2017 Oct;45:1339-53.

INVESTIGATING THE IMPACT OF COGNITIVE LOAD AND MOTIVATION ON RESPONSE CONTROL IN RELATION TO DELAY DISCOUNTING IN CHILDREN WITH ADHD.

Martinelli MK, Mostofsky SH, Rosch KS.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by deficits in impulse control across a range of behaviors, from simple actions to those involving complex decision-making (e.g., preference for smaller-sooner versus larger later rewards). This study investigated whether changes in motor response control with increased cognitive load and motivational contingencies are associated with decision-making in the form of delay discounting among 8–12 year old children with and without ADHD. Children with ADHD (n = 26; 8 girls) and typically developing controls (n = 40; 11 girls) completed a standard go/no-go (GNG) task, a GNG task with motivational contingencies, a GNG task with increased cognitive load, and two measures of delay discounting: a real-time task in which the delays and immediately consumable rewards are experienced in real-time, and a classic task involving choices about money at longer delays. Children with ADHD, particularly girls, exhibited greater delay discounting than controls during the real-time discounting task, whereas diagnostic groups did not significantly differ on the classic discounting task. The effect of cognitive load on response control was uniquely associated with greater discounting on the real-time task for children with ADHD, but not for control children. The effect of motivational contingencies on response control was not significantly associated with delay discounting for either diagnostic group. The findings from this study help to inform our understanding of the factors that influence deficient self-control in ADHD, suggesting that impairments in cognitive control may contribute to greater delay discounting in ADHD

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J Adolesc. 2017;61:40-49.

THE ROLE OF THE MOTHER-CHILD RELATIONSHIP IN THE ROUTE FROM CHILD ADHD TO ADOLESCENT SYMPTOMS OF DEPRESSED MOOD.

Giannotta F, Rydell A-M.

We attempt to explain the co-variation between ADHD and symptoms of depressed mood, focusing on the family context and testing whether the mother-child relationship mediates or moderates the link between child ADHD and youth depressed mood symptoms. In a longitudinal study, we used mother and youth reports for 596 Swedish youth, 50% boys, from a community sample at 10, 15, and 18 years of age. The results did not support the mediation hypothesis. Only one moderation effect was found. Mother-child conflicts in mid-adolescence, as rated by mothers, increased symptoms of depressed mood symptoms in late adolescent only for youth with high levels of hyperactivity symptoms. However, depressed mood symptoms at age 18 were predicted by low mother-child involvement in mid-adolescence, over and above the effects of inattention symptoms. This latter finding was consistent across mother and youth ratings of the relationship. Implications of these results are discussed

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J Autism Dev Disord. 2017;1-8.

PARENT STRESS IN A RANDOMIZED CLINICAL TRIAL OF ATOMOXETINE AND PARENT TRAINING FOR CHILDREN WITH AUTISM SPECTRUM DISORDER.

Lecavalier L, Pan X, Smith T, et al.

We previously reported a 2 +ù 2 randomized clinical trial of atomoxetine (ATX) and parent training (PT) for attention deficit hyperactivity disorder (ADHD) symptoms and behavioral noncompliance in 128 children with autism spectrum disorder, ages 5ΓÇô14 years. Children were randomized to one of four conditions: ATX alone, placebo alone, ATX + PT, or PT + placebo. Both ATX and PT improved some indices of ADHD and behavioral compliance. In this report, we describe parent stress over time and across conditions. All four treatments improved parent self-rated stress from baseline to week 10. However, there were no statistically significant differences between treatment groups. Significantly more improvement in parent stress scores was observed for clinical responders than non-responders. ClinicalTrials.gov Title: Atomoxetine, Placebo and Parent Management Training in Autism (Strattera) ClinicalTrials.gov Identifier: NCT00844753

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Journal of Behavioral Addictions. 2017;6:345-53.

ASSOCIATION BETWEEN CHILDHOOD AND ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN KOREAN YOUNG ADULTS WITH INTERNET ADDICTION.

Kim D, Lee D, Lee J, et al.

Background and aims: Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric comorbidities of Internet addiction (IA); however, the possible mechanisms that contribute to this high comorbidity are still under debate. This study aims to analyze these possible mechanisms by comparing the effect of IA severity and childhood ADHD on inattention, hyperactivity, and impulsivity in young adults with IA. We hypothesized that IA might have associations with ADHD-like cognitive and behavior symptoms aside from childhood ADHD.

Methods: Study participants consisted of 61 young male adults. Participants were administered a structured interview. The severity of IA, childhood and current ADHD symptoms, and psychiatry comorbid symptoms were assessed through self-rating scales. The associations between the severity of IA and ADHD symptoms were examined through hierarchical regression analyses.

Results: Hierarchical regression analyses showed that the severity of IA significantly predicted most dimensions of ADHD symptoms. By contrast, childhood ADHD predicted only one dimension.

Discussion: The high comorbidity of inattention and hyperactivity symptoms in IA should not solely be accounted by an independent ADHD disorder but should consider the possibility of cognitive symptoms related to IA. Functional and structural brain abnormalities associated with excessive and pathologic Internet

usage might be related to these ADHD-like symptoms. Conclusion: Inattention and hyperactivity in young adults with IA are more significantly associated with the severity of IA than that of childhood ADHD

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J Child Adolesc Ment Health. 2017;29:137-45.

CHALLENGES EXPERIENCED BY PARENTS LIVING WITH A CHILD WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Mofokeng M, van der Wath AE.

Objective: The aim of this South African study was to explore parentsΓÇÖ experiences of living with a child with attention deficit hyperactivity disorder (ADHD).

Methods: A qualitative research design was followed. Purposive sampling was used to select ten parents living with children diagnosed with ADHD receiving outpatient treatment at a psychiatric facility. Data, collected through unstructured individual interviews, were analysed using open coding. Measures to ensure trustworthiness and ethical research practices were applied.

Results: Five themes emerged: burden of care; emotional effects; social effects; impact of the educational challenges, and attempts to cope with the burden of care.

Conclusion: Parents living with a child with ADHD experience stress as they struggle to cope with the child's symptoms amidst the stigmatising attitudes from family and community members. Parents experience burdensome emotions and impaired social and occupational functioning. Health care practitioners need to take note of the challenges inherent to parenting a child with ADHD in order to provide multi-disciplinary interventions aimed at empowering and supporting parents

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J Child Adolesc Psychopharmacol. 2017;27:700-07.

LONG-TERM, OPEN-LABEL, SAFETY STUDY OF EDIVOXETINE MONOTHERAPY IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Nery ESM, Bangs M, Liu P, et al.

Objective: The purpose of this study was to assess the long-term safety and tolerability of edivoxetine, a selective norepinephrine reuptake inhibitor, which was being developed as monotherapy in pediatric attention-deficit/hyperactivity disorder (ADHD).

Methods: This was an open-label study of edivoxetine once daily dosing (0.1-0.3 mg/kg) as treatment for ADHD in children (6-11 years) and adolescents (12-17 years) to assess safety for up to 5 years. The safety assessments included the incidence of adverse events, vital signs, electrocardiograms, laboratory tests, percentile changes in weight, height, and body mass index, and Tanner staging. Efficacy of treatment with edivoxetine was also assessed using the Attention-Deficit/Hyperactivity Disorder Rating Scale-Version IV-Parent Reported: Investigator Scored (ADHDRS-IV) and Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S).

Results: A total of 267 children and adolescents were enrolled and 20 completed the 5-year study. Most of the participants were male (70.4%) and white (67.4%), and the mean age was 11.6 years. Two hundred three participants (76.9%; N = 264) experienced at least one adverse event. Treatment-emergent adverse events reported in >10% of participants were headache, vomiting, nausea, and upper respiratory tract infection. Serious adverse events (SAEs) were reported by seven participants (2.7%) during study treatment periods, and one participant was diagnosed with suspect epilepsy during the follow-up period after discontinuation of edivoxetine.

Conclusion: Long-term open-label treatment with edivoxetine as monotherapy in children and adolescents with ADHD revealed a safety profile that was consistent with its pharmacological effects on norepinephrine transmission and with that reported in short-term studies of edivoxetine. The study was terminated early due to slow enrollment and the very low number of 5-year completers. Lilly is not proceeding with further development of edivoxetine, as announced in 2013

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J Child Adolesc Psychopharmacol. 2017;27:715-22.

EARLY MORNING FUNCTIONAL IMPAIRMENTS IN STIMULANT-TREATED CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER VERSUS CONTROLS: IMPACT ON THE FAMILY.

Faraone SV, Schachar RJ, Barkley RA, et al.

Objective: Children with attention-deficit/hyperactivity disorder (ADHD) frequently manifest early morning functional (EMF) impairments before school. We conducted a quantitative research survey to assess the impact of these EMF impairments on the family unit (caregiver, spouse/partner, and siblings).

Study Design: We developed an online survey questionnaire to collect data from 300 primary caregivers of children with ADHD and 50 primary caregivers of children who did not have ADHD.

Results: Although the ADHD children we surveyed were currently treated with stable doses of stimulants as their primary ADHD medication for at least 3 months, their parents reported high levels of EMF impairments in the child, which had a substantial negative effect on the emotional well-being of parents, on parents' functioning during the early morning routine, and on the level of conflict with siblings. The impact of EMF impairments on family functioning was mediated by the severity of the index child's impairments.

Conclusions: EMF impairments exert a pervasive and significantly negative emotional and functional burden on not only the primary caregiver but also on the spouse/partner and siblings. This work suggests that adequate ADHD symptom control during the early morning period may be an unmet need for school-age children with ADHD being treated with stimulants. More work is needed to confirm this finding and determine the degree to which symptom control at other times of day is also an unmet need

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J Child Adolesc Psychopharmacol. 2017;27:741-46.

HOUSEHOLD DIVERSION OF PRESCRIPTION STIMULANTS: MEDICATION MISUSE BY PARENTS OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Pham T, Milanaik R, Kaplan A, et al.

Objectives: The primary objective of this study is to investigate household diversion of stimulant medication. Secondary objectives are to examine clinical/demographic predictors of diversion, types of formulations diverted, exposure to household diversion in the media, and storage of prescription stimulants within households.

Methods: Questionnaires were completed by 180 parents of youth who were currently taking stimulant medication for treatment of attention-deficit/hyperactivity disorder (ADHD). Parents were asked whether they or another adult in the home had ever taken their child's stimulant medication or given one child's stimulant medication to another child in the home. Additionally, data regarding demographics, parental ADHD (diagnosed or suspected), past suspicions of missing medication, and medication storage were also collected. Responses were compared using Pearson's chi-squared test with Yates' continuity correction.

Results: Sixteen percent of parents reported diversion of stimulant medication to another household member, with the majority admitting to taking the medication themselves. Another 13% had been tempted to illicitly self-administer their child's medication. Parents with suspected or diagnosed ADHD showed greater risk of self-administration or temptation to do so, compared to parents without (33% vs. 17%, $p = 0.01$). The majority of parents (71%) stored prescription stimulants "in plain sight," or "out of sight but available to all."

Conclusion: Although previous research has focused on peer diversion among adolescents and young adults, clinicians must be vigilant for the possibility of diversion by parents of children treated with stimulant medication

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J Child Adolesc Psychopharmacol. 2017;27:747-54.

PREDICTORS OF LONG-TERM RISKY DRIVING BEHAVIOR IN THE MULTIMODAL TREATMENT STUDY OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Johnson JA, Jakubovski E, Reed MO, et al.

Objective: This study examines predictors of later risky driving behavior in children with attention-deficit/hyperactivity disorder (ADHD).

Methods: Stepwise logistic regression and receiver operating characteristic (ROC) analysis were used to explore baseline predictors of risky driving behavior for adolescents who completed the 8-year follow-up assessment in the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA).
Results: Stepwise logistic regression analysis explained 19% of the total variance in risky driving behavior. Increased likelihood of risky driving behavior was associated with parental history of conduct disorder, low parental monitoring and supervision, and increased age. ROC analysis identified discriminative predictors for adolescents older and younger than 16 years of age at follow-up. The most discriminative predictors of later risky driving behavior were parental stress at baseline (for children 16 years or older) and increased child-rated parental protectiveness (for children less than 16 years old).
Conclusion: Risky driving behavior was significantly predicted by baseline characteristics for the MTA cohort. Aspects of parenting behavior (or the child's perception of them), including parental stress levels, parental protectiveness, and parental levels of monitoring and supervision, were most informative in predicting these outcomes. Our results suggest that interventions to reduce high-risk behaviors in these high-risk children with ADHD might involve targeted parenting interventions

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J Child Adolesc Psychopharmacol. 2017;27:755-56.
PILOT DATA SUPPORTING OMEGA-3 FATTY ACIDS SUPPLEMENTATION IN MEDICATED CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND DEFICITS IN EMOTIONAL SELF-REGULATION.
Wilens TE, Carrellas NW, Zulauf C, et al.

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J Child Adolesc Psychopharmacol. 2017;27:723-30.
WEIGHT, HEIGHT, AND BODY MASS INDEX IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATED WITH METHYLPHENIDATE.
Dez-Suírez A, Vallejo-Valdivielso M, et al.
Objective: To describe the methylphenidate (MPH) effects on weight, height, and body mass index (BMI) in a Spanish sample diagnosed with attention-deficit/hyperactivity disorder (ADHD).
Methods: Patients (6-18 years) diagnosed with ADHD treated at our Unit with MPH in the last 10 years were included in an observational longitudinal study. Weight, height, and BMI Z scores were measured at baseline and at last follow-up.
Results: Three hundred forty-two patients (mean [standard deviation] age: 10.7 [3.8] years, 80% males) were included. Mean dose was 1.25 (0.40) mg/(kg-Àd). After 27 (14-41) months taking MPH, weight and BMI standard deviation score (SDS) were reduced by treatment (baseline weight-SDS: 0.34 [1.22], follow-up weight-SDS: -0.06 [1.38], t-test $p < 0.001$; baseline BMI-SDS: 0.35 [1.10], and follow-up BMI-SDS [SDS]: -0.23 [1.08], t-test $p < 0.001$). In the whole sample, no differences in height before and after treatment were observed. However, considering only the group of patients who were children 6-12 years (68.6%) when starting treatment, height was slightly affected (baseline height-SDS: 0.04 [1.14], follow-up: -0.10 [1.11], $p < 0.001$). This effect was not observed if treatment was started during adolescence. Linear regression analysis showed that age starting MPH ($B = 0.07$, $p = 0.003$), dose ($B = -0.50$, $p = 0.001$), and duration of treatment ($B = 0.07$, $p = 0.031$) affect follow-up height.
Conclusion: MPH slightly decreased weight and BMI in this group of ADHD patients followed naturalistically over 2.2 years, and slightly affected height only if treatment was started before the age of 12. Girls, children who started treatment being younger or children on higher MPH doses, showed greater impact in height

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J Child Adolesc Psychopharmacol. 2017;27:731-34.

TREATED PREVALENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER INCREASED FROM 2009 TO 2015 AMONG SCHOOL-AGED CHILDREN AND ADOLESCENTS IN THE UNITED STATES.

Nyarko KA, Grosse SD, Danielson ML, et al .

Objectives: The purpose of this brief is to describe changes in the treated prevalence of medically managed attention-deficit/hyperactivity disorder (ADHD) among insured school-aged children and adolescents in the United States from 2009 to 2015. We examine the differences between those with employer-sponsored insurance (ESI) and with Medicaid insurance.

Methods: We utilized two large longitudinal administrative datasets containing medical and drug claims data on individuals with ESI and Medicaid insurance from Truven Health MarketScan-« Administrative Claims Databases. Treated prevalence was measured as the percentage of school-aged children and adolescents enrolled in a calendar year who met the criteria for medically managed ADHD in the same calendar year. Subjects were eligible for inclusion if they were aged 6-17 years and were continuously enrolled during a calendar year.

Results: The annual prevalence of treated ADHD among school-aged children and adolescents with ESI increased from 4.5% in 2009 to 6.7% in 2015. Among those with Medicaid it increased from 11.3% in 2009 to 13.3% in 2012, and fell after 2012, remaining steady from 2013 through 2015.

Conclusion: Treated prevalence of ADHD increased continuously over time among school-aged children and adolescents with ESI, but declined slightly after 2012 among those in the Medicaid sample

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J Child Adolesc Psychopharmacol. 2017;27:690-99.

EFFICACY AND SAFETY OF A CHEWABLE METHYLPHENIDATE EXTENDED-RELEASE TABLET IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wigal SB, Childress A, Berry SA, et al.

Objective: This phase 3, laboratory classroom study assessed the efficacy and safety of methylphenidate hydrochloride extended-release chewable tablets (MPH ERCT) compared with placebo in children with attention-deficit/hyperactivity disorder (ADHD).

Methods: Following a 6-week, open-label, dose-optimization period, children 6-12 years of age (n = 90) with ADHD were randomly assigned to double-blind MPH ERCT at the final optimized dose (20-60 mg/day) or placebo. After 1 week of double-blind treatment, efficacy was assessed predose and 0.75, 2, 4, 8, 10, 12, and 13 hours postdose in a laboratory classroom setting. The primary efficacy measure was the average of postdose Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale-Combined scores, analyzed using a mixed-model, repeated-measures analysis. Secondary efficacy measures included Permanent Product Measure of Performance (PERMP) total number of problems attempted and total number of problems correct. Safety assessments included adverse event (AE) monitoring and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Results: MPH ERCT treatment statistically significantly reduced the average of all postdose SKAMP-Combined scores versus placebo (least-squares mean difference [95% confidence interval], -7.0 [-10.9, -3.1]; $p < 0.001$). Statistically significant treatment differences in SKAMP-Combined scores were observed at 2 hours postdose through 8 hours postdose (p-values <0.001). Statistically significant differences between MPH ERCT and placebo in PERMP total number of problems attempted and total number of problems correct were observed at 0.75 hours postdose through 8 hours postdose (p-values 0.049). Common AEs in the open-label period (5%) were decreased appetite, upper abdominal pain, mood swings, irritability, insomnia, upper respiratory tract infection (URTI), dysgeusia, and headache; URTI was the only AE reported by >1 subject receiving MPH ERCT in the double-blind period (placebo: URTI, contusion, wound, and initial insomnia). No suicidal ideation or behavior was reported on the C-SSRS at baseline or at any postbaseline assessment.

Conclusions: MPH ERCT 20-60 mg significantly improved ADHD symptoms compared with placebo at 2 hours postdose through at least 8 hours postdose. MPH ERCT was generally safe and well tolerated, with a safety profile consistent with other MPH ER formulations. ClinicalTrials.gov Identifier: NCT01654250

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J Child Adolesc Psychopharmacol. 2017;27:735-40.

EFFECTIVENESS AND SIDE EFFECT PROFILE OF STIMULANT MEDICATION FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN YOUTH WITH EPILEPSY.

Kral MC, Lally MD, Boan AD.

Objectives: This clinical case series examined the effectiveness and potential side effects associated with stimulant medication for the treatment of attention-deficit/hyperactivity disorder (ADHD) in 20 youth with epilepsy.

Methods: Response to stimulant medication was examined through symptom reduction on the Conners-Third Edition: Parent Rating Scale, Short Form [Conner 3-P(S)], which was administered to caregivers before initiation of treatment and following dosage titration to achieve therapeutic efficacy. Stimulant medication side effects were examined with the Side Effect Rating Scale before treatment and following dosage titration. Repeated measures mixed model approach was used to compare symptom reduction and side effects between the two time points.

Results: Repeated measures ANOVA revealed significant ADHD symptom reduction as measured by the Conner 3-P(S). Review of patient medical records and caregiver report did not reveal seizure exacerbation. Caregivers, in fact, reported fewer side effects following treatment for ADHD compared with baseline.

Conclusion: These results contribute to growing evidence in support of the effectiveness of stimulant medication, without seizure exacerbation or medication side effects, for treatment of ADHD in youth with epilepsy

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J Clin Exp Neuropsychol. 2017 Oct;39:854-65.

COMPARATIVE EFFICACY AND SAFETY OF METHYLPHENIDATE AND ATOMOXETINE FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: META-ANALYSIS BASED ON HEAD-TO-HEAD TRIALS.

Liu Q, Zhang H, Fang Q, et al.

Introduction: Comparative efficacy and safety are important issues for appropriate drug selection for attention-deficit hyperactivity disorder (ADHD) treatment. Therefore we conducted a meta-analysis, where we compared atomoxetine (ATX) and methylphenidate (MPH) for ADHD treatment in children and adolescents.

Method: Literature retrieval was conducted in relevant databases from their inception to April 2016 to select head-to-head trials that compared ATX and MPH in children and adolescents. Outcomes like response rate, ADHD Rating Scale (ADHD–RS) score, and adverse events were compared between ATX and MPH treatments. The standardized mean difference (SMD) and risk ratio (RR) with their corresponding 95% confidence intervals (CIs) were used as the effect size for continuous data or dichotomous data, respectively.

Results: Eleven eligible randomized-controlled trials were included, and two of them were double-blind, while the remaining were open-label. Compared to ATX, MPH showed a higher response rate (RR = 1.14, 95% CI [1. 09, 1.20]), decreased inattention (SMD = -0.13, 95% CI [-0.25, -0.01]) and lower risk of adverse events (drowsiness: RR = 0.17, 95% CI [0.11, 0.26; nausea: RR = 0.49; 95% CI [0.29, 0.85; vomiting: RR = 0.41, 95% CI [0.27, 0.63]). However, MPH presented a higher risk of insomnia than ATX (RR = 2.27, 95% CI [1.63, 3.15], $p < .01$).

Conclusion: Results of the meta-analysis add additional evidence of the effectiveness of both ATX and MPH and suggest that MPH should be a first treatment option in most patients with ADHD. (PsycINFO Database Record (c) 2017 APA, all rights reserved)

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J Clin Psychopharmacol. 2017 Oct;37:590-94.

A NATURALISTIC COMPARISON OF METHYLPHENIDATE AND RISPERIDONE MONOTHERAPY IN DRUG-NAIVE YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER COMORBID WITH OPPOSITIONAL DEFIANT DISORDER AND AGGRESSION.

Masi G, Manfredi A, Nieri G, et al.

Background/Purpose: Attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) are frequently co-occurring in youth, but data about the pharmacological management of this comorbidity are scarce, especially when impulsive aggression is prominent. Although stimulants are the first-line medication for ADHD, second-generation antipsychotics, namely, risperidone, are frequently used. We aimed to assess effectiveness and safety of monotherapy with the stimulant methylphenidate (MPH) and risperidone in a consecutive sample of 40 drug-naive male youths diagnosed as having ADHD-combined presentation, comorbid with ODD and aggression, without psychiatric comorbidities, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria and a structured clinical interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version).

Methods: Twenty males treated with MPH (mean age, 8.95 ± 1.67 years) and 20 males treated with risperidone (mean age, 9.35 ± 2.72 years), followed up to 6 months, were assessed according to efficacy measures (Child Behavior Checklist [CBCL], Clinical Global Impression–Severity [CGI-S] and Improvement [CGI-I], Children Global Assessment Scale), and safety measures. At the end of the follow-up, both medications were similarly effective based on CBCL subscales of aggression and rule-breaking behaviors, on Diagnostic and Statistical Manual of Mental Disorders–oriented oppositional defiant problems and conduct problems, and on CGI-S, CGI-I, and Children Global Assessment Scale, but only MPH was effective on CBCL attention problems and attention-deficit/ hyperactivity problems. Risperidone was associated with weight gain and elevated prolactin levels.

Implications/Conclusions: Although the nonrandomized, nonblind design limits the conclusions of our exploratory study, our findings suggest that when ADHD is comorbid with ODD and aggression MPH and risperidone are both effective on aggressive behavior, but only stimulants are effective on ADHD symptoms

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J Dev Behav Pediatr. 2017 Oct;38:573-83.

DISTANCE-LEARNING, ADHD QUALITY IMPROVEMENT IN PRIMARY CARE: A CLUSTER-RANDOMIZED TRIAL.

Fiks AG, Mayne SL, Michel JJ, et al.

Objective: To evaluate a distance-learning, quality improvement intervention to improve pediatric primary care provider use of attention-deficit/hyperactivity disorder (ADHD) rating scales.

Methods: Primary care practices were cluster randomized to a 3-part distance-learning, quality improvement intervention (web-based education, collaborative consultation with ADHD experts, and performance feedback reports/calls), qualifying for Maintenance of Certification (MOC) Part IV credit, or wait-list control. We compared changes relative to a baseline period in rating scale use by study arm using logistic regression clustered by practice (primary analysis) and examined effect modification by level of clinician participation. An electronic health record–linked system for gathering ADHD rating scales from parents and teachers was implemented before the intervention period at all sites. Rating scale use was ascertained by manual chart review.

Results: One hundred five clinicians at 19 sites participated. Differences between arms were not significant. From the baseline to intervention period and after implementation of the electronic system, clinicians in both study arms were significantly more likely to administer and receive parent and teacher rating scales. Among intervention clinicians, those who participated in at least 1 feedback call or qualified for MOC credit were more likely to give parents rating scales with differences of 14.2 (95% confidence interval [CI], 0.6–27.7) and 18.8 (95% CI, 1.9–35.7) percentage points, respectively.

Conclusion: A 3-part clinician-focused distance-learning, quality improvement intervention did not improve rating scale use. Complementary strategies that support workflows and more fully engage clinicians may be needed to bolster care. Electronic systems that gather rating scales may help achieve this goal. Index terms: ADHD, primary care, quality improvement, clinical decision support

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J ECT. 2014;30:256.

RESOLUTION OF CHILDHOOD ONSET ATTENTION DEFICIT HYPERACTIVITY DISORDER AFTER ELECTROCONVULSIVE THERAPY FOR MAJOR DEPRESSION IN ADOLESCENCE.

Coffey MJ, Rogalski KM.

We describe the resolution of childhood onset attention-deficit/hyperactivity disorder (ADHD) after electroconvulsive therapy (ECT) for major depression in adolescence. Case Report: A 16-year-old right-handed male patient was referred for ECT by his pediatric psychiatrist who had diagnosed a major depressive episode not responsive to adequate trials of fluoxetine, venlafaxine, and cognitive behavior therapy. The illness severity led to his withdrawing from school, abusing illicit drugs, and attempting suicide. With his mother's fully informed consent and his assent, he completed an index course of bifrontal brief pulse ECT that was without complication. He discontinued all medications before commencing ECT. The depression fully remitted, and remission was sustained over the next 2 years during a course of continuation maintenance ECT. The patient's only other health problem was combined type ADHD first diagnosed by a pediatric psychiatrist when the patient was in second grade. A school-based neuropsychological evaluation supported the diagnosis. His symptoms responded to psychostimulant medication, which he continued into adolescence. After the index course of ECT, he experienced no recurrence of ADHD symptoms and was prescribed no treatment. He reentered school, graduated, and entered college. Ultimately, 18 months after he began ECT, his pediatric psychiatrist concluded that he no longer met diagnostic criteria for ADHD and removed it from his problem list. Discussion: Although ADHD does not represent an indication for ECT, this case demonstrates the profound effect of ECT in an adolescent with ADHD and a comorbid mood disorder

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J Invest Med. 2017;65:1062-67.

ATTENTION AND MEMORY IMPAIRMENTS IN PEDIATRIC PATIENTS WITH CYSTIC FIBROSIS AND INFLAMMATORY BOWEL DISEASE IN COMPARISON TO HEALTHY CONTROLS.

Piasecki B, Stanisawska-Kubiak M, Strzelecki W, et al.

The main aim of the study was to analyze and compare attention and memory performance in pediatric patients with cystic fibrosis (CF), inflammatory bowel disease (IBD) and in healthy controls. 28 patients with CF, 30 patients with IBD and 30 healthy subjects took part in the study (all in age range of 7-17). All subjects were in intellectual norm. To analyze the functioning of attention, the d2 Test of Attention by Brickenkamp (d2 test) was applied. Memory performance was assessed using the Benton Visual Retention Test (BVRT) and the Trial of 10 words. The CF and IBD groups committed significantly more errors in the d2 test than the healthy controls. The CF group also had significantly higher fluctuation rates and received significantly lower scores in overall concentration performance than the control group. Patients with CF made more mistakes and had fewer correct memory projections in BVRT than the healthy controls. Patients with IBD committed significantly more errors in BVRT than the control group. Patients with CF and IBD also got significantly lower scores in the Trial of 10 words than the control group. Pediatric patients with CF and IBD performed more poorly than the healthy controls on attention and memory tests. More distinct cognitive impairments were observed in the CF group. Further research is needed to find the underlying mechanisms and clinical and/or functional significance of observed cognitive deficits

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Journal of Lipids. 2017;2017.

DO OMEGA-3/6 FATTY ACIDS HAVE A THERAPEUTIC ROLE IN CHILDREN AND YOUNG PEOPLE WITH ADHD?

Derbyshire E.

Attention deficit hyperactivity disorder (ADHD) is a debilitating behavioural disorder affecting daily ability to function, learn, and interact with peers. This publication assesses the role of omega-3/6 fatty acids in the treatment and management of ADHD. Methods. A systematic review of 16 randomised controlled trials was undertaken. Trials included a total of 1,514 children and young people with ADHD who were allocated to take an omega-3/6 intervention, or a placebo. Results. Of the studies identified, 13 reported favourable benefits on ADHD symptoms including improvements in hyperactivity, impulsivity, attention, visual learning, word reading, and working/short-term memory. Four studies used supplements containing a 9: 3: 1 ratio of eicosapentaenoic acid: Docosahexaenoic acid: Gamma linolenic acid which appeared effective at improving erythrocyte levels. Supplementation with this ratio of fatty acids also showed promise as an adjunctive therapy to traditional medications, lowering the dose and improving the compliance with medications such as methylphenidate. Conclusion. ADHD is a frequent and debilitating childhood condition. Given disparaging feelings towards psychostimulant medications, omega-3/6 fatty acids offer great promise as a suitable adjunctive therapy for ADHD

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J Ment Health Res Intellect Disabil. 2017 Oct;10:345-59.

DISRUPTIVE MOOD DYSREGULATION DISORDER SYMPTOMS BY AGE IN AUTISM, ADHD, AND GENERAL POPULATION SAMPLES.

Mayes SD, Kokotovich C, Mathiowetz C, et al.

Disruptive mood dysregulation disorder (DMDD) is a controversial DSM-5 diagnosis. It is not known how DMDD symptoms vary by age and if differences are similar for autism, ADHD, and general population samples. Our study analyzed the two DMDD symptoms (irritable-angry mood and temper outbursts) in 1,827 children with autism or ADHD (with or without oppositional defiant disorder/ODD) and 657 general-population children 2–16 years of age. DMDD symptoms were rated by mothers on the Pediatric Behavior Scale. For all age groups, mean DMDD scores were less than sometimes a problem in the general population and ADHD-Inattentive (ADHD-I) samples, greater than sometimes but less than often a problem in autism and ADHD-Combined (ADHD-C), and greater than often a problem in children with autism or ADHD who also had ODD. DMDD symptoms were unrelated to age in children six and older. Preschool children with ADHD-C, ADHD-I, and ODD had more DMDD symptoms than school-age children, but DMDD symptoms did not differ by age in autism. DMDD symptoms were found in 45% of children with autism and were common at all ages. Evidence-based interventions are discussed

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J Neural Transm. 2017;124:1294-95.

STRESSOR-INDUCED CONFLICTS IN YOUNG MALES WITH ADHD: IMPLICATIONS FOR TRANSITION TO MENTALIZATION AND SELF-MANAGEMENT.

Rademacher J, Michalek S.

Objective: Attention deficit hyperactivity disorder (ADHD) is associated with a high rate of persistence into adulthood. This implies the need for a developmental approach toward treatment. Successful transfer of young people to an adult ADHD clinic requires anticipation of changing family roles for patients and their parents. These individuals are facing a significant number of personal and social demands, increasing the risk for internalizing and externalizing psychopathology at a time of increased vulnerability. Psychodynamically, they may show difficulty in achieving autonomy and lack self-management skills. We report findings on young men with a childhood diagnosis of ADHD who disengaged from health services.

Methods: A feasibility study was conducted on 40 male outpatients (18-25 years) consecutively diagnosed with ADHD. Diagnosis (DSM-V) was evaluated with Conners' Adult ADHD Rating Scales (CAARS) and the Wender Utah Rating Scale (WURS). Psychiatric comorbidity was assessed clinically, psychological distress by use of the SCL-90-R Global Severity Index (GSI). Alexithymia was defined as a TAS-20 score >60

(Toronto Alexithymia Scale). OPD-2 (Operationalized Psychodynamic Diagnostic) was used for psychodynamic analysis of relationship patterns. The Mindful Attention Awareness Scale (MAAS) was applied initially and 6 months after restarting treatment with methylphenidate.
Results: 24 patients were of the combined ADHD subtype, 16 patients of the inattentive subtype. 83% of these individuals had received stimulant therapy as a child or adolescent, in most cases combined with behavioural psychotherapy (76%). (Self-)referral to our service was anteceded (88%) by a history of increasing distress (educational or work circumstances). Family relationships had become strained and experienced as unsupportive (90%). There was an interruption of ADHD specific treatment (median: 60 months) in 95% of cases. Comorbidity: depressive episode (15%), anxiety disorder (38%), history of substance use (45%), mainly cannabis. Psychological distress was high (mean GSI 1.23), as was the proportion of patients with alexithymia (70%). Most individuals (63%) showed dysfunctional relationship patterns (dependence vs. autonomy) and had a history of aggressive behaviour (53%). Low MAAS scores increased in most of the subjects after 6 months.
Conclusion: Current treatment strategies for adolescents with ADHD cannot prevent the interruption of treatment in the 'twilight zon+® from adolescence to adulthood. Our observations in a real-life adult healthcare setting may show that transition is poorly experienced and drop-out from services may be frequent and potentially disastrous. In a developmental framework, treatment should also focus on what makes young adults with ADHD vulnerable, such as compromised mindfulness and deficient mentalization abilities

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J Neural Transm. 2017;124:1285-86.
STRESS RELATED IMPAIRMENTS IN ADHD PATIENTS: INFLUENCE OF SELF-REGULATION AND EMOTION-REGULATION.
Gawrilow C.
Inattention, hyperactivity, and impulsivity are the core symptoms of ADHD. Children, adolescents, and adults with ADHD show impairments in multiple domains of self-regulation and emotion-regulation. Thus, the ability to regulate and control one's own thoughts, emotions, and actions is altered in patients with ADHD and they often experience difficulties with respect to academic achievement, interpersonal relationships, and mental health. For instance, patients with ADHD are at risk for cognitive problems, show impaired physical and psychological functioning, and are prone to stress related impairments. To investigate the association between ADHD symptoms, selfregulation, emotion-regulation, and experienced stress in real life, it is important to take into account that the disorder is a highly heterogeneous condition. Two sources are assumed to contribute to this heterogeneity: between-person differences and within-person fluctuations in ADHD symptoms. This talk will discuss how self-regulation and emotion-regulation correlate in patients with ADHD from a cognitive, motivational, and neuronal perspective. Furthermore, the talk will present completed and ongoing studies on intraindividual variability in ADHD

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J Am Acad Child Adolesc Psychiatry. 2017 Oct;56:801-02.
HERE/IN THIS ISSUE AND THERE/ABSTRACT THINKING: DOES THIS ANSWER YOUR QUESTION?
Rogers CE.
This article discusses the factors promoting resilience and reducing risk are key to the clinician's ultimate goal of reducing impairment from child psychiatric disorders and their treatments. Using a variety of study methods, articles in this month's issue of the Journal specifically investigate many of these factors influencing child psychopathology. Fairly unique to the Journal this month is a clinical update by the American Academy of Child and Adolescent Psychiatry (AACAP)'s committees on tele-psychiatry and quality issues that reviews tele-psychiatry and its use in child and adolescent psychiatry by updating the AACAP Practice Parameter. This update covers multiple relevant topics including legal and ethical issues and use in nonclinical settings such as schools, the juvenile justice system, and direct to the family in their homes. Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders and also one that may be most plagued by parental concerns, particularly when it comes to its diagnosis and treatment. Caregivers faced with a new diagnosis of ADHD in their child often worry whether using stimulant

medications will lead their child down the path toward substance abuse. Counter to the perceptions of many in the lay public, these data continue to emphasize that treatment of ADHD with stimulants may actually be protective for later development of substance use disorders rather than the other way around. Another frequent question that parents ask mental health clinicians treating their children with ADHD is whether their child will 'grow out of it.' Studies suggest that this indicates that children whose ADHD remits in adulthood are those who develop better cognitive control as reflected in normalization of prefrontal cortex activity

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J Tokyo Med Univ. 2017;75:252-57.

A CASE OF ADHD DIAGNOSED AS HYPERADRENERGIC POTS TREATED WITH ATOMOXETINE.

Saito N, Go S, Kato K, et al.

Recently, studies on postural tachycardia syndrome (POTS) have been actively promoted, particularly in the USA, and several pathogeneses, including hyperadrenergic POTS characterized by elevated noradrenaline levels, have been speculated. An abnormal noradrenaline transporter gene has also been reported to play a role in the pathogenesis of hyperadrenergic POTS, and pathological conditions based on genetic abnormality are suspected. Atomoxetine, which is used in the treatment of ADHD, inhibits the reuptake of noradrenaline transporter in nerve endings. The present report describes the case of a 14-year-old boy who showed various intolerance symptoms when standing up during oral administration of atomoxetine for ADHD. The eventual diagnosis was hyperadrenergic POTS based on tachycardia and elevated systolic blood pressure. His noradrenaline level was abnormally high, at 2,061 pg/ml, during the standing examination. His clinical symptoms and noradrenaline level improved with discontinuation of atomoxetine, leading to a suspected causal relationship with the drug. To our knowledge, there have been no other reports to date on changes in noradrenaline levels in the circulation and standing up reactions before and after discontinuation of atomoxetine. We believe that this report, therefore, has significant implications with regard to the need for more effective and safe treatments for ADHD

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Journal of Vocational Rehabilitation. 2017;47:159-74.

PREDICTORS OF EMPLOYMENT OUTCOMES FOR TRANSITION-AGE STATE-FEDERAL VOCATIONAL REHABILITATION CONSUMERS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Glynn K, Schaller J.

BACKGROUND: Relationships among consumer demographic variables, services, and employment outcomes for 7,776 16 to 19 year old and 2,183 20 to 24 year old consumers with ADHD were examined.

OBJECTIVE: To examine employment outcomes, relationships among demographic and case service variables, and weekly earnings for African American, White, and Hispanic consumers with ADHD ages 16-19 and 20-24.

: For research question one the criterion variable was successful employment or not employed. The predictor variables included consumer demographic and vocational rehabilitation service variables. Participants in both the 16-19 and 20-24 age groups were randomly split for cross validation.

RESULTS: Demographic variables of Hispanic and African American, high school graduation and postsecondary education, public support at application, and case service variables of college training, on the job training, job search assistance, and job placement were related to successful employment. White consumers earned significantly more than African American and Hispanic consumers in the 16-19 group, and significantly more than African American consumers in the 20-24 group.

CONCLUSIONS: Implications for practice include: characteristics identified by ethnically diverse parents of professionals who made a positive difference in the life of their child and guidelines for collaboration identified by ethnically diverse parents

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Medicine (Baltimore). 2017 Oct;96:e8281.

FACTORS RELATED TO PEDIATRIC OBSTRUCTIVE SLEEP APNEA-HYPOPNEA SYNDROME IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN DIFFERENT AGE GROUPS.

Wu J, Gu M, Chen S, et al.

This study aimed to retrospectively investigate the factors related to pediatric obstructive sleep apnea-hypopnea syndrome (OSAHS) with attention deficit hyperactivity disorder (ADHD) in children younger than 6 years and those older than 6 years.A total of 437 children who were hospitalized due to OSAHS between January 2014 and December 2014 were retrospectively reviewed. The children were further divided into OSAHS group and OSAHS + ADHD group. The general characteristics, OSA-18 quality of life, intention-hyperactivity score, and polysomnographic parameters (apnea-hypopnea index and the lowest oxygen saturation) were collected and compared between groups.There were 298 boys and 139 girls with the male to female ratio of 2.14:1. ADHD was found in 146 children including 105 boys and 41 girls with the male to female ratio of 2.56:1. Of these children, 31.62% and 35.46% had concomitant ADHD in children aged 4 to 5 years and those aged 6 to 11 years, respectively. In children aged 4 to 5 years, the incidence of allergic rhinitis was significantly higher (P = .016) and the adenoid hypertrophy was more severe (P = .001) in those with concomitant ADHD. In children aged 6 to 11 years, the tonsil hypertrophy was more severe in those with concomitant ADHD (P = .019). In children with concomitant ADHD, OSA-18 score was higher than in those with OSAHS alone (P < .001). Higher frequency of respiratory events (P < .001) and more severe hypoxia (P < .001) were found in children with concomitant ADHD than in those with OSAHS alone.As high as 30% of OSAHS children have concomitant ADHD, and the incidence of ADHD in OSAHS children is increasing over age. Boys are more likely to develop OSAHS and incidence of ADHD in OSAHS boys is higher than in OSAHS girls. In addition, risk factors of ADHD also vary between age groups. The ADHD is related to the severity of allergic rhinitis and adenoid hypertrophy in children aged 4 to 5 years, and to the severity of tonsil hypertrophy in children aged 6 to 11 years. Hypoxia may be an important factor causing ADHD. OSAHS should be treated as early as possible to reduce the incidence of ADHD in children

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Mol Med Rep. 2017;16:6837-45.

ISOLATED CHROMOSOME 8P23.2-PTER DELETION: NOVEL EVIDENCE FOR DEVELOPMENTAL DELAY, INTELLECTUAL DISABILITY, MICROCEPHALY AND NEUROBEHAVIORAL DISORDERS.

Shi S, Lin S, Chen B, et al.

The current study presents a patient carrying a de novo Γê+6Mb deletion of the isolated chromosome 8p23.2-pter that was identified with a single-nucleotide polymorphism array. The patient was characterized by developmental delay (DD)/intellectual disability (ID), microcephaly, autism spectrum disorder, attention-deficit/hyperactivity disorders and mildly dysmorphic features. The location, size and gene content of the deletion observed in this patient were compared with those in 7 patients with isolated 8p23.2 to 8pter deletions reported in previous studies (4 patients) or recorded in the Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources (DECIPHER) database (3 patients). The deletions reported in previous studies were assessed using a chromosomal microarray analysis. The 8p23.2-pter deletion was a distinct microdeletion syndrome, as similar phenotypes were observed in patients with this deletion. Furthermore, following a detailed review of the potential associations between the genes located from 8p23.2 to 8pter and their clinical significance, it was hypothesized that DLG associated protein 2, ceroid-lipofuscinosis neuronal 8, Rho guanine nucleotide exchange factor 10 and CUB and sushi multiple domains 1 may be candidate genes for DD/ID, microcephaly and neurobehavioral disorders. However, firm evidence should be accumulated from high-resolution studies of patients with small, isolated, overlapping and interstitial deletions involving the region from 8p23.2 to 8pter. These studies will allow determination of genotype-phenotype associations for the specific genes crucial to 8p23.2-pter

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Neuroimage Clin. 2017;14:441-49.

POLYGENIC RISK FOR FIVE PSYCHIATRIC DISORDERS AND CROSS-DISORDER AND DISORDER-SPECIFIC NEURAL CONNECTIVITY IN TWO INDEPENDENT POPULATIONS.

Wang T, Zhang X, Li A, et al.

Major psychiatric disorders, including attention deficit hyperactivity disorder (ADHD), autism (AUT), bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SZ), are highly heritable and polygenic. Evidence suggests that these five disorders have both shared and distinct genetic risks and neural connectivity abnormalities. To measure aggregate genetic risks, the polygenic risk score (PGRS) was computed. Two independent general populations (N = 360 and N = 323) were separately examined to investigate whether the cross-disorder PGRS and PGRS for a specific disorder were associated with individual variability in functional connectivity. Consistent altered functional connectivity was found with the bilateral insula: for the left supplementary motor area and the left superior temporal gyrus with the cross-disorder PGRS, for the left insula and right middle and superior temporal lobe associated with the PGRS for autism, for the bilateral midbrain, posterior cingulate, cuneus, and precuneus associated with the PGRS for BD, and for the left angular gyrus and the left dorsolateral prefrontal cortex associated with the PGRS for schizophrenia. No significant functional connectivity was found associated with the PGRS for ADHD and MDD. Our findings indicated that genetic effects on the cross-disorder and disorder-specific neural connectivity of common genetic risk loci are detectable in the general population. Our findings also indicated that polygenic risk contributes to the main neurobiological phenotypes of psychiatric disorders and that identifying cross-disorder and specific functional connectivity related to polygenic risks may elucidate the neural pathways for these disorders

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NeuroImage Clin. 2018;17:53-59.

ADHD AND MATURATION OF BRAIN WHITE MATTER: A DTI STUDY IN MEDICATION NAIVE CHILDREN AND ADULTS.

Bouziane C, Caan MWA, Tamminga HGH, et al.

Several diffusion tensor imaging (DTI) studies in attention deficit hyperactivity disorder (ADHD) have shown a delay in brain white matter (WM) development. Because these studies were mainly conducted in children and adolescents, these WM abnormalities have been assumed, but not proven to progress into adulthood. To provide further insight in the natural history of WM maturation delay in ADHD, we here investigated the modulating effect of age on WM in children and adults. 120 stimulant-treatment naive male ADHD children (10-12 years of age) and adults (23-40 years of age) with ADHD (according to DSM-IV; all subtypes) were included, along with 23 age and gender matched controls. Fractional anisotropy (FA) values were compared throughout the WM by means of tract-based spatial statistics (TBSS) and in specific regions of interest (ROIs). On both TBSS and ROI analyses, we found that stimulant-treatment naive ADHD children did not differ in FA values from control children, whereas adult ADHD subjects had reduced FA values when compared to adult controls in several regions. Significant age group interactions for whole brain FA ($p = 0.015$), as well as the anterior thalamic radiation ($p = 0.015$) suggest that ADHD affects the brain WM age-dependently. In contrast to prior studies conducted in medicated ADHD children, we did not find WM alterations in stimulant treatment na+»ve children, only treatment-na+»ve adults. Thus, our findings suggest that the reported developmental delay in WM might appear after childhood, and that previously reported differences between ADHD children and normal developing peers could have been attributed to prior ADHD medications, and/or other factors that affect WM development, such as age and gender

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Neurosci Biobehav Rev. 2017 Jun;77:107-21.

RISK MITIGATION FOR CHILDREN EXPOSED TO DRUGS DURING GESTATION: A CRITICAL ROLE FOR ANIMAL PRECLINICAL BEHAVIORAL TESTING.

Zucker I.

Many drugs with unknown safety profiles are administered to pregnant women, placing their offspring at risk. I assessed whether behavioral outcomes for children exposed during gestation to antidepressants,

anxiolytics, anti-seizure, analgesic, anti-nausea and sedative medications can be predicted by more extensive animal studies than are part of the FDA approval process. Human plus rodent data were available for only 8 of 33 CNS-active drugs examined. Similar behavioral and cognitive deficits, including autism and ADHD emerged in human offspring and in animal models of these disorders after exposure to fluoxetine, valproic acid, carbamazepine, phenytoin, phenobarbital and acetaminophen. Rodent data helpful in identifying and predicting adverse effects of prenatal drug exposure in children were first generated many years after drugs were FDA-approved and administered to pregnant women. I recommend that enhanced behavioral testing of rodent offspring exposed to drugs prenatally should begin during preclinical drug evaluation and continue during Phase I clinical trials, with findings communicated to physicians and patients in drug labels

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Neurosciences. 2017;22:287-91.

FRONTAL THETA/BETA RATIO CHANGES DURING TOVA IN EGYPTIAN ADHD CHILDREN.

Halawa IF, El Sayed BB, Amin OR, et al.

Objective: To spot the frontal theta/beta ratio alterations during Tests of Variance of Attention (TOVA) in Egyptian attention deficit hyperactivity disorder (ADHD) children.

Methods: This is a cross sectional study performed in Clinical Neurophysiology Unit, Cairo University, Egypt. It included 2 groups, each of 52 children (one of them with ADHD and the other were normal control). EEG was recorded for every subject during normal relaxing circumstance with eyes opened as well as during TOVA.

Results: Comparing both groups revealed statistically significant difference in the theta/beta ratio in both state (normal relaxing with eyes opened and during TOVA), also we found that the theta/beta ratio decreased in normal group (during concentration) while in the ADHD group it increased with a specific pattern.

Conclusion: The theta/beta ratio can be of value in helping for differential diagnosis in patients presenting with mild ADHD

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Obesity. 2017;25:1802-08.

ADHD MEDICATION, DIETARY PATTERNS, PHYSICAL ACTIVITY, AND BMI IN CHILDREN: A LONGITUDINAL ANALYSIS OF THE ECLS-K STUDY.

Bowling A, Davison K, Haneuse S, et al.

Objective: This study examined relationships between attention-deficit/hyperactivity disorder (ADHD), stimulant use, and BMI change in a nationally representative cohort of children as well as differences in diet and physical activity that may mediate associations between stimulant use and BMI change.

Methods: By using the Early Childhood Longitudinal Study-Kindergarten Cohort 1998-1999 (N = 8,250), we modeled BMI and z score change by ADHD and stimulant start time, examined the odds of unhealthy diet and physical activity predicted by ADHD and stimulant use, and performed mediation analysis assessing indirect effects of health behaviors.

Results: Early stimulant use predicted short-term BMI reductions, but any stimulant use predicted increased BMI growth between fifth grade (mean age = 11.2 years) and eighth grade (mean age = 14.3 years). Children with ADHD had higher odds of poor diet regardless of medication. Health behaviors were not associated with BMI change after controlling for medication use.

Conclusions: Stimulant use predicted higher BMI trajectory between fifth and eighth grade but did not affect dietary or physical activity patterns. Future research should explore potential mechanisms by which early and long-term stimulant use may affect metabolism, while clinicians should initiate nutrition counseling with families of children with ADHD, regardless of medication prescription, at or shortly after diagnosis

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Pers Individ Dif. 2017 Oct;116:289-95.

THE USE OF MULTIMETHOD IMPULSIVITY ASSESSMENT IN THE PREDICTION OF ADHD, CONDUCT PROBLEMS, AND CALLOUS-UNEMOTIONAL SYMPTOMS.

Haas SM, Derefinko KJ, Waschbusch DA.

The purpose of the current study was to examine the relationship between multiple forms of behavioral and trait impulsivity and the externalizing symptoms of Attention-Deficit Hyperactivity Disorder (ADHD), conduct problems (CP), and callous-unemotional (CU) traits. Participants were 182 elementary school age children (142 boys and 40 girls) ranging in age from 5.6 to 12.5years, recruited through a university-based ADHD clinic. Data showed that symptoms of ADHD were characterized by playing fewer trials on the Reward Dominance task, UPPS Urgency, and UPPS lack of perseverance. Symptoms of conduct problems were characterized by playing fewer trials on the Reward Dominance task and UPPS urgency. In contrast, callous-unemotional traits were characterized by only UPPS urgency and not by performance on either of the behavioral tasks. These results indicate some convergence in terms of trait impulsivity across externalizing syndromes, as well as divergence in terms of behavioral impulsivity and perseverance on tasks. The implications of these findings are discussed with particular emphasis on the importance of different facets of impulsivity characterizing different childhood externalizing syndromes

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Personalized Medicine in Psychiatry. 2017;3:8-17.

IDENTIFICATION OF BIOTYPES IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, A REPORT FROM A RANDOMIZED, CONTROLLED TRIAL.

Leikauf JE, Griffiths KR, Saggar M, et al.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a heterogeneous disorder. Current subtypes lack longitudinal stability or prognostic utility. We aimed to identify data-driven biotypes using multiple cognitive measures, then to validate these biotypes using EEG, ECG, and clinical response to atomoxetine as external validators. Study design was a double-blind, randomized, placebo-controlled crossover trial of atomoxetine including 116 subjects ages 6 through 17 with diagnosis of ADHD and 56 typically developing controls. Initial features for unsupervised machine learning included a cognitive battery with 20 measures affected in ADHD. External validators included baseline mechanistic validators (using electroencephalogram/EEG and electrocardiogram/ECG) and clinical response (ADHD Rating Scale and correlation with cognitive change). One biotype, labeled impulsive cognition, was characterized by increased errors of commission and shorter reaction time, had greater EEG slow wave (theta/delta) power and greater resting heart rate. The second biotype, labeled inattentive cognition, was characterized by longer/more variable reaction time and errors of omission, had lower EEG fast wave (beta) power, resting heart rate that did not differ from controls, and a strong correlation ($r = -0.447$, $p < 0.001$) between clinical response to atomoxetine and improvement in verbal memory immediate recall. ADHD comprises at least two biotypes that cut across current subtype criteria and that may reflect distinct arousal mechanisms. The findings provide evidence that further investigation of cognitive subtypes may be at least as fruitful as symptom checklist-based subtypes for development of biologically-based diagnostics and interventions for ADHD

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PLoS ONE. 2017;12:e0185300.

PARENT PERCEPTIONS OF THE QUALITY OF LIFE OF PET DOGS LIVING WITH NEURO-TYPICALLY DEVELOPING AND NEURO-ATYPICALLY DEVELOPING CHILDREN: AN EXPLORATORY STUDY.

Hall SS, Wright HF, Mills DS.

There is growing scientific and societal recognition of the role that pet dogs can play in healthy development of children; both those who are neuro-typically developing and those who live with a neuro-developmental disorder, such as autism or attention deficit hyperactivity disorder. However, little attention has been paid to how living with children positively and negatively affects quality of life of a pet dog. In this exploratory study we conducted semi-structured interviews with parents of neuro-typically developing children (n = 18) and those with a neuro-developmental disorder (n = 18) who owned a pet dog, until no new factors were identified.

Living with children brought potentially positive benefits to the dog's life including: imposition of a routine, participation in recreational activities and the development of a strong bond between the child and the dog. The importance of maintaining a routine was particularly prevalent in families with children with neuro-developmental disorders. Potential negative factors included having to cope with child meltdowns and tantrums, over stimulation from child visitors, harsh contact and rough and tumble play with the child. The regularity and intensity of meltdowns and tantrums was particularly evident in responses from parents with children with a neuro-developmental disorder. However, child visitors and rough play and contact were mentioned similarly across the groups. Protective factors included having a safe haven for the dog to escape to, parent's awareness of stress signs and child education in dog-interaction. Parents were also asked to complete a stress response scale to provide an initial quantitative comparison of stress responses between dogs living with the two family-types. Parents with neuro-typically developing children more frequently observed their dog rapidly running away from a situation and less frequently observed their dog widening their eyes, than parents with children with a neuro-developmental disorder. We propose the development of a stress audit based on the findings reported here, to prevent potential dangerous situations, which may lead to dog bites and dog relinquishment and allow owners to maximise the benefits of dog ownership

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PLoS ONE. 2017;12:e0182258.

DELIBERATE SELF-HARM BEHAVIOR AMONG YOUNG VIOLENT OFFENDERS.

Laporte N, Ozolins A, Westling S, et al.

Deliberate self-harm behavior (DSH) can have profound effects on a person's quality of life, and challenges the health care system. Even though DSH has been associated with aggressive interpersonal behaviors, the knowledge on DSH in persons exhibiting such behaviors is scarce. This study aims to (1) specify the prevalence and character of DSH, (2) identify clinical, neurocognitive, psychosocial, and criminological characteristics associated with DSH, and (3) determine predictors of DSH among young violent offenders. Data were collected from a nationally representative cohort of 270 male violent offenders, 18-25 years old, imprisoned in Sweden. Participants were interviewed and investigated neuropsychologically, and their files were reviewed for psychosocial background, criminal history, mental disorders, lifetime aggressive antisocial behaviors, and DSH. A total of 62 offenders (23%) had engaged in DSH at some point during their lifetime, many on repeated occasions, yet without suicidal intent. DSH was significantly associated with attention deficit hyperactivity disorder, mood disorders, anxiety disorders, various substance use disorders, being bullied at school, and repeated exposure to violence at home during childhood. Mood disorders, anxiety disorders, and being bullied at school remained significant predictors of DSH in a total regression model. Violent offenders direct aggressive behaviors not only toward other people, but also toward themselves. Thus, DSH must be assessed and prevented in correctional institutions as early as possible, and more knowledge is needed of the function of DSH among offenders

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PLoS ONE. 2017;12:e0184964.

SKILLS AND COMPENSATION STRATEGIES IN ADULT A.

Canela C, Buadze A, Dube A, et al.

OBJECTIVE: The primary objectives of this study were to investigate how adult patients with ADHD coped with their symptoms prior to diagnosis and treatment, what skills and compensation strategies they had developed and what their self-perceptions of these strategies were.

METHODS: We used a qualitative approach to analyze interviews with 32 outpatients of a specialty care unit at a university hospital.

RESULTS: Patients reported frequent use of diverse compensatory strategies with varying degrees of effectiveness. These were classified into five categories (organizational, motoric, attentional, social, psychopharmacological). In certain circumstances, ADHD symptoms were even perceived as useful.

CONCLUSION: Before diagnosis and treatment, patients with ADHD may develop a variety of skills to cope with their symptoms. Several of these skills are perceived as helpful. Knowledge of self-generated coping

strategies may help better understand patients and their histories and thus facilitate patient cooperation. Moreover, knowing ways in which such patients cope with their symptoms may help elucidate reasons for late or under-diagnosing of the disorder

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PLoS ONE. 2017;12:e0183509.

GUT MICROBIOME IN ADHD AND ITS RELATION TO NEURAL REWARD ANTICIPATION.

Aarts E, Ederveen THA, Naaijen J, et al.

BACKGROUND: Microorganisms in the human intestine (i.e. the gut microbiome) have an increasingly recognized impact on human health, including brain functioning. Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder associated with abnormalities in dopamine neurotransmission and deficits in reward processing and its underlying neuro-circuitry including the ventral striatum. The microbiome might contribute to ADHD etiology via the gut-brain axis. In this pilot study, we investigated potential differences in the microbiome between ADHD cases and undiagnosed controls, as well as its relation to neural reward processing.

METHODS: We used 16S rRNA marker gene sequencing (16S) to identify bacterial taxa and their predicted gene functions in 19 ADHD and 77 control participants. Using functional magnetic resonance imaging (fMRI), we interrogated the effect of observed microbiome differences in neural reward responses in a subset of 28 participants, independent of diagnosis.

RESULTS: For the first time, we describe gut microbial makeup of adolescents and adults diagnosed with ADHD. We found that the relative abundance of several bacterial taxa differed between cases and controls, albeit marginally significant. A nominal increase in the Bifidobacterium genus was observed in ADHD cases. In a hypothesis-driven approach, we found that the observed increase was linked to significantly enhanced 16S-based predicted bacterial gene functionality encoding cyclohexadienyl dehydratase in cases relative to controls. This enzyme is involved in the synthesis of phenylalanine, a precursor of dopamine. Increased relative abundance of this functionality was significantly associated with decreased ventral striatal fMRI responses during reward anticipation, independent of ADHD diagnosis and age.

CONCLUSIONS: Our results show increases in gut microbiome predicted function of dopamine precursor synthesis between ADHD cases and controls. This increase in microbiome function relates to decreased neural responses to reward anticipation. Decreased neural reward anticipation constitutes one of the hallmarks of ADHD

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PLoS ONE. 2017;12.

RELATIONSHIP BETWEEN PARENTING STRESS AND INFORMANT DISCREPANCIES ON SYMPTOMS OF ADHD/ODD AND INTERNALIZING BEHAVIORS IN PRESCHOOL CHILDREN.

Chen Y-C, Hwang-Gu S-L, Ni H-C, et al.

Parent and teacher ratings of child behaviors are often discrepant, and these discrepancies may be correlated with parenting stress. The present study explored whether various parenting stress factors are associated with discrepancies between parent and teacher ratings of attention-deficit/hyperactivity disorder and oppositional defiant disorder (ODD) as well as internalizing symptoms in preschool children. We recruited 299 Taiwanese preschool children (aged 4ΓÇô6 years) from the community or via clinical referrals. A structural equation modeling was used to analyze the relationships among three factors derived from the Parenting Stress Index-Short Form and informant discrepancies on symptoms of inattention, hyperactivity/impulsivity, ODD, and internalizing behaviors. Scores reported by parents were higher for each of the symptoms examined than those reported by teachers, and the degree of agreement between informants ranged from low to moderate. The parental distress factor of parenting stress was associated only with parent ratings, whereas other factors of parenting stressΓÇöparent-child dysfunctional interaction and parentsΓÇÖ stress resulted from their childΓÇÖs temperamentΓÇöwere correlated with both parent and teacher ratings. Only parental distress factor predicted informant discrepancies for all behavioral symptoms

assessed. Our findings suggest that parental distress should be considered when parent rating scores show significant discrepancies from that of teacher rating scores

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Psychiatr Psychol Klin. 2017;17:195-202.

ADULT ADHD - DIAGNOSIS, CAUSES AND OUTCOMES.

Kupnicka Z, Poraj G, Kamierski J.

Attention-deficit/hyperactivity disorder is a neurobiological condition, which has its onset in childhood and often persists into adulthood. The clinical picture of the disorder changes at different developmental stages. Hyperactivity and impulsiveness decrease, whereas attention deficits increase with age. Genetic, anatomical and functional anomalies within the cerebral structures and the resulting patterns of information processing, specific neurometabolism, neurodevelopmental disorders as well as the influence of prenatal and environmental factors are the primary causes of the syndrome. Global research confirms that attention-deficit/hyperactive disorder has negative lifetime consequences. People affected by this disorder often enter adulthood burdened with negative experiences and coexisting disorders, which contribute to psychosocial impairment. Adults with attention-deficit/hyperactive disorder are faced with numerous social, family, professional and health problems. Lack of professional diagnosis and knowledge of the disorder often prevents adequate and professional treatment. The paper discusses different factors that contribute to the development of the disorder as well as the symptoms that occur in adult life. It also points to the significant burden associated with functioning with the symptoms in various spheres of life. The article emphasises the need for increased public and professionals' awareness of the prevalence, the nature and the consequences of attention-deficit/hyperactive disorder in adulthood

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Psychiatr Invest. 2017;14:693-97.

ASSOCIATION BETWEEN GABA3 GENE POLYMORPHISMS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN KOREAN CHILDREN.

Kwon HJ, Kim W, Lim MH.

Objective Attention deficit hyperactivity disorder (ADHD) is common disorder of the school-age population. ADHD is familial and genetic studies estimate heritability at 80-90%. The aim of the present study was to investigate the association between the genetic type and alleles for gamma-aminobutyric acid receptor subunit beta-3 (GABA3) gene in Korean children with ADHD.

Methods The sample consisted of 180 ADHD children and 159 control children. We diagnosed ADHD according to DSM-IV. ADHD symptoms were evaluated with Conners' Parent Rating Scales and Dupaul Parent ADHD Rating Scales. Blood samples were taken from the 339 subjects, DNA was extracted from blood lymphocytes, and PCR was performed for GABA3 rs2081648, rs1426217 and rs981778 Polymorphism. Alleles and genotype frequencies were compared using the chi-square test. We compared the allele and genotype frequencies of GABA3 gene polymorphism in the ADHD and control groups.

Results This study showed that there was a significant correlation among the frequencies of the rs2081648 (OR=0.71, 95% CI=0.51ΓÇô0.98, p=0.040) of alleles of MAO, but the final conclusions are not definite. Follow up studies with larger patient or pure subgroups are expected.

Conclusion These results suggested that GABA3 might be related to ADHD symptoms

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Psychiatry Res Neuroimaging. 2017;269:97-105.

NEURAL DYSFUNCTION DURING TEMPORAL DISCOUNTING IN PAEDIATRIC ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND OBSESSIVE-COMPULSIVE DISORDER.

Norman LJ, Carlisi CO, Christakou A, et al.

Both Attention-Deficit/Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD) are associated with choice impulsivity, i.e. the tendency to prefer smaller immediate rewards over larger delayed

rewards. However, the extent to which this impulsivity is mediated by shared or distinct underlying neural mechanisms is unclear. Twenty-six boys with ADHD, 20 boys with OCD and 20 matched controls (aged 12ΓÇô18) completed an fMRI version of an individually adjusted temporal discounting (TD) task which requires choosing between a variable amount of money now or -ú100 in one week, one month or one year. Activations to immediate and delayed reward choices were compared between groups using a three-way ANCOVA. ADHD patients had steeper discounting rates on the task relative to controls. OCD patients did not differ from controls or patients with ADHD. Patients with ADHD and OCD showed predominantly shared activation deficits during TD in fronto-striato-insular-cerebellar regions responsible for self-control and temporal foresight, suggesting that choice impulsivity is mediated by overlapping neural dysfunctions in both disorders. OCD patients alone showed dysfunction relative to controls in right orbitofrontal and rostrolateral prefrontal cortex, extending previous findings of abnormalities in these regions in OCD to the domain of choice impulsiveness

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Psychiatry Res. 2017.

PATTERNS OF EMOTION REGULATION AND EMOTION-RELATED BEHAVIORS AMONG PARENTS OF CHILDREN WITH AND WITHOUT ADHD.

Shenaar-Golan V, Wald N, Yatzkar U.

Parent emotion regulation is a crucial factor in child adjustment. This study examined the patterns and correlation of emotion regulation and emotion-related behaviors for parents of children with and without ADHD. The study emphasized specific parental emotion regulation strategies used in parent-child interactions. Of the 177 participating parents 55.4% had at least one child with ADHD. Participants were asked to complete questionnaires measuring their emotion regulation and emotion-related behaviors (supportive vs. unsupportive) with regard to a specific child, noting whether the child had ADHD. Results indicated that parents of children with ADHD used more emotion regulation strategies than parents of children without ADHD. No differences were found in emotion-related behaviors. Patterns of relations between reappraisal and suppression emotion regulation and supportive and non-supportive emotion-related behaviors revealed that parent reappraisal was an effective emotion regulation strategy for both subgroups, whereas suppression was ineffective only for parents of children without ADHD. These findings shed light on the relation of parent reappraisal and suppression strategies to emotion-related behaviors for different parenting experiences and emphasize the importance of addressing parent specific emotion regulation in parenting intervention programs

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Psychol Sci. 2017 Oct;28:1375-86.

ATTENTIONAL LAPSES IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: BLANK RATHER THAN WANDERING THOUGHTS.

Van den Driessche C, Bastian M, Peyre H, et al.

People with attention-deficit/hyperactivity disorder (ADHD) have difficulties sustaining their attention on external tasks. Such attentional lapses have often been characterized as the simple opposite of external sustained attention, but the different types of attentional lapses, and the subjective experiences to which they correspond, remain unspecified. In this study, we showed that unmedicated children (ages 6–12) with ADHD, when probed during a standard go/no-go task, reported more mind blanking (a mental state characterized by the absence of reportable content) than did control participants. This increase in mind blanking happened at the expense of both focused and wandering thoughts. We also found that methylphenidate reverted the level of mind blanking to baseline (i.e., the level of mind blanking reported by control children without ADHD). However, this restoration led to mind wandering more than to focused attention. In a second experiment, we extended these findings to adults who had subclinical ADHD. These results suggest that executive functions

impaired in ADHD are required not only to sustain external attention but also to maintain an internal train of thought

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Psychopharmacology. 2017;1-10.

ABSTINENCE-INDUCED WITHDRAWAL SEVERITY AMONG ADOLESCENT SMOKERS WITH AND WITHOUT ADHD: DISENTANGLING EFFECTS OF NICOTINE AND SMOKING REINSTATEMENT.

Bidwell LC, Balestrieri SG, Colby SM, et al.

Rationale: Individuals with attention deficit hyperactivity disorder (ADHD) start smoking earlier, are more likely to progress to nicotine dependence, and have a more difficult time quitting smoking compared to their non-ADHD peers. Little is known about the underlying behavioral mechanisms associated with this increased risk, particularly at the adolescent stage.

Objective: This study aimed to assess the effects of overnight nicotine abstinence and smoking reinstatement on subjective withdrawal states in adolescent smokers with and without ADHD.

Methods: Adolescent daily smokers (27 with ADHD and 17 without ADHD) completed three experimental sessions: (1) a placebo patch followed by smoking a nicotine cigarette, (2) placebo patch followed by smoking a nicotine-free cigarette, and (3) nicotine patch followed by smoking a nicotine-free cigarette. Subjects abstained overnight before each session, and patches were administered 45 min before smoking. The primary outcome measure was a smoking withdrawal symptom questionnaire.

Results: ADHD smokers experienced greater difficulty concentrating and impatience/restlessness during abstinence than non-ADHD smokers. Smoking a cigarette improved abstinence-induced difficulty concentrating and restlessness, regardless of its nicotine content, and regardless of whether transdermal nicotine was received or not.

Conclusions: Thus, sensorimotor aspects of smoking, rather than nicotine itself, appeared to relieve withdrawal. Although ADHD smokers report greater withdrawal symptoms than non-ADHD smokers, they responded strongly to the sensorimotor aspects of smoking during withdrawal. These findings suggest that even lighter, adolescent smokers with ADHD are vulnerable to smoking progression through altered smoking abstinence and withdrawal relief processes

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Res Dev Disabil. 2017 Apr;63:28-37.

REACTIVE ATTACHMENT/DISINHIBITED SOCIAL ENGAGEMENT DISORDERS: CALLOUS-UNEMOTIONAL TRAITS AND COMORBID DISORDERS.

Mayes SD, Calhoun SL, Waschbusch DA, et al.

BACKGROUND: DSM-5 Reactive Attachment Disorder (RAD) and Disinhibited Social Engagement Disorder (DSED) are rare, understudied, and controversial disorders.

METHODS: Comorbidity in children diagnosed with RAD or DSED was compared with comorbidity in ADHD and autism to determine if RAD/DSED comorbidity differed from that for the two most common disorders in child psychiatric clinics. Samples included 4-17-year-olds, 20 with RAD and/or DSED, 933 with autism, and 895 with ADHD. Children with RAD/DSED were removed from their neglectful environments at a mean of 4 years and were a mean 10 years when studied. Mothers rated the children on the Pediatric Behavior Scale assessing oppositional behavior, conduct problems, ADHD, anxiety, depression, and other symptoms.

RESULTS: Five of the 20 children with RAD/DSED had DSED without RAD, 15 had RAD with DSED, and none had RAD without DSED. All children with RAD had callous-unemotional traits (CU) and 73% had conduct disorder (CD). No children with DSED-no RAD had CU or CD. Children with RAD+DSED were considerably more impaired than children with DSED-no RAD, autism, and ADHD.

CONCLUSIONS: Findings are consistent with other studies indicating high CD/CU comorbidity in RAD and extreme rarity of RAD without DSED, findings which are not noted in the DSM-5

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Res Dev Disabil. 2017;70:175-84.

INATTENTION AND HYPERACTIVITY/IMPULSIVITY AMONG CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY-DISORDER, AUTISM SPECTRUM DISORDER, AND INTELLECTUAL DISABILITY.

McClain MB, Hasty Mills AM, Murphy LE.

Background Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and Intellectual Disability (ID) are common co-occurring neurodevelopmental disorders; however, limited research exists regarding the presentation and severity of overlapping symptomology, particularly inattention and hyperactivity/impulsivity, when a child is diagnosed with one of more of these neurodevelopmental disorders.

Aims As difficulties with inattention and hyperactivity/impulsivity are symptoms frequently associated with these disorders, the current study aims to determine the differences in the severity of inattention and hyperactivity/impulsivity in children diagnosed with ADHD, ASD, ID, and co-occurring diagnosis of ADHD/ID, ASD/ADHD, and ASD/ID.

Methods and procedures **Participants** in the current study included 113 children between the ages of 6 and 11 who were diagnosed with ADHD, ASD, ID, ADHD/ID, ASD/ADHD, or ASD/ID. Two MANOVA analyses were used to compare these groups witih respsect to symptom (i.e., inattention, hyperactivity/impulsivity) severity.

Outcomes and results Results indicated that the majority of diagnostic groups experienced elevated levels of both inattention and hyperactivity/impulsivity. However, results yielded differences in inattention and hyperactivity/impulsivity severity. In addition, differences in measure sensitivity across behavioral instruments was found.

Conclusions and implications Children with neurodevelopmental disorders often exhibit inattention and hyperactivity/impulsivity, particularly those with ADHD, ASD, ASD/ADHD, and ADHD/ID; therefore, differential diagnosis may be complicated due to similarities in ADHD symptom severity. However, intellectual abilities may be an important consideration for practitioners in the differential diagnosis process as children with ID and ASD/ID exhibited significantly less inattention and hyperactive/impulsive behaviors. Additionally, the use of multiple behavior rating measures in conjunction with other assessment procedures may help practitioners determine the most appropriate diagnosis

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Rev Neurol. 2017;64:S111-S116.

DISCRIMINATORY POWER OF EXECUTIVE FUNCTIONS AND OF THEORY OF MIND IN ATTENTION DEFICIT HYPERACTIVITY DISORDER. RATIONALE FOR INTERVENTION.

Miranda-Casas A, Berenguer-Forner C, Rosell+¦-Miranda B, et al.

Introduction. Executive functions and theory of mind (ToM) deficits are present in children with attention deficit hyperactivity disorder (ADHD). Identifying the magnitude of the association between executive functions and ToM is important for understanding the disorder.

Aims. This study adopts a naturalistic evaluation approach to analyze the executive functions versus ToM ability to discriminate between children with ADHD and typically developing children and to identify the degree of association between deficits in the components of executive functions (behavioral regulation and metacognitive) and ToM.

Subjects and methods. Thirty-five children with ADHD and 37 typically developing children-7 to 11 years old, matched in age and intelligence quotient, participated in this study. Parents assessed ToM skills and teachers estimated the executive functions.

Results and conclusions. The percentage of children with ADHD classified correctly was higher in the discriminant analysis where the executive functions components were introduced as an independent variable than in the discriminant analysis performed with the ToM. However, a high percentage of children with executive functions deficits had also problems in ToM. Interventions focused on the development of a broad range of executive processes are reviewed

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Lancet Psychiatry. 2017.

ADHD IN CHILDREN AND YOUNG PEOPLE: PREVALENCE, CARE PATHWAYS, AND SERVICE PROVISION.

Sayal K, Prasad V, Daley D, et al.

Attention-deficit hyperactivity disorder (ADHD) is a common childhood behavioural disorder. Systematic reviews indicate that the community prevalence globally is between 2% and 7%, with an average of around 5%. At least a further 5% of children have substantial difficulties with overactivity, inattention, and impulsivity that are just under the threshold to meet full diagnostic criteria for ADHD. Estimates of the administrative prevalence (clinically diagnosed or recorded) vary worldwide, and have been increasing over time. However, ADHD is still relatively under-recognised and underdiagnosed in most countries, particularly in girls and older children. ADHD often persists into adulthood and is a risk factor for other mental health disorders and negative outcomes, including educational underachievement, difficulties with employment and relationships, and criminality. The timely recognition and treatment of children with ADHD-type difficulties provides an opportunity to improve long-term outcomes. This Review includes a systematic review of the community and administrative prevalence of ADHD in children and adolescents, an overview of barriers to accessing care, a description of associated costs, and a discussion of evidence-based pathways for the delivery of clinical care, including a focus on key issues for two specific age groups-younger children (aged Γëñ6 years) and adolescents requiring transition of care from child to adult services

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Lancet Psychiatry. 2017.

RELATIVE AGE WITHIN THE SCHOOL YEAR AND DIAGNOSIS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A NATIONWIDE POPULATION-BASED STUDY.

Sayal K, Chudal R, Hinkka-Yli-Salom+ñki S, et al.

BACKGROUND: Findings are mixed on the relationship between attention-deficit hyperactivity disorder (ADHD) and younger relative age in the school year. We aimed to investigate whether relative age is associated with ADHD diagnosis in a country where prescribing rates are low and whether any such association has changed over time or relates to comorbid disorders (eg, conduct disorder [CD], oppositional defiant disorder [ODD], or learning disorder [LD]).

METHODS: We used nationwide population-based registers to identify all Finnish children born between Jan 1, 1991, and Dec 31, 2004, who were diagnosed with ADHD from age 7 years onwards (age of starting school). We calculated incidence ratios to assess the inter-relations between relative age within the school year, age at ADHD diagnosis, and year of diagnosis (1998-2003 vs 2004-11).

FINDINGS: Between Jan 1, 1998, and Dec 31, 2011, 6136 children with ADHD were identified. Compared with the oldest children in the school year (ie, those born between January and April), the cumulative incidence of an ADHD diagnosis was greatest for the youngest children (ie, those born between September and December); for boys the incidence ratio was 1·26 (95% CI 1·18-1·35; p<0·0001) and for girls it was 1·31 (1·12-1·54; p=0·0007). The association between relative age and age at ADHD diagnosis reflected children diagnosed before age 10 years, and the strength of this association increased during recent years (2004-11). Thus, compared with children born between January and April, for those born between May and August, the ADHD incidence ratio was 1·37 (95% CI 1·24-1·53; p<0·0001) and for those born between September and December, the incidence ratio was 1·64 (1·48-1·81; p<0·0001). The relative age effect was not accounted for by comorbid disorders such as CD, ODD, or LD.

INTERPRETATION: In a health service system with low prescribing rates for ADHD, a younger relative age is associated with an increased likelihood of receiving a clinical diagnosis of ADHD. This effect has increased in recent years. Teachers, parents, and clinicians should take relative age into account when considering the possibility of ADHD in a child or encountering a child with a pre-existing diagnosis.

FUNDING: Academy of Finland, Finnish Medical Foundation, Orion Pharma Foundation, Finnish Cultural Foundation

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REVIEW ABOUT COMORBIDITIES OF BEHAVIOURAL DISORDERS IN CHILDREN AND ADOLESCENTS: THE FOCUS ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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**Equal contribute for Authorship*

ABSTRACT

Disruptive behavior disorders (DBD) present high comorbidity rate mainly for opposite-defiant disorders that are frequent among children, adolescents and adults affected by with attention deficit and hyperactivity disorder (ADHD), probably as result of common temperamental risk factors such as attention, distraction, impulsivity. ADHD tend to manifest in about 50% of individuals diagnosed as disruptive behavioral disorders.

***Keywords**: Behavioural disorders, comorbidities, ADHD.*

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Background

Disruptive behavior disorders (DBD) present high comorbidity rate mainly for opposite-defiant disorders that are frequent among children, adolescents and adults affected by with attention deficit and hyperactivity disorder (ADHD), probably as result of common temperamental risk factors such as attention, distraction, impulsivity. ADHD tend to manifest in about 50% of individuals diagnosed as disruptive behavioral disorders[1-6].

Actually, ADHD is included in the DSM-5 chapter of neurodevelopmental disorders and defined as a persistent pattern of inattention and/or hyperactivity-impulsivity interfering with the normal functioning or development[1-6].

Inattention tends to manifests as inability to remain focused on a certain task, easy distraction, lack of perseverance, difficulty in paying attention to details, and organizing tasks or other daily activities. This inattention is not caused by a challenging attitude, as can be the case in provocative opposition disorder or lack of understanding[7-15].

Hyperactivity refers to excessive motor activity in contexts and places when inappropriate, therefore the subject fails to stand still, and even when it is stopped shaking, moving hands or feet, often leaves the place in situations where he/she must be sitting (i.e. school, work), but hyperactivity can also be manifested as extreme loquacity[16-20].

Impulsivity refers to the inability to reflect, mediate, and possibly expel behavioral responses,

taking into account the needs defined by the context. The subject does not think before acting, cannot waiting for their turn in games or activities, intrudes into the games and activities of others in an intrusive way or in interrupting conversations[21-30].

Depending on which symptom is most expressed, the DSM-5 distinguishes the ADHD in three categories: if there are both signs of inattention, hyperactivity and impulsivity, we have a combined manifestation, if there is only neglect, we talk about manifestation with predominant inattention , and finally the presence of hyperactivity and impulsiveness without any negligence outlines a manifestation with predominant hyperactivity / impulsivity[31-50].

On the other hand, the ICD-10 defines attention deficit and hyperactivity disorder as hyperkinetic disorder (code F90), whose diagnosis requires simultaneous inattention, impulsivity and hyperactivity. Additionally, DSM-5 includes mild forms, if there are few symptoms or if they cause minor compromises in the overall functioning of the subject, serious forms if the symptoms are many or involve marked functional impairment, and moderate forms of horseback between the mild forms and those serious. Attention deficit and hyperactivity disorder begins in childhood, in fact the symptoms must occur before 12 years, without specifying an early onset due to the difficulty in establishing the exact moment in which the symptoms appear. Disturbance events must be present in multiple contexts (eg home and school, work) for more than six months, and must interfere with the normal social or work performance of the subject. The symptoms of ADHD tend to have some evolution over time: in preschool age the main manifestation is hyperactivity, while in primary school the prevalence of inattention becomes impacting[51-70].

During adolescence, signs of hyperactivity are less common and leave more room for inner agitation, restlessness, and an inner sensation of nervousness. In adulthood tend to persist in inactivity and impulsiveness, which express themselves in making important decisions without considering the long-term consequences, in a daunting way, of accepting a job without information. Population studies indicate that ADHD is present in most cultures in about 5% of children and 2.5% in adults.

In the general population, ADHD is more common in males with an approximate ratio of 2: 1 in children and 1.6: 1 in adults. Females also tend to have males to show primarily inattention features. Among the risk factors for the development of the ADHD plays an important role in the presence of familiarity, especially the presence of this disorder in the parents of affected people is very high[49-61].

Etiology

ADHD's inheritance is consistent even though no specific genes involved in genesis have been identified this disorder. Among the relevant causes, we can assume that the very low birth weight (<1500g) represents a doubled or tripled risk of developing this disorder, but on the other hand, most children with low birth weight will not develop ADHD. Exposure to toxic environmental factors during intrauterine life such as alcohol, cigarette smoking and childhood contact with neurotoxic substances (such as lead) or infections (encephalitis) are related to subsequent development of ADHD but It is not known whether they are related to a causal relationship. In children with this disorder can also be present a history of abuse during childhood, neglect and multiple adoptions[49-61].

ADHD outcomes

ADHD children show reduced school outcomes as a result of attentive difficulties, and will also be rejected by their companions because they are considered annoying or lazy because of their impulsive behavior and hyperactivity. Family relationships are often characterized by discord and negative interactions that, together with peer rejection, can lead to adolescence to develop comorbidity in a behavioral or mood disorder and in adulthood an antisocial personality disorder, increasing both the risk of Suicide attempts that are likely to develop substance abuse disorders and get into jail. Moreover, individuals with ADHD reach a lower level of schooling and have less personal success. In the diagnostic test, once established that symptoms of hyperactivity, impulsivity, and / or discomfort reach a level that meets the criteria for diagnosing ADHD, it is necessary to rule out that these do not fall into other diagnostic categories, often for example children with intellectual disabilities Presenting hypercinetic behaviors, poor pulse control or easy distraction, but secondary, or cognitive-like difficulties. In children with anxiety disorders there is great difficulty in concentration and high levels of activity, even in this case secondary to an anxious background picture. A highly impulsive behavior is present in intermittent explosive disorder which is, however, rare in infancy. An increase in motor activity is also present in other neurode-

velopmental disorders such as stereotyped motion disorders and in some cases of autistic spectrum disorder, but in these cases the motions are fixed, stereotyped while in the ADHD the motor hyperactivity is typically generalized. Inattention can also be observed in children with specific learning disabilities, but in these cases it is more due to frustration and is still limited to the school context. Many children with mood disorders exhibit increased levels of activity, poor pulse control and difficulty concentrating, but in this case they are also attributed to mood disorder.

ADHD is also common as comorbid disorders, first of all the provocative opposition disorder that occurs in concomitant use in half the children with ADHD. A disorder of conduct can occur in about a quarter of children or adolescents with ADHD. The specific learning disorder commonly occurs in conjunction with ADHD, while less commonly the disorder of disruptive mood disorder, anxiety disorder, major depressive disorder, intermittent explosive disorder, obsessive-compulsive disorder, Tic disorders, and autistic spectrum disorders. Adulthood may occur in conjunction with the ADHD for substance abuse, even if in a minority of cases, antisocial personality disorder and other personality disorders. By referring to the comorbidity of disruptive behavioral disorders, often provocative opposition disturbances.

The disorder of conduct, although this seems to be more common in children with childhood recurrence. Individuals with provocative opposition disorder are also at greater risk of anxiety disorders and more depressive disorder, and this seems largely attributable to the presence of symptoms of anguish / irritability. Adolescents and adults with provocative opposition disorder also exhibit a higher rate of substance use disorders, although it is unclear whether this association is independent of comorbidity with the behavioral disorder.

How long it is common to find provocative opposition disorder and attention deficit and hyperactivity disorder, and this comorbid situation predicts the worst outcomes. Individuals with personality features associated with antisocial personality disorder often violate the fundamental rights of others or the main age-appropriate social norms, and consequently their patterns of behavior often meet the criteria for behavioral disorders. This may also coexist with one or more of specific learning disorders, anxiety disorders (depressive or bipolar), and substance-related disorders.

School outcomes, particularly in reading and other verbal skills, are often inferior to those expected by age and intelligence and can justify the additional diagnosis of specific learning disorder or communication disorder[71-100].

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REVIEW ARTICLE

The Challenge of Pharmacotherapy in Children and Adolescents with Epilepsy-ADHD Comorbidity

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Abstract Epilepsy is common in children and adolescents where its prevalence is 3.2–5.5/1000. About one-third of patients also have attention deficit hyperactivity/impulsivity disorder (ADHD). The possible relationship between epilepsy and ADHD is still unclear, and ADHD symptoms (such as inattention, hyperactivity, behavioral disturbances) are frequently considered as adverse effects of antiepileptic drugs (AEDs). The literature was searched for data on the behavioral effects of AEDs. Phenobarbital is the most frequently reported medication to induce symptoms of ADHD, followed by topiramate and valproic acid. Phenytoin seems to exert modest effects, while for levetiracetam there are contrasting data. Lacosamide induces some beneficial effects on behavior; carbamazepine and lamotrigine exert favorable effects on attention and behavior. Gabapentin and vigabatrin have limited adverse effects on cognition. Oxcarbazepine, rufinamide, and eslicarbazepine do not seem to aggravate or induce ADHD symptoms, whereas perampanel can lead to a high incidence of hostile/aggressive behavior, which increases with higher dosages. Information about the behavioral effects of ethosuximide, zonisamide, tiagabine, pregabalin, stiripentol, and retigabine is still limited. Because ADHD significantly affects the quality of life of epilepsy patients, the clinical management of this neuropsychiatric disorder should be a priority. Methylphenidate is effective most children and adolescents with ADHD symptoms and comorbid epilepsy, without a significant increase of seizure risk, although data are still limited with few controlled trials.

Key Points

Epilepsy is a common disease in children and adolescents, and in one-third of cases it is associated with ADHD symptoms.

Some antiepileptic drugs have the potential of inducing/worsening ADHD symptoms.

Methylphenidate is safe and effective in most patients with epilepsy/ADHD comorbidity.

1 Introduction

Epilepsy is a common condition in children, where its prevalence is approximately 3.2–5.5/1000 in developed world [1]. It has been estimated that 12 %–39 % of children with epilepsy also have from attention deficit hyperactivity/impulsivity disorder (ADHD) [2, 3].

Several hypotheses have been advanced to explain the association, including a similar genetic predisposition and a common pathophysiology, as in frontal lobe epilepsy and subclinical epileptiform activity [4, 5]. Animal models of ADHD suggest that abnormal excitatory glutamatergic

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transmission may determine an increased susceptibility to both epilepsy and ADHD, giving some clues to identify common pathophysiological pathways between the two conditions [6–8]. There is some preclinical evidence that monoaminergic dysfunction might contribute to this comorbidity [9]. ADHD is associated with cortical gray matter volume deficits, and may represent a state of diminished dopamine stimulation that is equally disruptive to normal mechanisms of synaptic plasticity [10].

ADHD is characterized by inattention and hyperactivity present alone or in combination but impulsivity, aggressiveness and behavioral disturbance are frequently present [11]. ADHD symptoms in patients with epilepsy are frequently underestimated and undertreated, or considered as adverse effects of antiepileptic drugs (AEDs) or as a consequence of poor seizure control [12]. Indeed, ADHD can be present in a variety of different ways in children with epilepsy, and symptoms often predate the onset of epilepsy. Several mechanisms may account for its high prevalence, including underlying brain pathology, a genetic predisposition, dysregulation of the noradrenergic system, the chronic effects of seizures, the effects of AEDs, as well as psychosocial factors. Despite the relatively high incidence of ADHD and epilepsy, their possible relationship is still unclear. Some studies have shown that children with ADHD and epilepsy show a prevalence of the inattentive subtype compared with those with ADHD alone, who show higher rates of the combined subtype [13]; according to other studies, the combined subtype is more common in children with epilepsy who also have ADHD, as in the general population [14]. Although Socanski et al described that the male to female ratio appears to be close to 3:1, similar to that seen in the general population, several series have found no difference or even a female preponderance [14, 15]. Since patients with both conditions have a poorer health-related quality of life compared with those with epilepsy alone, diagnosing ADHD is clearly a priority. ADHD diagnosis and assessment in these patients is quite a complex process that requires the concomitant use of ADHD-specific measures and rating scales as well as evaluation of longitudinal history to understand the time course of the two sets of symptoms [16]. Detailed expert clinical interviews are highly useful to discriminate the effects of seizures from those of AEDs, if present, particularly on attention [16].

Seizure frequency is positively associated with ADHD, and symptoms of hyperactivity are often associated with intractable epilepsy [5]. Benign childhood epilepsy with centrotemporal spikes (BECTS), complex focal seizures, frontal lobe epilepsy, and absence seizures are more often associated with such symptoms. In particular, ADHD is present in the majority of children with frontal lobe epilepsy; in these patients, seizure control does not ameliorate either behavioral or attentional symptoms [2, 17].

Several AEDs present neurologic/neuropsychiatric adverse effects, including ideomotor slowing, inattention, aggression and various behavioral disturbances, thus having the potential of acting on core and comorbid symptoms of ADHD. Therefore, AED selection is crucial, since besides achieving seizure control it should not worsen ADHD symptoms, and if possible, it should improve them [18]. Notably, rapid titration and high dosage for some drugs, such as perampanel, have been shown to worsen ADHD symptoms, and polytherapy may be associated with worse cognitive performance compared with monotherapy [5, 19].

The objectives of this review are to give clinicians some practical clues to drive the choice of the most appropriate AED in children and adolescents with epilepsy-ADHD comorbidity, and to highlight benefits and risks of ADHD treatments on seizures (Tables 1, 2).

2 Literature Search

The records were obtained by searching the PubMed, MEDLINE, and EMBASE databases for studies conducted in children and adolescents. Search terms were “Phenobarbital”, “Valproic Acid”, “Phenytoin”, “Topiramate”, “Perampanel”, “Carbamazepine”, “Lamotrigine”, “Lacosamide”, “Levetiracetam”, “Oxcarbazepine”, “Gabapentin”, “Vigabatrin”, “Rufinamide”, “Eslicarbazepine”, “Ethosuximide”, “Zonisamide”, “Tiagabine”, “Pregabalin”, “Stiripentol”, “Retigabine” and “Epilepsy” and “ADHD” or “Attention-Deficit/Hyperactivity Disorder” and “children” and “adolescents” and “pediatric age”. Only studies in English were included and their reference lists was consulted for any additional relevant papers. Reviews, systematic reviews, textbooks, and case reports were examined for any further publications. The date of the last search was September 2017.

3 Effects of AEDs on Behavior

AEDs have been classified according to their mechanism of action. When multiple mechanisms of action are known for a same drug, they have been grouped on the basis of the principal one.

3.1 AEDs Acting on Sodium and/or Calcium Channels

A double-blind, randomized controlled clinical trial on 453 children, evaluating efficacy, tolerability, and

Table 1 Effects of antiepileptic drugs (AEDs) on behavior

AEDs with negative behavioral effects[a]	AEDs with positive behavioral effects[b]	AEDs with neutral, uncertain or conflicting data on behavioral effects	No data
Phenobarbital	Carbamazepine	Levetiracetam	Retigabine
Valproic Acid	Lamotrigine	Oxcarbazepine	Stiripentol
Phenytoin		Gabapentin	Tiagabine
Topiramate		Vigabatrin	Pregabalin
Perampanel		Rufinamide	
Ethosuximide		Eslicarbazepine	
Zonisamide		Lacosamide	

[a] First column lists all the antiepileptic drugs for which there is evidence of negative effects on behavior and whose administration should therefore be limited in children and adolescents with comorbid attention deficit hyperactivity/impulsivity disorder (ADHD)

[b] Second column reports the only two AEDs for which there are clear data reporting benefits on behavior. Then there is a list of all drugs for which there are no specific (positive or negative) or conflicting data

Table 2 Principal studies about the effects of antiepileptic drugs (AEDs) on cognition and behavior in children and adolescents

Drugs	Reference no.	Study design	No. patients	Outcome cognitive	Outcome behavioral
Lacosamide	[29]	Prospective	33	Neutral	Neutral
Lacosamide	[28]	Retrospective	70	Positive	Neutral
Lacosamide	[30]	Open label	79	Neutral	Neutral
Levetiracetam	[43]	Double blind	99	Neutral	Negative
Levetiracetam	[41]	Open label	103	Neutral	Neutral
Levetiracetam	[42]	Retrospective	76	Neutral	Neutral
Oxcarbazepine	[31]	Open label	112	Neutral	Neutral
Oxcarbazepine	[32]	Open label	52	Neutral	Neutral
Perampanel	[44]	Double blind	143	Neutral	Negative
Perampanel	[45]	Retrospective	58	Neutral	Negative
Perampanel	[46]	Retrospective	62	Neutral	Negative
Perampanel	[48]	Prospective	154	Neutral	Negative
Perampanel	[49]	Double blind	79	Neutral	Negative
Perampanel	[50]	Double blind	1038	Neutral	Negative
Rufinamide	[34]	Double blind	189	Neutral	Neutral
Valproic acid	[20]	Double blind	453	Negative	Neutral

For the aim of this table, the term "neutral" refers to the lack of specification, in the original paper, of differential results for specific cognitive areas or behaviors, and to the presence of conflicting data in the same manuscript (for example a manuscript could give an overall positive interpretation of behavioral effects of a drug, but specifying that a certain number of patients presented a cognitive/behavioral adverse event)

neuropsychological effects of ethosuximide, valproic acid, and lamotrigine in children with newly diagnosed childhood absence epilepsy demonstrated that attentional dysfunction was more common with valproic acid [20]. A double-blind randomized controlled clinical trial evaluating short-term neuropsychological effects on attention of ethosuximide, valproic acid and lamotrigine, including assessment of attention and executive functions in childhood absence epilepsy, reported attention deficit in 49% of subjects receiving valproic acid, 32% of those receiving ethosuximide, and in 24% of those receiving lamotrigine. These results provide a Class I evidence that valproic acid is associated with more significant attention problems than ethosuximide or lamotrigine in children with newly diagnosed childhood absence epilepsy [21].

In a 12-week open-label study exploring the cognitive outcome of 53 children treated with topiramate, no significant changes were revealed; topiramate monotherapy was associated with better cognitive outcomes than treatment with add-on therapy [22].

A retrospective study investigating the long-term effects of zonisamide as a monotherapy in different seizure types

on 60 patients, revealed memory loss in 35% of patients, and attention deficit in 27% [23]. A case-control study specifically aimed at determining the incidence of psychiatric and cognitive adverse events of zonisamide leading to discontinuation, included a total of 544 patients [24]. The incidence of discontinuation due to psychiatric adverse events was 6.9%, and to cognitive adverse events 5.8%. The discontinuation appeared to be associated with a higher number of concomitant AEDs and a lower maximum zonisamide serum concentration [24].

In a study of pediatric patients with a new diagnosis of epilepsy and comorbid ADHD, lamotrigine was administered for treating ADHD symptoms [25]. It has been found to significantly decrease ADHD scores in a recent retrospective study on 90 patients [25], unfortunately full interpretation of these results is limited because of the use of a Korean test to measure ADHD symptoms.

Riva and Devoti [26] evaluated the neuropsychological effects of carbamazepine withdrawal in children with symptomatic epilepsy and reported that this drug, at therapeutic level, didn't have consequences on intellectual-attentional skills; nevertheless, carbamazepine withdrawal led to a significant improvement of scores on frontal function tests, suggesting that these functions could be better without carbamazepine treatment, maybe because its ability to decrease neuron membrane excitability could reduce the information circuitry, particularly in the frontal area [26]. This was not confirmed by a more recent multicenter, randomized, open-label trial comparing the cognitive and behavioral effects of lamotrigine to carbamazepine as monotherapy for pediatric results [27]. A total of 67 children completed the study, with a statistically significant improvement of externalizing behavior in the carbamazepine-treated children [27].

A retrospective controlled study evaluating the impact of adjunctive lacosamide on cognition in patients with epilepsy, compared to topiramate and lamotrigine, demonstrated that lacosamide does not induce negative cognitive effects, rather it seems to have an enhancing effect similar that of lamotrigine [28]. An open prospective clinical study including 33 patients with refractory epilepsy treated with adjunctive lacosamide showed that lacosamide does not have negative effects on information processing speed [29]. A prospective open-label treatment study of 79 children with a mean age of 8.84 years has found a significant improvement in behavior as measured with the Conners Comprehensive Behavior Rating Scales; however, hyperactivity was among the most commonly reported adverse events and led to discontinuation in one patient [30]. Although some data suggest that lacosamide may improve cognition and behavior, the available evidence is insufficient to formulate recommendations.

A multicenter open-label, randomized study evaluated the cognitive effects of oxcarbazepine versus carbamazepine or valproic acid in children with newly diagnosed focal seizures [31]. Among the 99 patients completing the study, an improvement of mental processing speed in the absence of cognitive impairment was observed in all the three groups of treatment over a 6-month period [31]. The lack of adverse events on cognition was also confirmed by a smaller clinical study on 52 drug-naïve patients, evaluated before and after 6 and 12 months of oxcarbazepine treatment [32].

Two single-blind studies have been conducted to evaluate the cognitive and psychomotor effects of eslicarbazepine acetate in healthy volunteers aged 18–45 years; however, the adverse effects in this age range might be different from those in children. The results of several tests, including executive function and memory, showed that eslicarbazepine does not cause clinically relevant cognitive impairment or ADHD symptoms in these subjects [33]. Here too, the available data are insufficient to draw any conclusion.

Rufinamide is one of most investigated drugs among the new AEDs. A double-blind, randomized, placebo-controlled multicenter study of 189 patients aged 15–64 years receiving one of four daily doses of rufinamide (200, 400, 800, 1660 mg) evaluated cognitive skills, including attention and working memory [34]. After 12 weeks, none of the patients showed a significant worsening compared with baseline (before rufinamide) on any cognitive test. However, the age range of the sample studied significantly limits the interpretation of the results. In a pooled analysis of safety and tolerability data from seven clinical studies of epilepsy, rufinamide was not associated with an increased risk of psychiatric adverse events. There is no evidence suggesting that it could worsen ADHD symptoms when administered to children with epilepsy and ADHD. Unfortunately, the available data are still insufficient to advance any recommendation.

3.2 GABAergic AEDs

In a double-blind crossover study of 21 children, measuring the effects of phenobarbital and valproic acid on cognitive functioning and behavior, children performed significantly less well while receiving phenobarbital [35].

In a Phase 3, randomized, double-blind study analyzing data from 194 children and adolescents with Lennox-Gastaut syndrome treated with clobazam, aggression-related events have been reported in 13.9% of patients with a dose dependency [36]. In a clinical study of 63 children treated with clobazam, 7 (11%) developed incessant motor activity, aggressive agitation, self-injurious behavior, and insomnia [37].

A recent retrospective study described 1.3% of intolerable psychiatric and behavior adverse events leading to discontinuation among a total of 76 children and adolescents treated with gabapentin [38]. In the same study, when vigabatrin was administered to 30 patients aged <18 years, psychiatric and behavioral adverse events were described in 6.7% of patients, and led to discontinuation in 3.3% [38–40].

3.3 AED Acting on Synaptic Vesicle Protein 2A

In a long-term open-label extension study of adjunctive levetiracetam to evaluate cognition and behavior in children with focal seizures, Schiemann-Delgado et al reported an improvement in memory tests [41]. Opposite results have however been obtained by different studies. A retrospective study on 76 patients with inadequate control of seizures with AEDs assessed the efficacy and tolerability of long-term levetiracetam treatment [42]. Irritability and hyperactivity were more frequent than in previous studies, especially in children who also had autism or ADHD, and suggested that behavioral changes should carefully be monitored during levetiracetam treatment in these patients, since they represented the most common cause for discontinuation [42]. A randomized, double-blind, placebo-controlled study evaluating neurocognitive effects of adjunctive levetiracetam in 98 children with focal seizures, found a significant rate (≥10%) of aggression [43]. More recently, a retrospective chart analysis of 922 epileptic children and adolescents, including 308 treated with levetiracetam, found that it was the AED most frequently associated with psychiatric and behavioral side effects, often leading to dosage reduction or drug withdrawal [38]. Overall, available data on levetiracetam are still contradictory, but suggest that caution should be used when administering it to children and adolescents with epilepsy and comorbid ADHD.

3.4 AEDs Acting on Glutamate Receptors

Perampanel is the most recent and the most intensively investigated of the "newest" AEDs. The FDA lists "serious psychiatric and behavioral reactions" as potential adverse effects of perampanel. A pooled analysis derived from three Phase III trials and an open-label extension study found that 8.2% of 143 adolescents receiving perampanel showed aggressive behavior [44]. Challenging behaviors (e.g. aggressiveness, irritability, and other behavioral disturbances) have been described in 11 % of the 355 pediatric patients for whom data are available in the literature [44–49], whereas psychiatric adverse events appeared to be associated with higher daily doses (up to 12 mg) [50]. These events were much more frequent during the titration phase, in the first six weeks of treatment. Slow titration seems to reduce their incidence and severity. Perampanel withdrawal due to psychiatric adverse events occurred in a minority (2.5%) of patients in Phase III trials, and the dose was sometimes reduced, suggesting that such psychiatric events can be avoided with dose adjustments [50]. The available data do not allow establishing whether a history of psychiatric illness involves a higher risk of perampanel-induced psychiatric adverse effects. Since most clinical trials exclude patients with active psychiatric symptoms, real-world data are needed to gain additional information [48].

As regards tiagabine, pregabalin, stiripentol, and retigabine, no studies that examined their cognitive or behavioral effects in children and adolescents were found. Tables 1 and 2 summarizes the effects on behavior and cognition of AEDs, and the main studies evaluating these effects.

4 Efficacy and Safety of Treatment Options for ADHD in Children and Adolescents with Epilepsy

The guidelines for the treatment of children with ADHD suggest a comprehensive multimodal therapeutic strategy where medication is an important component. Drug treatment is started with a trial dose of a stimulant, either methylphenidate or amphetamine, or with atomoxetine according to the individual characteristics, comorbidities and specific issues for compliance [51, 52].

Amphetamines appear to be the most effective drugs when compared to methylphenidate and non-stimulant drugs [53]; however, there is a paucity of data regarding the real risk of these drugs of inducing seizures.

Methylphenidate blocks dopamine and noradrenaline reuptake into neurons, it appears to stimulate the cerebral cortex and subcortical structures. Information suggesting a seizure threshold decrease with methylphenidate is very limited. Gross-Tsur et al. [54], in a double-blind crossover study on 30 children, showed that no significant changes on EEG findings were observed; however, 3 out of 5 children with active seizures presented an increase in seizure frequency [54]. An open label study of 25 children with ADHD and active epilepsy showed that 2 children had seizure attacks during the study, without having to discontinue the trial drug [55]. A clinical study of methylphenidate in 57 patients with ADHD and active epilepsy and 62 patients with ADHD and EEG abnormalities aged 6 to 16 years, showed that seizure frequency did not change from baseline and no increase of EEG abnormalities were observed [56]. A more recent open-label, noncontrolled trial aimed at evaluating methylphenidate safety in children

with comorbid epilepsy and ADHD, enrolled 30 patients [57]. The Authors found a significant reduction in seizure frequency and severity, while only one out of 30 patients withdrew because of seizure worsening, underlining that methylphenidate is safe and effective in patients with ADHD and difficult-to-treat epilepsies [57]. Overall, these studies strongly suggest that methylphenidate does not increase seizure risk in children and adolescents with active epilepsy and ADHD.

Atomoxetine, a non-stimulant drug approved for the treatment of ADHD, is usually considered as a second-line therapy since its efficacy is lower than methylphenidate and amphetamines [58]. In a large cohort study of the risk of seizures in a pediatric population treated with atomoxetine or stimulant medications, McAfee et al [59] found that atomoxetine was associated with a non-statistically significant 28% lower risk of seizure compared to stimulant therapy. These findings do not support an increase of seizure frequency and severity with atomoxetine therapy.

5 Discussion and Conclusion

Since ADHD significantly and adversely affects quality of life and cognitive functioning in children and adolescents with epilepsy, its clinical management is a clear priority. Treatment of ADHD symptoms in children and adolescents with active epilepsy is still challenging for clinicians, who should avoid drugs that may reduce attention while trying to choose the most appropriate AED according to seizure type. In the clinical practice, the risk of psychiatric adverse events induced by AEDs seems to be largely related to several factors, including previous psychiatric history, severity of epilepsy, polytherapy, rapid titration, and high dosage.

In patients with epilepsy and ADHD, carbamazepine and lamotrigine may exert more favorable effects compared with other AEDs, since besides controlling seizures they enhance attention and behavior. With regard to the newest AEDs, lacosamide has demonstrated some beneficial effects on behavior, while rufinamide and eslicarbazepine have shown no potential to worsen/induce ADHD symptoms. Perampanel has been reported to involve a higher incidence of hostility and aggression, suggesting that patients should be monitored for these events during treatment, especially during titration and during administration of higher doses. Data on the tolerability profile of the newest AEDs in children and adolescents are still limited. However, some indirect information on their effects on ADHD patients can be garnered from the literature regarding the effects of AEDs on both cognition and behavior. In such patients, seizure control may improve attentional problems, and further improvement can be obtained with stimulant treatment.

The available evidence on the treatment of epilepsy and ADHD comorbidity in children and adolescents is still insufficient due to several limitations such as the inadequate sample size, the lack of controlled trials, the short periods of treatment, and the heterogeneity of clinical series (e.g. patients with different epilepsy duration, different etiologies, type, treatment, seizure-free period before treatment, and follow-up). Furthermore, most published papers fail to provide an accurate ADHD diagnosis with appropriate neuropsychological evaluations, and include children with both normal intelligence and intellectual disability.

More work should be done to better understand the pathophysiological mechanisms of action leading to neuropsychiatric adverse events of AEDs, thus paving the way for improving our knowledge of how different AEDs can negatively affect behavior, and for more individualized treatment strategies for children and adolescents with epilepsy and comorbid ADHD. Future studies should include larger samples of children, possibly with a definite epilepsy syndrome treated with one single AED, with evaluations of neuropsychological deficits, emotional and behavioral aspects, to clarify and disentangle behavioral, cognitive and neuropsychological effects of AEDs in children and adolescents with comorbid ADHD.

Compliance with Ethical Standards

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Conflict of interest Romina Moavero and Paolo Curatolo have received honoraria from Novartis. Alberto Verrotti, Gianvito Panzarino, Claudia Di Paolantonio and Renata Rizzo declared no conflict of interest

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JAMA Psychiatry | Original Investigation

Association of Risk of Suicide Attempts With Methylphenidate Treatment

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IMPORTANCE Patients with attention-deficit/hyperactivity disorder (ADHD) are at an increased risk of attempting suicide. Stimulants, such as methylphenidate hydrochloride, are the most common treatment for ADHD, but the association between their therapeutic use and suicide is unclear.

OBJECTIVE To investigate the association between methylphenidate and the risk of suicide attempts.

DESIGN, SETTING, AND PARTICIPANTS A population-based, electronic medical records database from the Hong Kong Clinical Data Analysis & Reporting System was used to identify 25 629 individuals aged 6 to 25 years who were treated with methylphenidate between January 1, 2001, and December 31, 2015. Those who had attempted suicide were included in the analysis. A self-controlled case series design was used to control for time-invariant characteristics of the patients.

MAIN OUTCOMES AND MEASURES Relative incidence of suicide attempt during periods when patients were exposed to methylphenidate compared with nonexposed periods.

RESULTS Among 25 629 patients with methylphenidate prescriptions, 154 had their first recorded suicide attempt within the study period; of these individuals, 111 (72.1%) were male; mean (SD) age at baseline was 7.15 (2.19) years. The overall incidence of suicide attempts during methylphenidate treatment was 9.27 per 10 000 patient-years. An increased risk of suicide attempts was detected during the 90-day period before methylphenidate was initiated, with an incidence rate ratio (IRR) of 6.55 (95% CI, 3.37-12.72). The IRR remained elevated during the first 90 days of treatment (IRR, 3.91; 95% CI, 1.62-9.42) before returning to baseline levels during ongoing treatment (IRR, 1.35; 95% CI, 0.77-2.38). When the risk during the first 90 days of treatment was compared with the 90 days preceding first treatment, the incidence of suicide attempts was not elevated (IRR, 0.78; 95% CI, 0.26-2.35).

CONCLUSIONS AND RELEVANCE The incidence of suicide attempts was higher in the period immediately before the start of methylphenidate treatment. The risk remained elevated immediately after the start of methylphenidate treatment and returned to baseline levels during continuation of methylphenidate treatment. The observed higher risk of suicide attempts before treatment may reflect emerging psychiatric symptoms that trigger medical consultations that result in a decision to begin ADHD treatment. Therefore, this study's results do not support a causal association between methylphenidate treatment and suicide attempts.

Supplemental content

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Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children, with worldwide prevalence rates in school-aged children estimated at 5% to 7%.[1,2] In Hong Kong (HK), the reported prevalence of ADHD is estimated to be 6.1% in schoolboys and 3.9% in early adolescents.[3,4] Attention-deficit/hyperactivity disorder is associated with a diverse range of mental health comorbidities and adverse health, academic, and psychosocial outcomes.[5-8] Individuals with ADHD are at increased risk of both attempted and completed suicide, even if comorbid psychiatric disorders are clinically treated.[9]

National guidelines recommend psychostimulant medication for the treatment of ADHD.[10-12] During the past 2 decades, the rate of medication use for ADHD has risen rapidly worldwide.[13-18] The prevalence of ADHD medication use in HK is approximately 1% in school-aged children and adolescents and has increased 14-fold over the past decade.[18] Methylphenidate hydrochloride, in particular, is commonly used as the first-line therapy. In 2009, the European Medicines Agency conducted a review of the safety of methylphenidate. The review concluded that further research on the association between methylphenidate and psychiatric adverse effects, including suicide risk, was needed.[19]

Although there has been some concern about a potential association between methylphenidate and suicide-related events,[20] few studies have addressed this issue directly. One Swedish register-based study investigated the risk of suicidal behavior among individuals receiving methylphenidate and other stimulants.[21] When comparing treated and nontreated patients with ADHD, this study found that methylphenidate or other stimulant use was associated with a 31% increase in the rate of suicide-related events.[21] However, this analysis did not adjust for potential confounding factors that may account for this association. For instance, a recent study on suicide in school-aged children and adolescents showed that ADHD was overrepresented in suicide victims.[22] Previous studies have also suggested that comorbid disorders and familial/social factors may all play important roles in the association between ADHD and suicide.[9,23-25] In a follow-up analysis in the abovementioned register study, when periods with and without treatment were compared within the same patient, no increased risk of suicide-related events during the treatment periods was found.[21] Therefore, at present, there is still uncertainty around the potential effects of methylphenidate on the suicidal behavior of patients. Hence, the aim of the present study was to examine the association between methylphenidate and the risk of suicide attempts.

Key Points

Question Is treatment with methylphenidate associated with an increased risk of suicide attempts?

Findings In this population-based, case series study of 154 patients with a suicide attempt identified from 25 629 patients who were receiving methylphenidate for treatment of attention-deficit/hyperactivity disorder, the risk of suicide attempts was 6.5-fold higher during the 90-day period before methylphenidate was initiated, remained elevated 4-fold during the first 90 days of treatment, and returned to baseline levels during ongoing treatment.

Meaning The increased risk of suicide attempts preceding the initiation of methylphenidate is not causally related to the drug's effects.

Methods

Data Source

This study used data from the Clinical Data Analysis & Reporting System (CDARS), an electronic health record database developed by the HK Hospital Authority, a statutory body that manages all public hospitals and their ambulatory clinics in HK. The service is available to all HK residents (>7.3 million) and covers approximately 80% of all hospital admissions in HK.[26] Data from CDARS have been validated and used for various investigations of medication safety.[26-33] Patient-specific data in CDARS include diagnosis, prescription, information on hospital admissions and discharges, payment method, and prescription and dispensing information.[34] CDARS contains inpatient, outpatient, and emergency department admissions records, anonymized to protect patient confidentiality. The study protocol was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

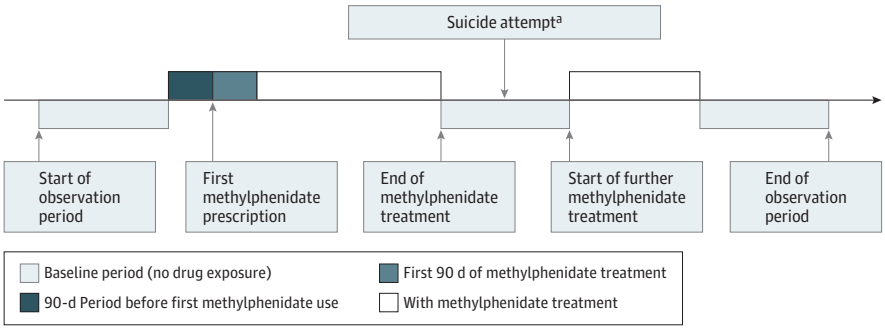
Self-controlled Case Series Design

We used the self-controlled case series (SCCS)[35] study design to investigate the association between methylphenidate and suicide attempts. In this design, used previously to investigate the effects of methylphenidate on trauma and psychosis risk,[30,31] patients serve as their own control.[36] The SCCS design relies on within-person comparisons in a population of individuals who have experienced both the outcome and exposure of interest.[36] Incidence rate ratios (IRRs) are derived by comparing the rate of events during periods of medication exposure with the rate during all other observed time periods (ie, without medication). A major advantage of this design over the classic design is that it controls for potential effects of measured and unmeasured time-invariant confounders that vary between individuals (ie, genetic factors, disease severity, and socioeconomic factors). Furthermore, we adjusted for time-varying factors, such as age and season, which are known to affect methylphenidate treatment prescribing.[37,38] In addition to the standard SCCS analysis, the nonparametric SCCS approach was applied to investigate risk changes during the observation period.[39,40]

Case Identification

Individuals aged 6 to 25 years who received at least 1 prescription for methylphenidate and who had made at least 1 suicide attempt during the study period (January 1, 2001, to December 31, 2015) were identified in CDARS. The suicide attempt codes were identified through the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic codes E950 to E959.[41] The statistical modeling of the SCCS analysis requires incident cases to fulfill the

Figure 1. Illustration of Self-controlled Case Series Study Design



[a] Event can take place any time throughout the observation period; no censoring on the event date.

model assumption[36]; therefore, patients who had made a suicide attempt before the study period were excluded. Only methylphenidate and atomoxetine are licensed for the treatment of ADHD in HK; therefore, the observation periods were censored by atomoxetine treatment to avoid coprescribing situations that could affect comparisons.

We commenced follow-up at age 6 years, as methylphenidate is not recommended for younger children.[42] There has been an increasing trend of methylphenidate use in college-aged young adults up to age 25 years.[43] Observation periods began on January 1, 2001, or the sixth birthday of the patient (whichever was later) and ended on December 31, 2015, the 26th birthday of the patient, date of receiving atomoxetine treatment, or date of registered death (whichever was earlier). Because the aim of this study was to investigate the association between methylphenidate and suicide attempts, all methylphenidate users, regardless of the presence of a formal diagnosis of ADHD, were included.

Exposures and Outcomes

For each included participant, all methylphenidate prescriptions and suicide attempts were identified. All methylphenidate formulations (standard and extended release) and all strengths were included in the analysis. Exposed periods were defined as time receiving medication, with the duration between prescription start and end dates recorded in CDARS for each prescription. More than 99% of the prescriptions had the intended start and end dates as recorded in our data set. Daily dosages and the quantity prescribed were used to determine the duration of treatment if the prescription end date was not available. Median values for exposure duration were imputed when the above information was missing. We divided patient time into 4 discrete categories: absence of methylphenidate (baseline period, including patient-time before and after methylphenidate exposure), 90 days before the first methylphenidate exposure (pre-exposure period), first 90 days of methylphenidate use, and subsequent methylphenidate use. We did not assume that participants received continuous treatment on initiation of methylphenidate, because clinicians may offer drug holidays to patients with ADHD during school holidays and treatment may be stopped and started for various other reasons.[30,31] The pre-exposure period was defined as the time before the first methylphenidate prescription; thus, there were no pre-exposure periods before the second or subsequent methylphenidate treatments. The study design and timeline for a single hypothetical participant are given in **Figure 1**. The corresponding date of a suicide attempt was identified as an event date, and only the first recorded suicide attempt for each patient was included in the analysis. In SCCS designs, there should be no censoring by the outcome of interest, as this would violate their assumption and invalidate the results.[36] We conducted a validation analysis by reviewing the information in CDARS. Through doing this, we identified that, in 153 of 154 (99.4%) cases, the *ICD-9-CM* diagnosis code of a suicide attempt was confirmed in the medical records by an emergency department clinician, hospital pediatrician, and/or psychiatrist. Consequently, the risk of misclassification is considered to be low.

Statistical Analysis

The association between methylphenidate treatment and suicide attempts was calculated by comparing the rate of suicide attempts during exposure periods with that during baseline periods. Adjusted IRR and the corresponding 95% CIs were calculated using conditional Poisson regression, adjusted for age in 1-year bands and season. A 90-day pre-exposure period was added to take account of the possibility that the suicide attempt may affect the likelihood of methylphenidate treatment, which in turn may introduce bias into the risk estimate during treatment. We separated the first 90 days of methylphenidate use to allow the detection of any temporary change in the IRR of suicide attempts, and we also compared the rate of suicide attempts between the pre-exposure period and the methylphenidate-exposed periods. To investigate whether emergent psychiatric disorders could lead to methylphenidate treatment, post hoc analyses were conducted, using the same setting as the original analysis, to test the association between methylphenidate treatment and other psychiatric conditions (*ICD-9-CM* codes 290-319). A significance level of 5% was used in all statistical analyses. SAS, version 9.4 (SAS Institute Inc) and R, version 3.3.1 (http://www.R-project.org) were used for data manipulation and analysis.

Sensitivity Analyses

Sensitivity analyses were planned to test the validity and robustness of the initial study results. These analyses tested the

Table 1. Patient Characteristics

Characteristic	No. of Patients (%)	Age at Baseline, Mean (SD), y	Dose, Median (Range) [IQR], mg/d	Length of Prescription, Median (Range) [IQR], d	Exposed Period		Unexposed Period	
					Events, No.	Total Follow-up Time, Patient-years	Events, No.	Total Follow-up Time, Patient-years
All	154 (100)	7.15 (2.19)	20 (2.5-60) [15-35]	70 (1-1023) [35-105]	44	342.1	110	1529.6
Male	111 (72.1)	7.13 (2.05)	20 (2.5-60) [15-35]	71 (1-838) [42-107]	32	265.4	79	1085.4
Female	43 (27.9)	7.20 (2.54)	20 (5-60) [15-35]	56 (1-1023) [28-96]	12	76.7	31	444.2

Abbreviation: IQR, interquartile range.

Table 2. Incidence of Suicide Attempts Among Methylphenidate Users in Different Risk Windows

Risk Window	No. of Events	Patient-years	Incidence per 10 000 Patient-years (95% CI)
Before prerisk	19	65 362	2.91 (1.86-4.54)
90 d Before first methylphenidate treatment	12	5594	21.45 (12.28-37.46)
First 90 d of methylphenidate treatment	6	4687	12.80 (5.87-27.90)
Subsequent methylphenidate treatment	36	42 728	8.43 (6.09-11.66)
After methylphenidate treatment	81	68 636	11.80 (9.50-14.66)

effects of (1) different drug nonadherence scenarios; (2) restricting the sample to a 6-month age band; (3) more than 10 weeks of methylphenidate exposure; (4) removing patients with a diagnosis of substance misuse/dependence; (5) restricting observation periods to the date of prescription of any antidepressant or antipsychotic medications; (6) removing patients where the event occurred on the first day of prescription; (7) redefining the observation period to January 1, 2001, the sixth birthday of the patient, the first observed date of ADHD diagnosis, or the first date of methylphenidate treatment, whichever occurred last; and (8) restricting to incident patients receiving methylphenidate. The details of these variables can be found in eAppendix 1 in the Supplement.

Results

Among 25 629 patients with methylphenidate prescriptions, 19 had attempted suicide before the observation period and were therefore removed from the analysis, as per protocol. One hundred fifty-four patients had their first recorded suicide attempt within the observation period (eFigure 1 in the Supplement); of these, 111 (72.1%) were male and 43 (27.9%) were female. The mean (SD) age at commencement of observation was 7.15 (2.19) years (range, 6.0-16.47 years), and the mean duration of follow-up per participant was 12.15 (2.82) years. Mean methylphenidate exposure was 2.22 (2.33) years per participant. The median length of each prescription was 70 days (interquartile range [IQR], 35-105 days; range, 1-1023 days), and 3617 of 4300 (84.1%) of the prescriptions were for short-acting methylphenidate. Of 154 patients, 112 (72.7%) had an ADHD diagnosis, and the median age at diagnosis was 10.4 years (IQR, 8.3-13.4 years). Seventy-two (46.8%) patients had at least 1 prescription for an antidepressant or antipsychotic during the study period; 17 began receiving an antidepressant or antipsychotic before their first methylphenidate treatment, and 55 patients started after initiation of methylphenidate. Broader psychiatric comorbidities for these patients are reported in eTable 1 in the Supplement. Among patients without an ADHD diagnosis, 39 of 42 (92.9%) had at least 1 other psychiatric diagnosis (*ICD-9-CM* codes 290-319); 16 of 42 (38.1%) of these had a diagnosis of autism spectrum disorder (eTable 2 in the Supplement). Of the 154 suicide attempts, 44 occurred during methylphenidate treatment and 110 occurred during the off-treatment period (**Table 1**). The median age of the index suicide attempt group was 15.4 years (IQR, 12.7-18.1 years) (eFigure 2 in the Supplement). The overall incidence of suicide attempts during methylphenidate treatment was 9.27 per 10 000 patient-years. The crude incidence of suicide attempts in the different risk windows is summarized in **Table 2**. No participants in the SCCS died of completed suicide during the study period.

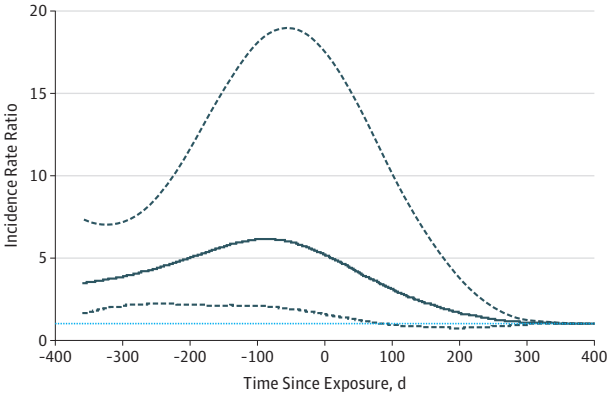
The analysis indicated some association between the decision to start methylphenidate treatment and suicide attempts (**Table 3**). After age and season were adjusted, an increased risk of suicide attempts was detected during the 90-day period before methylphenidate initiation (IRR, 6.55; 95% CI, 3.37-12.72). The IRR remained elevated during the first 90 days of methylphenidate treatment (IRR, 3.91; 95% CI, 1.62-9.42) before returning to baseline levels during prolonged treatment (IRR, 1.35; 95% CI, 0.77-2.38) (Table 3). A direct comparison between the risk of suicide attempts during the pre-exposure period and the methylphenidate treatment period showed that the corresponding risk was not increased during the first 90 days of methylphenidate treatment (IRR, 0.78; 95% CI, 0.26-2.35). However, a 72% lower risk was found in the subsequent period of methylphenidate treatment (IRR, 0.28; 95% CI, 0.08-0.94) compared with the pre-exposure period. Further analysis using nonparametric, spline-based SCCS showed that the risk of suicide attempts increased significantly before the initiation of methylphenidate treatment and reached a peak within 100 days before methylphenidate treatment (**Figure 2**). The age- and sex-stratified results showed a similar pattern to the overall analysis (eTable 3 in the Supplement). Post hoc analysis revealed that an increased risk of any

Table 3. Results From the Self-Controlled Case Series Analyses

Risk Window	Adjusted IRR (95% CI)	*P* Value
Suicide Attempt (n = 154)		
90 d Before 1st methylphenidate treatment	6.55 (3.37-12.72)	<.01
First 90 d with methylphenidate treatment	3.91 (1.62-9.42)	<.01
Subsequent methylphenidate treatment	1.35 (0.77-2.38)	.30
Sensitivity Analyses		
6-mo Age band (n = 154)		
90 d Before 1st methylphenidate treatment	5.36 (2.81-10.23)	<.01
First 90 d with methylphenidate treatment	4.04 (1.87-8.75)	<.01
Subsequent methylphenidate treatment	1.44 (0.88-2.36)	.15
Patients with >10 wk methylphenidate exposure (n = 113)		
90 d Before 1st methylphenidate treatment	5.05 (2.04-12.48)	<.01
First 90 d with methylphenidate treatment	3.38 (1.15-9.89)	.03
Subsequent methylphenidate treatment	1.38 (0.77-2.46)	.28
Censor by antidepressants/antipsychotics (n = 154)		
90 d Before 1st methylphenidate treatment	8.08 (3.88-16.85)	<.01
First 90 d with methylphenidate treatment	5.79 (2.28-14.73)	<.01
Subsequent methylphenidate treatment	1.14 (0.56-2.33)	.72
Remove patients with substance dependence (n = 114)		
90 d Before 1st methylphenidate treatment	6.91 (3.44-13.87)	<.01
First 90 d with methylphenidate treatment	3.69 (1.42-9.6)	<.01
Subsequent methylphenidate treatment	1.42 (0.77-2.61)	.26
Remove cases with event on the 1st day of treatment (n = 137)		
90 d Before 1st methylphenidate treatment	5.54 (2.72-11.29)	<.01
First 90 d with methylphenidate treatment	3.76 (1.56-9.05)	<.01
Subsequent methylphenidate treatment	1.32 (0.75-2.33)	.33
Start of observation at January 1, 2001; the 6th birthday of the patient; the first observed date of ADHD diagnosis; or first date of methylphenidate treatment, whichever occurred last (n = 126)		
90 d Before 1st methylphenidate treatment	7.28 (3.22-16.5)	<.01
First 90 d with methylphenidate treatment	3.65 (1.45-9.18)	<.01
Subsequent methylphenidate treatment	1.25 (0.69-2.28)	.46
Incident methylphenidate users only (n = 140)		
90 d Before 1st methylphenidate treatment	6.57 (3.37-12.8)	<.01
First 90 d with methylphenidate treatment	4.02 (1.66-9.73)	<.01
Subsequent methylphenidate treatment	1.32 (0.73-2.4)	.36

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; IRR, incidence rate ratio.

Figure 2. Results From the Spline-Based Self-controlled Case Series Analysis



Incidence rate ratio (IRR) of suicide attempts throughout the time before and after methylphenidate exposure. The solid line is the estimated IRR, the dashed lines indicate the 95% CI, and the blue dashed line indicates baseline IRR.

psychiatric disorder was detected during the 90-day period before methylphenidate initiation (IRR, 22.14; 95% CI, 21.31-22.99). The risk remained elevated during the first 90 days of methylphenidate treatment (IRR, 9.40; 95% CI, 8.94-9.88) and during prolonged treatment (IRR, 1.53; 95% CI, 1.44-1.62) (eTable 4 in the Supplement). The additional sensitivity analyses did not change this general picture of results (eFigures 3-5 in the Supplement and Table 3).

Discussion

In this population-based, retrospective study, the incidence of methylphenidate-related suicide attempts demonstrated a 6.5-fold and 4-fold elevation during the 90-day periods before and after the start of treatment, respectively. This finding suggests that the decision to start methylphenidate treatment follows the period of increasing risk for suicide attempts, with the risk remaining elevated and then beginning to fall after initiation of methylphenidate. The most parsimonious interpretation of this pattern of temporal association is that the observed increased risk of suicide attempts is not due to methylphenidate but precedes it, perhaps reflecting changes in behavioral and mental health symptoms or associated impairment that lead to a medical consultation, which in turn may contribute to the decision to prescribe methylphenidate. This hypothesis fits with the finding that the incidence of suicide attempts just after treatment initiation was comparable to that just before it, while after more than 90 days of methylphenidate use, the incidence was similar to that during the baseline period. In addition, the spline-based SCCS analysis showed a decreasing incidence of suicide attempts on the initiation of methylphenidate treatment. However, our results cannot be interpreted as demonstrating that methylphenidate has an immediate effect on lowering the risk of suicide attempts. The increased risk of suicide attempts before treatment may have been missed in a classic cohort study in which patients with

either events or exposures before the commencement of the study are usually excluded. To our knowledge, this is the first study investigating the risk of suicide attempts before and after the start of methylphenidate treatment. The study results thus provide new evidence with which to interpret reports of an elevated risk of suicide attempts after initiation of methylphenidate treatment.

Several factors may explain why the initiation of methylphenidate treatment tends to coincide with the times of increased risk of suicide attempts. The initiation of new medication often occurs at a time of specific concerns about patients' health. Patients with ADHD are at higher risk of suicide-related events.[9,21,44] The decision to start treatment with methylphenidate may be a response to changes in behavioral or related psychiatric problems. These problems could be transient psychiatric disorders with ADHD or clinical observation in the period leading to initiation of methylphenidate. It is also well recognized that patients with ADHD are prone to cognitive, emotional, and behavioral comorbidities, for example, depression or disruptive behavioral disorders.[8] These comorbidities may increase the likelihood of suicide attempts, which may consequently increase both the likelihood of medical and psychiatric consultations and receiving a methylphenidate prescription. This position is further supported by the post hoc analysis that found an increased risk of other psychiatric disorders before methylphenidate initiation. A previous study investigating the association between antidepressant medication and suicide also found the peak incidence of suicide attempts to be immediately before initiation of an antidepressant, suggesting that the attempt was a precipitant for initiation of antidepressant treatment.[45] Only 2 patients in our sample died within the study period, and neither of them was receiving methylphenidate treatment at the time of death. Furthermore, the cause of death was not recorded as suicide. Therefore, in our cohort, death by suicide while receiving methylphenidate treatment is a rare outcome.

The suicidal ideation that precedes a suicide attempt may not be an acute event; patients with suicidal ideation may not carry out the attempt immediately.[46] Therefore, there may be a time lag between the beginning of suicidal ideation and the suicide attempt event. This lag could possibly contribute to the increased risk during the first 90 days of methylphenidate treatment (IRR, 3.91; 95% CI, 1.62-9.42).

To our knowledge, only 1 published report evaluated the risk of suicidal behavior in patients receiving methylphenidate and/or other stimulant users. Chen et al[21] identified an increased risk of suicidal behavior in patients receiving ADHD medications (hazard ratio [HR], 1.31; 95% CI, 1.19-1.44) compared with nontreated patients with ADHD. Chen et al further applied a within-individual methodology (ie, comparing patient time with and without medication) and found no increased risk of suicide-related events (HR, 0.89; 95% CI, 0.79-1.00). Among stimulant users, a reduced within-patient rate of suicide-related events was seen during treatment periods (HR, 0.81; 95% CI, 0.70-0.94). Chen et al assumed the risk of suicidal behavior to be constant in nontreatment periods. However, in the present study, we found an increased risk of suicide attempts before the initiation of treatment. This finding suggests, therefore, that the estimate of risk derived by Chen et al may need to be reevaluated.

Limitations

There are a number of limitations to our study. First, CDARS does not have linkage to data from private medical practitioners. However, in HK, the public sector is the main provider of specialist care[47] and there are very few private child and adolescent psychiatrists.[18,48] As a consequence, the vast majority of patients receiving methylphenidate are likely to have been included in this study, and our sample should be highly representative of the HK population. In addition, our cohort included only clinically referred patients who had sufficiently severe ADHD symptoms and/or impairment to have received methylphenidate treatment. Therefore, our cohort may have a higher baseline risk compared with nonmedicated patients. However, since we applied an SCCS design, individual baseline risk does not affect our study results and conclusion. Second, CDARS provides data on drug prescriptions, but not on adherence, which may lead to misclassification of exposure periods. Third, because we had a comparatively long follow-up time, other time-varying cofounding factors may affect the study results. Therefore, we conducted various sensitivity analyses to explore the potential effects of nonadherence and other confounding factors, and the results were consistent.

Conclusions

The incidence of suicide attempts peaked before the start of methylphenidate treatment, remained high immediately after the start of methylphenidate treatment, and declined during continuation of treatment. Our data, therefore, do not support a causal association between methylphenidate treatment and suicide attempts.

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A Naturalistic Comparison of Methylphenidate and Risperidone Monotherapy in Drug-Naive Youth With Attention-Deficit/Hyperactivity Disorder Comorbid With Oppositional Defiant Disorder and Aggression

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Abstract:

Background/Purpose: Attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) are frequently co-occurring in youth, but data about the pharmacological management of this comorbidity are scarce, especially when impulsive aggression is prominent. Although stimulants are the first-line medication for ADHD, second-generation antipsychotics, namely, risperidone, are frequently used. We aimed to assess effectiveness and safety of monotherapy with the stimulant methylphenidate (MPH) and risperidone in a consecutive sample of 40 drug-naive male youths diagnosed as having ADHD-combined presentation, comorbid with ODD and aggression, without psychiatric comorbidities, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria and a structured clinical interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version).

Methods: Twenty males treated with MPH (mean age, 8.95 ± 1.67 years) and 20 males treated with risperidone (mean age, 9.35 ± 2.72 years), followed up to 6 months, were assessed according to efficacy measures (Child Behavior Checklist [CBCL], Clinical Global Impression–Severity [CGI-S] and Improvement [CGI-I], Children Global Assessment Scale), and safety measures. At the end of the follow-up, both medications were similarly effective based on CBCL subscales of aggression and rule-breaking behaviors, on *Diagnostic and Statistical Manual of Mental Disorders*–oriented oppositional defiant problems and conduct problems, and on CGI-S, CGI-I, and Children Global Assessment Scale, but only MPH was effective on CBCL attention problems and attention-deficit/hyperactivity problems. Risperidone was associated with weight gain and elevated prolactin levels.

Implications/Conclusions: Although the nonrandomized, nonblind design limits the conclusions of our exploratory study, our findings suggest that when ADHD is comorbid with ODD and aggression MPH and risperidone are both effective on aggressive behavior, but only stimulants are effective on ADHD symptoms.

Key Words: ADHD, aggression, methylphenidate, oppositional defiant disorder, risperidone, rule-breaking behaviors

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Attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) are frequently co-occurring in youth.[1] This comorbid group shows an earlier age at symptom onset; more physical aggression and delinquency; significantly higher ODD, conduct disorder (CD), and ADHD symptom severity; and greater functional impairments than a group with these disorders as a single diagnosis.[1] Aggression is a common behavioral symptom in ADHD-ODD comorbidity and a frequent indication for referral.[2] A careful understanding of treatment options is thus a priority.[3]

Stimulants, the most used and effective class of medication for ADHD,[4] exert a medium to large effect on aggression in ADHD children comorbid with ODD and/or CD, with a mean effect size of 0.84 for overt and 0.69 for covert aggression[5]; 0.78 and 0.84, respectively, on teachers' measures[6]; and 0.55 on parent-rated oppositional behavior, conduct problems, and aggression.[7] Albeit these findings, antipsychotics, namely, second-generation antipsychotics (SGAs), are frequently and increasingly used to manage aggression,[3,8] even within the context of ADHD.[6,9–11] However, they are often associated with significant adverse events, especially weight gain, metabolic adverse effects, extrapyramidal side effects, and increased prolactin levels.[12]

Although risperidone is by far the most frequently used SGA for aggression in children with different diagnoses, including also ODD and ADHD, a Cochrane review found evidence of limited short-term (4–10 weeks) efficacy in ameliorating aggression and conduct problems in youth.[10] More recently, in children with ADHD, co-occurring ODD/CD and severe physical aggression, who failed to improve after a 3-week trial of parent training and stimulant medication, add-on risperidone was associated with a better response on parent-rated physical and object aggression, but no significant effect in teacher-rated peer aggression.[13]

The aim of our naturalistic study was to assess the effectiveness and safety of 2 treatments in drug-naive children and adolescents with ADHD comorbid with ODD, without other psychiatric comorbidities, receiving either methylphenidate (MPH) or risperidone monotherapy for 6 months.

MATERIALS AND METHODS

Study Design

In this naturalistic study, a consecutive sample of drug-naive youth initially referred for aggression to the ADHD unit or to the disruptive behavior disorders unit of our department participated in the study. Inclusion criteria were an age between 6 and 16 years, a diagnosis of ADHD comorbid with ODD or ODD comorbid with ADHD; no comorbidities with other mental disorders according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria and a structured clinical interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version[14]; and no current or previous pharmacotherapy with psychoactive

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medications. Additional criteria were Clinical Global Impression (CGI) Severity (CGI-S) score of 4 or higher,[15] Children Global Assessment Scale (C-GAS) score of 50 or less,[16] and Full Scale IQ greater than 70. Among this consecutive, unselected sample, the first 20 patients initiated to MPH, and the first 20 patients initiated to risperidone by their clinicians, according to their own clinical judgment, participated in the study. These patients were not included in previous studies from our group. The 2 groups were compared according demographic and clinical variables, including Child Behavior Checklist (CBCL) scores,[17] CGI-S, and C-GAS, and the differences between groups were not significant. There were no dropouts during the 6-month study.

Measures

Parents completed the CBCL, a 118-item standardized format, for recording behavioral problems and skills in children and adolescents from 6 to 18 years of age. The 118 behavior items are aggregated in 8 different syndrome scales. Each item is scored on a 3-step response scale. In order to evaluate children's improvement in aggressive behavior, in our study we used the nonstandardized scores of CBCL aggressive behavior and rule-breaking behavior syndrome scales. Reliability across the time points was 0.78 for the aggressive behavior and 0.85 for the rule-breaking behavior (Cronbach α). Furthermore, the CBCL syndrome scale attention problems and the CBCL total problems were considered, as well as CBCL *Diagnostic and Statistical Manual of Mental Disorders*–oriented scales attention-deficit/hyperactivity problems, oppositional defiant problems, and conduct problems.

Severity of the clinical picture at baseline was assessed by means of the CGI-S score, a single item, which rates the severity of global symptomatology on a scale from 1 ("normal") to 7 ("extremely ill"). Functional impairment was assessed with the C-GAS, which describes the severity on a scale from 0 (severe impairment) to 100 (superior functioning).

As a baseline routine safety procedure, all patients received physical and neurological examinations, including weight, heart rate, pulse monitoring, and blood pressure. Screening procedures included a blood cell count, electrolytes, blood urea nitrogen, fasting glucose, cholesterol (high-density lipoprotein, low-density lipoprotein, total), triglycerides, creatinine, liver function tests (aspartate aminotransferase, alanine aminotransferase), and prolactin serum levels, using an enzyme-linked immune-adsorbent assay, Access Prolactin assay, UniCel DxI 800 (Beckman Coulter, Italy). All baseline prolactin levels were within the reference range (males, 15.0 ng/mL). An electrocardiogram (ECG), with specific attention to the QTc interval, was also obtained.

The CBCL scales, CGI-S, and C-GAS were repeated by the same raters after a 6-month follow-up, along with the safety procedures. Furthermore, the CGI-Improvement (CGI-I) score was used to assess with a global measure the clinical changes in the last 6 months. The CGI-I score is a single item, recorded during the follow-up, rating behavior from 1 ("very much improved") to 7 ("very much worsened").[15] The primary outcome measures were the changes in the CBCL aggressive behavior and rule-breaking behavior syndrome scales. The secondary outcome measures were CBCL attention problems; total problems; *Diagnostic and Statistical Manual of Mental Disorders*–oriented CBCL scales attention-deficit/hyperactivity problems, oppositional defiant problems, and conduct problems; CGI-S; C-GAS; and CGI-I. Data from the assessments were reviewed by the principal investigator (G.M.) and by the interviewers' team for the purpose of consensus.

Treatments and Monitoring

All the 40 patients were drug naive and were treated in monotherapy during the follow-up. The starting dose of MPH was 5 to 10 mg, according to age and weight, with subsequent titrations of 5 to 10 mg no more frequently than at 5-day intervals, with flexible titration, depending on age and weight, clinical outcome, and occurrence of adverse effects, based on weekly monitoring visits during the first month, then monthly. The starting dose of risperidone was 0.25 mg/d, with subsequent titration of 0.25 mg no more frequently than at 2-day intervals, with flexible titration depending on weight, clinical outcome, and occurrence of adverse effects, based on monitoring visits.

In both the MPH and risperidone groups, blood cells count, blood chemistries, and physical examination were repeated after 1 and 4 weeks in the first months, then every 3 months. An ECG was repeated after 1 and 3 months, then every 3 months. An adverse effect checklist based on the most frequent adverse effects of MPH and risperidone was used to assess tolerability.

All subjects and parents received detailed information on the characteristics of the assessment instruments and different treatment options; all parents gave a written informed consent, and all the patients gave their consent as well.

Statistical Analyses

To compare the 2 groups on baseline clinical characteristics, *t* tests (2-tailed) were used; *t* tests (2-tailed) were used to evaluate improvements in C-GAS, CGI-S, and CGI-I in the 2 groups. A repeated-measures analysis of variance (ANOVA) was used with baseline and each assessment for efficacy variables as within-subject factors (labeled "time") and treatment group ("treatment") as between-subjects factor. A treatment × time interaction term was created to test whether the trajectory of response differed over time by treatment groups. $P = 0.05$ (2-tailed) was used to test statistical significance of all results. The analyses were performed using IBM SPSS Statistics version 21.0 for Windows (IBM Corp, Armonk, NY).

RESULTS

Baseline Features

The 20 patients receiving MPH were all males, with an age range between 6 and 12 years and a mean age of 9.35 ± 2.72 years, and received a dosing regimen appropriate for the clinical needs, with a mean final dose of 20 ± 8.2 mg/d (range, 10–40 mg/d). The patients receiving risperidone were all males as well, aged between 6 and 12 years, with a mean age of 8.95 ± 1.67 years, and received a dosing regimen appropriate for the clinical needs and a mean final dose of 1.50 ± 0.45 mg/d (range, 0.50–2.50 mg/d).

There were no statistically significant differences at the baseline between the 2 groups on any of demographic or clinical characteristics, including age, CBCL subscales CGI-S, C-GAS, and CBCL subscales.

Efficacy Measures

Regarding the CBCL scores, the comparison between baseline and 6-month follow-up of patients receiving MPH monotherapy shows that all CBCL scales significantly improved. More specifically, aggressive behavior passed from 18.28 ± 6.16 to 11.78 ± 6.56 ($P < 0.001$), rule-breaking behavior from 6.89 ± 3.22 to 4.61 ± 3.38 ($P = 0.002$), attention problems from 6.67 ± 2.72 to 8.44 ± 2.55 ($P < 0.001$), total problems from 72.50 ± 25.10 to 51.44 ± 23.57 ($P = 0.002$), attention-deficit/hyperactivity problems from 11.22 ± 1.96 to 7.83 ± 2.36 ($P < 0.001$), oppositional defiant problems from 7.44 ± 1.58 to

TABLE 1. Outcomes by Treatment Group (MPH and Risperidone): Baseline (T0)–to–End Point (T1) Changes on the Efficacy Measures (Repeated-Measures ANOVA)

	Mean Change From Baseline to End Point		Repeated-Measures ANOVA			
			Time Effect		Treatment × Time Effect	
	Risperidone (n = 20)	MPH (n = 20)	F	*P*	F	*P*
C-GAS	−7.56	−10.22	134.00	0.000	3.02	0.009
CGI-S	1.25	1.70	14.70	0.000	0.12	0.876
Attention	.94	4.23	22.32	0.000	8.98	0.005
Rule-B	3.22	2.28	15.56	0.000	0.46	0.503
Aggressive	3.56	6.50	21.50	0.000	1.84	0.183
Total	21.89	21.06	15.70	0.000	0.00	0.939
ADHD	1.50	3.39	31.69	0.000	4.73	0.037
ODD	1.50	2.94	32.26	0.000	3.72	0.062
CD	3.23	3.95	17.19	0.000	0.17	0.679

Attention, CBCL attention problems; Rule-B, CBCL rule-breaking behavior; Aggressive, CBCL aggressive behavior; Total, CBCL total problems; ADHD, CBCL ADHD; ODD, CBCL oppositional defiant problems; CD, CBCL conduct problems.

4.50 ± 2.50 ($P < 0.001$), and conduct problems from 9.39 ± 4.64 to 5.44 ± 4.16 ($P = 0.004$). In the patients treated with risperidone, among the CBCL scores, only attention problems and attention-deficit/hyperactivity problems failed to reach statistical significance. More specifically, aggressive behavior passed from 18.78 ± 6.90 to 15.22 ± 7.00 ($P < 0.038$), rule-breaking behavior from 8.72 ± 4.79 to 5.50 ± 3.22 ($P = 0.020$), attention problems from 11.15 ± 3.47 to 10.56 ± 3.26 (not statistically significant), total problems from 85.50 ± 37.46 to 63.61 ± 29.12 ($P = 0.021$), attention-deficit/hyperactivity problems from 10.67 ± 2.45 to 9.17 ± 2.55 (not statistically significant), oppositional defiant problems from 7.22 ± 1.90 to 5.72 ± 1.84 ($P = 0.024$), and conduct problems from 11.17 ± 6.26 to 7.94 ± 5.38 ($P = 0.035$).

The CGI-S improved in the MPH group from 4.6 ± 0.60 to 2.9 ± 0.97 ($t_{19} = 8.79$, $P < 0.001$) and in the risperidone group from 4.75 ± 0.64 to 3.5 ± 0.89 ($t_{19} = 6.6$, $P < 0.001$).

The C-GAS improved in the MPH group from 38.75 ± 4.43 to 47.95 ± 5.89 ($t_{19} = -12.7$, $P < 0.001$) and in the risperidone group from 36.90 ± 2.88 to 44.35 ± 3.88 ($t_{19} = -9.2$, $P = 0.001$).

The CGI-I was 2.3 ± 0.92 in the MPH group and 2.75 ± 0.79 in the risperidone group ($t_{38} = -1.7$, not statistically significant). According to a CGI-I score, 10 patients in the MPH group and 9 patients in the risperidone group scored 1 (very much improved) or 2 (much improved).

The repeated-measures ANOVA showed a significant treatment × time interaction effect only for C-GAS ($P = 0.009$), attention problems ($P = 0.005$), and attention-deficit/hyperactivity problems ($P = 0.037$) and a trend for significance for oppositional defiant problems ($P = 0.062$), indicating a significantly greater improvement in the MPH group. In the other outcome measures, both groups showed a similar pattern of improvement (significant time effect but not treatment × time effect) (Table 1).

Safety Measures

No patients discontinued treatment due to adverse effects. Patients receiving risperidone exhibited a mean weight inccrease in 3.60 ± 2.24 kg (mean baseline weight, 34.58 ± 11.13; mean final weight, 38.10 ± 11.84 kg). In 5 patients (25%), weight gain was greater than 5 kg during the 6-month follow-up, and in 2 of them, an effective reduction of the drug dosage was needed. Regarding the MPH group, 9 patients (45%) presented a transitory deccrease in appetite, but weight loss never exceeded 5 kg, and the mean weigh during the follow-up did not change significantly (mean baseline weight, 33.58 ± 8.63 kg; mean final weight, 34.19 ± 7.85 kg).

Regarding blood chemistries, total cholesterol level significantly increased in the risperidone group (from 150.06 ± 20.41 mg/dL to 157.94 ± 22.30 mg/dL, $P = 0.009$), but no patient exceeded the upper normal limit. In 2 patients, level of triglycerides increased over the upper normal limit of 150 mg/dL. In the MPH group, a decrease in the liver enzyme

TABLE 2. Cardiovascular Monitoring at the Baseline (T0) and at the End of the 6-Month Follow-up (T1) in Youth Receiving MPH and Risperidone

	MPH				Risperidone			
	T0		T1		T0		T1	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Systolic BP, mm Hg	111.89	11.29	106.72*	6.07	108.33	9.73	108.89	8.92
Diastolic BP, mm Hg	65.00	8.01	67.44	8.51	66.11	8.96	63.67	6.52
Cardiac frequency, beats/min	77.94	20.77	80.00	11.84	84.56	10.04	83.28	11.94
QTc interval, ms	417.17	16.42	425.78†	14.07	416.50	19.79	418.83	17.87

*$P < 0.05$.

†$P < 0.01$.

γ-glutamyltransferase was found from 14.00 ± 3.88 U/L to 12.67 ± 3.90 U/L ($P = 0.006$). Prolactin increased only in the risperidone group, from 8.80 ± 6.83 ng/mL to 19.88 ± 10.20 ng/mL, with levels greater than the reference of 15 ng/mL in 12 patients (60%) and greater than 30 ng/mL in 4 of them.

Regarding cardiovascular measures (blood pressure, cardiac frequency, and ECG, including QTc interval), data are reported in Table 2. Data show that in the MPH group the change of some measures (systolic blood pressure and QTc interval) was statistically significant, but clinically nonrelevant, because all the values were within the reference range. In the risperidone group, no significant differences were found in any of the cardiovascular parameters.

Regarding other adverse effects, somnolence was reported by 2 patients with risperidone, whereas 2 patients with MPH reported sleep problems (1 late sleeping and 1 nocturnal awakenings). Finally, in the MPH group, 3 patients exhibited transitory, mild exacerbation of motor tics and returned to the pretreatment level after a few weeks, and 5 had transitory headache in the first few weeks. No patient in the 2 groups showed extrapyramidal side effects.

DISCUSSION

This is a nonrandomized, nonblind, naturalistic study including drug-naive patients with ADHD and ODD and aggression treated with MPH or risperidone monotherapy. Given the treatment conditions and treatment assignment, our study is exploratory, and conclusions should be considered as tentative. Both treatments resulted effective in reducing aggressive behavior. General measures of severity and functional impairment significantly improved as well, in both the treatment groups. However, only MPH was effective on the CBCL scales attention problems and attention-deficit/hyperactivity problems. These findings suggest that in patients with ADHD and ODD MPH may be an effective treatment not only for the core symptoms of ADHD, but also for the behavioral symptoms of ODD, including aggression.

Regarding safety, health concerns for significant weight gain and prolactin increase were associated to risperidone. Although none of the patients required drug discontinuation, 2 patients in the risperidone group had to decrease the drug dosage because of marked weight gain. However, our findings should be used cautiously considering the limited duration of the study. Given the relative short follow-up, it may be hypothesized that some of the adverse effects (namely, weight gain, metabolic effects, cardiovascular adverse effects) may become more apparent later during the treatment. Slight increases in total cholesterol and triglycerides, sometimes greater than the upper normal levels, indicate the need of a careful monitoring of these metabolic features. No clinically significant QTc alterations were found in the 2 groups, as the changes during the MPH treatment fell within the reference range. However, this finding, consistent with the literature on both MPH and SGAs, indicates that a monitoring of cardiac function should be warranted.

A major limitation of the study is the nonblind design, although the patients were unselected and consecutive patients with both ADHD and ODD, referred to different sections of our department, not randomized, but initiated to MPH or risperidone monotherapy, according to their different prescribers' judgement, and the 2 treatment groups did not differ significantly in any demographic or clinical characteristics at the beginning of the trial. Possible confounding elements, such as psychiatric comorbidities or previous pharmacological treatments, were controlled, as our patients did not present associated disorders and were all drug naive. The small sample size and the limited period of observation may have limited the power of the study to detect group differences, and the limited follow-up time may preclude strong conclusions on safety.

Even considering these limitations, our data suggest that when behavioral disorders of ODD, and, namely, aggression, occur within the context of comorbid ADHD, addressing the core symptoms of ADHD with stimulants may result in a global improvement of behavior control. Although the efficacy of stimulants in patients with ADHD and severe behavior problems is supported by previous studies[18] and guidelines,[19] in the daily practice, aggression often leads to SGAs or mood stabilizers as the first treatment option, even in ADHD patients. Our findings suggest that when ADHD is comorbid with disruptive behavior disorders MPH may be a first option to improve aggression, considering the tolerability profile reported in the literature, including concerns about weight gain and metabolic risk during prolonged treatments with risperidone and other SGAs.

AUTHOR DISCLOSURE INFORMATION

G.M. was on the advisory boards for Eli Lilly, Shire, and Angelini; has received research grants from Eli Lilly, Shire, and Lundbeck; and has been a speaker for Eli Lilly, Shire, Lundbeck, and Otsuka. The other authors declare no conflicts of interest.

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Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
(Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI)
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(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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