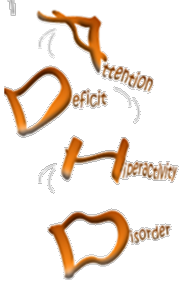
NEWSLETTER



INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD GENNAIO 2016

ADHD Atten Deficit Hyperact Disord. 2016;1-6.

ATTENTION DEFICIT AND HYPERACTIVITY IN SOCIAL ANXIETY DISORDER: RELATIONSHIP WITH TRAUMA HISTORY AND IMPULSIVITY.

Koyuncu A, Çelebi F, Ertekin E, Kök BE, et al.

The aim of this study is to investigate the rate of childhood traumatic experiences and assess the relationship between childhood trauma and impulsivity in the presence of attention deficitΓÇôhyperactivity disorder (ADHD) in patients with social anxiety disorder (SAD). A total of 123 patients with a primary diagnosis of SAD were enrolled. All patients were assessed by using the clinical version of Structured Clinical Interview for DSM-IV (SCID-I/CV) and Schedule for Affective Disorders and Schizophrenia for School Age ChildrenΓÇöPresent and Lifetime version (K-SADS-PL), ADHD module. A clinical and sociodemographic data form and rating scales were filled out. We found higher rates of emotional traumatic experiences and impulsivity along with more severe symptoms of depression, anxiety and social anxiety in the group of SAD patients with childhood ADHD than in SAD patients without ADHD in childhood. The presence of ADHD is associated with higher severity in several domains in patients with SAD. Patients with SAD should be assessed carefully whether they have ADHD, especially when their SAD symptoms are severe, when they have a history of traumatic experiences or problems with impulse control

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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.

Am J Med Genet C Semin Med Genet. 2012 Nov;160C:295-300.
COGNITIVE AND BEHAVIORAL ASPECTS OF SMITH-LEMLI-OPITZ SYNDROME.
Diaz-Stransky A, Tierney E.
The brain's high concentrations of cholesterol make it especially vulnerable to the cholesterol biosynthetic defect that characterizes Smith-Lemli-Opitz syndrome (SLOS). An attempt to characterize the cognitive and behavioral phenotype of SLOS has identified increased rates of intellectual disability, language and motor developmental delay, repeated self-injury behaviors, sensory hyperreactivity, hyperactivity, affect dysregulation, and sleep disturbances. Some research has suggested that carriers of the gene mutation that results in SLOS display increased risk of suicidal behavior. Cholesterol dysregulation impairs neuroplasticity, which may be a mechanism underlying some of the mentioned abnormalities. Discrete positive effects have been reported with the use of cholesterol supplementation in the treatment of SLOS. Research has been limited by the small number of subjects available, and a limited understanding of lipid metabolism in the brain. Hopefully future research will help clarify the role that cholesterol plays in cognitive and behavioral abnormalities like the ones associated with SLOS. This would accelerate the development of treatments for SLOS, and perhaps also further understanding of non-syndromic psychiatric disorders such as autism and attention deficit hyperactivity disorder

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Ambul Pediatr. 2007 May;7:226-31.
COMMUNITY PERSPECTIVES OF CHILDHOOD BEHAVIORAL PROBLEMS AND ADHD AMONG AFRICAN AMERICAN PARENTS.
Olaniyan O, DosReis S, Garriett V, et al.
OBJECTIVE: To explore parents' perceptions of childhood behavior problems and attentiondeficit/hyperactivity disorder (ADHD) among a sample of African American (AA) parents.
METHODS: Five focus groups were conducted in inner-city Baltimore and the Washington, DC, metropolitan region with 5 to 7 AA parents per group. Adults with children under the age of 17 years were recruited from pediatric practices. One investigator moderated each focus group, and a second took notes. Sessions averaged 1.5 hours long, were recorded on audiotape, and were transcribed verbatim. The narrative data were coded for recurring themes.
RESULTS: Five major themes emerged from the analysis: causes of behavioral problems in children, the legitimacy of ADHD as a diagnosis, attitudes about doctors, opinions of medication, and perceptions of the school environment. Many participants felt that behavior issues, including those accompanying ADHD, were caused by inappropriate parenting and disciplinary practices. Some viewed the diagnosis as a label applied with racial inequality to exert social control over AAs. Several expressed distrust in physicians who were quick to make a diagnosis of ADHD and recommend medications. Others worried that medication would lead to drug addiction in adulthood. Some perceived that children were labeled with ADHD because of poor educational environments that were unresponsive to the needs of AA children.
CONCLUSIONS: These focus groups identified important community perceptions about ADHD and its medical treatment. Understanding how these perceptions contribute to racial disparities in ADHD diagnosis and treatment can help inform culturally sensitive interventions to improve the management of ADHD among AA children

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Am J Med Genet Part B Neuropsychiatr Genet. 2015.
CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND THE DEVELOPMENT OF ADOLESCENT ALCOHOL PROBLEMS: A PROSPECTIVE, POPULATION-BASED STUDY OF SWEDISH TWINS. ***Quinn PD, Pettersson E, Lundstr+Âm S, et al.***
Children with attention-deficit/hyperactivity disorder (ADHD) are at increased risk of problematic alcohol and other substance use in adolescence. This study used data from an ongoing, prospective, population-based twin study of Swedish children and adolescents to evaluate the extent to which the association between ADHD symptoms and alcohol problems reflects a unique source of genetic or environmental risk related to

ADHD versus a broader predisposition to youth externalizing behavior. We used all available data from samesex monozygotic (MZ) and dizygotic (DZ) twins on ADHD symptoms in childhood (age 9/12; N=15,549) and alcohol problems in late adolescence (age 18; N=2,564). Consistent with prior longitudinal studies, the phenotypic association between hyperactive/impulsive ADHD symptoms and alcohol problems was small in magnitude, whereas the association for inattentive symptoms was even weaker. Additive genetic influences explained 99.8% of the association between hyperactive/impulsive symptoms and alcohol problems. Furthermore, we found that the genetic risk specifically associated with hyperactive/impulsive symptoms was attenuated when estimated in the context of externalizing behavior liability during childhood, of which ADHD symptoms were specific expressions. In sensitivity analyses exploring hyperactivity in mid-adolescence, we found a similar pattern of genetic associations. These results are consistent with previous findings of genetically driven overlap in the etiology of ADHD and problematic alcohol use. At least some of this cooccurrence may result from a general predisposition to externalizing behaviors in youth

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Am J Med Genet Part B Neuropsychiatr Genet. 2015.

GENETIC AND ENVIRONMENTAL INFLUENCES ON THE RELATIONSHIP BETWEEN ADHD SYMPTOMS AND INTERNALIZING PROBLEMS: A CHINESE TWIN STUDY. *Chen T-J, Ji C-Y, Wang S-S, et al.*

Several twin studies have investigated the overlap between attention deficit hyperactivity disorder (ADHD) and externalizing problems; however, limited information is known regarding the genetic and environmental contribution to the overlap between ADHD and internalizing problems. This study examined the genetic and environmental influences on the variation in and covariation between ADHD symptoms and internalizing problems by using the Child Behavior Checklist (CBCL). We investigated 1,316 child and adolescent twins, including 780 monozygotic twins and 536 dizygotic twins, aged 6 years to 18 years from the Chinese Child and Adolescent Twin Registry. ADHD symptoms and internalizing problems were quantified through parent rating by using the Attention Problems Scale and other three scales, which include Anxious/Depressed, Withdrawn, and Somatic Complaints of CBCL. Genetic and environmental susceptibilities common to ADHD symptoms and internalizing problems were examined through bivariate twin modeling. Results showed that genetic factors substantially influenced the ADHD symptoms with a heritability of 72%. Modest genetic influences and substantial shared environmental influences (20-77%) were observed in the three internalizing problem scales. Common genetic and shared environmental influences were essential for the overlap between ADHD and the three internalizing problems respectively. Approximately one-fifth of the genetic variance of ADHD symptoms was shared with anxiety/depression. In conclusion, substantial genetic and shared environmental influences on ADHD symptoms and internalizing problems were observed in Chinese children and adolescents. Our finding supports a common etiology between ADHD and internalizing problems. This finding can also help explain the co-existence of these behavior problems

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American Journal of Otolaryngology - Head and Neck Medicine and Surgery. 2016;37:27-30.

IMPACT OF ADENOTONSILLECTOMY ON ADHD AND NOCTURNAL ENURESIS IN CHILDREN WITH CHRONIC ADENOTONSILLAR HYPERTROPHY. *Somuk BT, Bozkurt H, Göktaş G, et al.*

OBJECTIVE: Children with chronic adenotonsillar hypertrophy (CAH) are more likely to have symptoms of attention deficit hyperactivity disorder (ADHD) and enuresis nocturna (EN) and benefit from surgery. The aim of this study was to evaluate the effect of adenotonsillectomy on ADHD and EN symptoms in children with CAH.

STUDY DESIGN: Cross-sectional study was conducted.

SETTING: Parent-based questionnaires.

METHODS: Parents of children with CAH were given Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV) and Nocturnal Enuresis Questionnaire (NEQ) before and

six months after adenotonsillectomy. Inattention (IA) and hyperactivity-impulsivity (HI) subscores of T-DSMIV were used in the present study. The rates of ADHD and EN were compared before and after surgery.
RESULTS: A total of 75 children between 5 and 16years of age and their families participated in the study. All 75 families completed T-DSM-IV and NEQ. Mean IA (5.69±4.88 versus 4.46±4.40) and HI (6.53±5.60 versus 5.93±5.45) scores as well as total ADHD scores (12.22±8.99 versus 10.42±8.70) improved significantly after surgery. This significance was found to be statistically important ($p<0.05$). Furthermore 26 of the subjects were diagnosed with primer EN before adenotonsillectomy and 14 of these enuretic children had total remission six months after surgery. The frequency of EN dropped from 34.7% to 16.0% and this remission rate was found to be statistically significant ($p<0.05$).
CONCLUSION: Children with CAH had high frequency of ADHD and EN symptoms in the present study. Adenotonsillectomy was found to be effective in improvement of these symptoms.

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Ann Acad Med Singapore. 2015;44:S407.
EFFECTIVENESS OF BRAIN-COMPUTER INTERFACE-BASED PROGRAMME BOOSTERS FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY IN CHILDREN-A PRELIMINARY ANALYSIS. *Poh XW, Fung DSS, Lee TS, et al.*
Background & Hypothesis: Children with attention deficit hyperactivity disorder (ADHD) are found to exhibit unique electroencephalography (EEG) patterns. The use of brain-computer interface (BCI)-based programme as a form of neurofeedback treatment for ADHD has been examined in 2 small trials. Forty children who went through the intensive BCI-based programme in the previous trials had shown significant improvements in ADHD symptoms. The study aims to examine the effectiveness of booster sessions following the intensive programme period. We hypothesised that participants with boosters will improve more on their ADHD symptoms than the group without.
Methods: Forty children with ADHD inattentive or combined subtype (M = 8.21, SD = 1.45) were recruited from the Child Guidance Clinic. Upon completion of the intensive BCI-based programme (week 8), participants returned for a follow up 3 months later (week 20). During this 3-month period, 20 participants did not go through any BCI-based booster, whereas another 20 did. ADHD rating scale (ADHD-RS) completed by parents at weeks 8 and 20 were used as the primary outcome measure.
Results: Repeated measures ANOVA analyses were conducted, and participants who dropped out before week 20 were excluded. No statistically significant change was found in ADHD symptoms at week 20 as compared to week 8, in children with and without booster sessions.
Discussion & Conclusion: From our preliminary analysis, booster at this dose does not appear to help in improving ADHD symptoms after the intensive period. Nonetheless, the current sample size is relatively small. To interpret the results more meaningfully, a larger randomised controlled trial is currently underway

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Asia-Pacific Psychiatry. 2015.
EXPLORATORY ANALYSIS OF EARLY TREATMENT DISCONTINUATION AND CLINICAL OUTCOMES OF PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER. *Wu SH, Wang K, Chen Y, et al.*
Introduction: This post-hoc analysis was to investigate the impact of treatment discontinuation on clinical outcomes in patients with attention-deficit/hyperactivity disorder (ADHD).
Methods: Data are from a 12-month, observational, multinational study that included outpatients aged 6-17 years who were diagnosed with ADHD and treated with atomoxetine, methylphenidate, or nootropic agents. Treatment effectiveness and proportions of patients who discontinued treatment were compared between China and the other non-Western countries/regions combined. Propensity score matching was used to further estimate the association between treatment discontinuation and effectiveness.
Results: Of the 546 patients who entered the study, 337 patients had complete data and were included in the analyses. Compared with the other countries/regions, China subgroup had a higher treatment discontinuation rate (odds ratio=25.80; $P<0.0001$) and poorer treatment effectiveness: least-squares (LS)

mean changes were 5.74 versus 8.56 (P=0.0225) for the Child Health and Illness Profile-Child Edition (CHIPCE) Achievement domain and -1.87 versus -2.13 (P=0.0401) for Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S). Further analyses of matched discontinuer-maintainer pairs showed that discontinuers demonstrated poorer effectiveness: LS mean changes for the CHIP-CE Achievement domain and CGIADHD-S (discontinuer versus maintainer) were 5.36 versus 9.10 (P=0.0255) and -1.32 versus -1.96 (P=0.0179) for overall population, respectively, and 4.40 versus 10.17 (P=0.0065) and -1.48 versus -2.45 (P=0.0089), respectively, for China subgroup.
Discussion: This analysis found that early treatment discontinuation was associated with worse clinical outcomes for patients with ADHD. China subgroup had substantially higher discontinuation rates and poorer effectiveness outcomes. Strategies to improve medication persistence have the potential to improve outcomes for ADHD patients in China

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Asim, Allerji, Immunoloji. 2015;13:65-70.
ASSOCIATION BETWEEN ALLERGIC DISEASES AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDHOOD.
Turan A, Kilic M, Güner SN, et al.
Objective: Attention Deficit Hyperactivity Disorder (ADHD) is a common childhood problem similar to allergic disorders. The aim of the study is to determine whether allergic disorders and atopy are associated with physician-diagnosed ADHD.
Materials and Methods: This study was designed as a nested case-control study. One hundred sixty children were divided into three groups; 55 patients with ADHD, 55 children of healthy siblings of the study group and 50 unrelated healthy children. For each subject, an International Study of Asthma and Allergies in Children (ISAAC) questionnaire was completed. The total eosinophil count, total IgE levels were measured and skin prick tests were performed.
Results: The prevalence of asthma was significantly higher in the ADHD group than the control group but was similar to the sibling group. Even though prevalence of rhinitis was significantly higher in ADHD group relative to the other groups, atopic rhinitis was similar in all groups. There were no significant differences for prevalence of eczema, elevated total IgE levels, eosinophil count and positive skin prick testing between any of the groups.
Conclusion: The rhinitis seems to be a risk factor for ADHD while atopic status does not appear to be involved. Nasal obstruction and sleep disturbances due to rhinitis may affect the cognitive functions of individuals with ADHD. These individuals should be evaluated to determine whether or not (allergic) rhinitis accompanies ADHD

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Autism Res. 2015 Feb;8:29-37.
TIME REPRODUCTION PERFORMANCE IS ASSOCIATED WITH AGE AND WORKING MEMORY IN HIGH-FUNCTIONING YOUTH WITH AUTISM SPECTRUM DISORDER.
Brenner LA, Shih VH, Colich NL, et al.
Impaired temporal processing has historically been viewed as a hallmark feature of attention deficit hyperactivity disorder. Recent evidence suggests temporal processing deficits may also be characteristic of autism spectrum disorder (ASD). However, little is known about the factors that impact temporal processing in children with ASD. The purpose of this study was to assess the effects of co-morbid attention problems, working memory (WM), age, and their interactions, on time reproduction in youth with and without ASD. Twenty-seven high-functioning individuals with ASD and 25 demographically comparable typically developing individuals (ages 9-17; 85% male) were assessed on measures of time reproduction, auditory WM, and inattention/hyperactivity. The time reproduction task required depression of a computer key to mimic interval durations of 4, 8, 12, 16, or 20 sec. Mixed effects regression analyses were used to model accuracy and variability of time reproduction as functions of diagnostic group, interval duration, age, WM, and inattention/hyperactivity. A significant group by age interaction was detected for accuracy, with the deficit in the ASD group being greater in younger children. There was a significant group by WM interaction for

consistency, with the effects of poor WM on performance consistency being more pronounced in youth with ASD. All participants tended to underestimate longer interval durations and to be less consistent for shorter interval durations; these effects appeared more pronounced in those who were younger or who had poorer WM performance. Inattention/hyperactivity symptoms in the ASD group were not related to either accuracy or consistency. This study highlights the potential value of temporal processing as an intermediate trait of relevance to multiple neurodevelopmental disorders

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Avicenna Journal of Phytomedicine. 2015;5:4.

THE EFFECT OF EPITHYMUM AND GINKGO BILOBA ON ADHD CHILDREN BASED ON IRANIAN TRADITIONAL MEDICINE AND COMPLEMENTARY MEDICINE.

Afrasiabian H, Shahlaei L, Hodoodi R.

Objectives: ADHD or Attention-deficit/hyperactivity disorder is a developmental behavioral disorder which is marked by unusual bodily activity, lack of concentration and impulsive behavior. This disease is the most common behavioral disorder of children with a nervous-mental origin based on genetics and influenced by the environment.

Materials and Methods: In this study 105 children within the age range of 6 to 12 years were selected based on DSM-V criteria and divided into three groups (n=35). Members of the witness group were not treated, 35 members only received20 mg TD Sepithymum extract for 14 days, and 35members received 20 mg TDS epithymum extract plus 20 mg TDS Ginkgo biloba for 14 days.

Results: The first group was active without concentration, the second group experienced usual bodily activity in 10.37 of the cases, and the third group experienced usual activity with increased concentration in 13.37 of the cases.

Conclusion: Based on Iranian traditional medicine, epithymum is a potent medicine for nervous-behavioral disorders. According on supplementary medicine, Ginkgo biloba is an effective factor in improvement of brain and reduction of its functional disorders. Combination of both of these drugs was effective in up to 37% of ADHD patients

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Avicenna Journal of Phytomedicine. 2015;5:110.

THE EFFECT OF ADDING ACUPUNCTURE TO TREATMENT WITH METHYLPHENIDATE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: A CASE SERIES. Moharari F, Khorsand A, Soltanifar A, et al.

Objectives: Attention deficit hyperactivity disorder (ADHD) is a disorder with symptoms such as inattentiveness, hyperactivity and impulsiveness which can be found in 3-12% of the children. Acupuncture is the process of inserting needles in the skin and underlying tissue in special places called acupoint, and it is considered to be an easy, cost-effective and safe treatment method as compared to the other common interventions. There are numerous articles published on the subject of acupuncture in treatment of ADHD all over the world, especially in China, but only some of them show a beneficial effect on ADHD.

Materials and Methods: This study was report of our experience from treating ADHD with the help of acupuncture in five children and adolescents in the age group of 11 to 16 who were under constant and standard treatment with methylphenidate. There were 12 acupuncture sessions. The patients were evaluated with ADHD Rating Scale-IV test, and Continuous Performance test before the treatment and three weeks after it.

Results: There was a 23-72% decrease in the score of ADHD Rating Scale-IV Test in all the five patients as compared to before the treatment. In the Continuous Performance Test, four cases showed a decrease in the number of commission and omission errors as compared to before the treatment, which were 75-100% and 66-100%, respectively. Also, the increase in the correct answers and a reduction in response time was seen in two cases, which were 2.7-3.5% and 7.2-13.4%, respectively.

Conclusion: Based on our findings, it seems that acupuncture can be effective in children and adolescents with ADHD. Although, there need to be more controlled evaluation about this subject with larger sample sizes in order to confirm our findings

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Behav Brain Funct. 2015 Dec;12.

ATTENTION DEFICIT HYPERACTIVITY DISORDER: GENETIC ASSOCIATION STUDY IN A COHORT OF SPANISH CHILDREN. ***Gomez-Sanchez CI, Riveiro-Alvarez R, Soto-Insuga V, et al.***

Background: Attention deficit hyperactivity disorder (ADHD) has a strong genetic component. The study is aimed to test the association of 34 polymorphisms with ADHD symptomatology considering the role of clinical subtypes and sex in a Spanish population.

Methods: A cohort of ADHD 290 patients and 340 controls aged 6–18 years were included in a case–control study, stratified by sex and ADHD subtype. Multivariate logistic regression was used to detect the combined effects of multiple variants.

Results: After correcting for multiple testing, we found several significant associations between the polymorphisms and ADHD (p value corrected =0.05): (1) SLC6A4 and LPHN3 were associated in the total population; (2) SLC6A2, SLC6A3, SLC6A4 and LPHN3 were associated in the combined subtype; and (3) LPHN3 was associated in the male sample. Multivariable logistic regression was used to estimate the influence of these variables for the total sample, combined and inattentive subtype, female and male sample, revealing that these factors contributed to 8.5, 14.6, 2.6, 16.5 and 8.5 % of the variance respectively.

Conclusions: We report evidence of the genetic contribution of common variants to the ADHD phenotype in four genes, with the LPHN3 gene playing a particularly important role. Future studies should investigate the contribution of genetic variants to the risk of ADHD considering their role in specific sex or subtype, as doing so may produce more predictable and robust models.

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Biol Psychiatry. 2016.

ABERRANT CROSS-BRAIN NETWORK INTERACTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND ITS RELATION TO ATTENTION DEFICITS: A MULTISITE AND CROSS-SITE REPLICATION STUDY. ***Cai W, Chen T, Szegletes L, et al.***

Background: Attention-deficit/hyperactivity disorder (ADHD) is increasingly viewed as a disorder stemming from disturbances in large-scale brain networks, yet the exact nature of these impairments in affected children is poorly understood. We investigated a saliency-based triple-network model and tested the hypothesis that cross-network interactions between the salience network (SN), central executive network, and default mode network are dysregulated in children with ADHD. We also determined whether network dysregulation measures can differentiate children with ADHD from control subjects across multisite datasets and predict clinical symptoms.

Methods: Functional magnetic resonance imaging data from 180 children with ADHD and control subjects from three sites in the ADHD-200 database were selected using case-control design. We investigated between-group differences in resource allocation index (RAI) (a measure of SN-centered triple network interactions), relation between RAI and ADHD symptoms, and performance of multivariate classifiers built to differentiate children with ADHD from control subjects.

Results: RAI was significantly lower in children with ADHD than in control subjects. Severity of inattention symptoms was correlated with RAI. Remarkably, these findings were replicated in three independent datasets. Multivariate classifiers based on cross-network coupling measures differentiated children with ADHD from control subjects with high classification rates (72% to 83%) for each dataset. A novel cross-site classifier based on training data from one site accurately (62% to 82%) differentiated children with ADHD on test data from the two other sites.

Conclusions: Aberrant cross-network interactions between SN, central executive network, and default mode network are a reproducible feature of childhood ADHD. The triple-network model provides a novel, replicable,

and parsimonious systems neuroscience framework for characterizing childhood ADHD and predicting clinical symptoms in affected children

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BMC Psychiatry. 2015 Dec;15.

PREVALENCE OF ADHD IN NONPSYCHOTIC ADULT PSYCHIATRIC CARE (ADPSYC): A MULTINATIONAL CROSS-SECTIONAL STUDY IN EUROPE.

Deberdt W, Thome J, Lebrec J, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) often persists into adulthood.
Method: ADHD diagnosis was made using the Diagnostic Interview for ADHD in Adults, version 2.0 (DIVA), according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) and 5th Edition (DSM-5).
Results: Of 5662 patients present/approached, 2284 (40.3 %) consented, of whom 1986 patients (87.0 %) completed the study. Based on the DIVA, and applying DSM-IV-TR or DSM-5 criteria, 15.8 % (95 % confidence interval [CI] 14.2 %-17.4 %) or 17.4 % (95 % CI 15.7 %-19.0 %) of patients were diagnosed with ADHD, respectively. The prevalence of ADHD was 15.3 % when counting as non-ADHD those patients who screened positive but did not complete the DIVA (DSM-5).
Conclusions: Estimates from this study indicate that a relevant part of the psychiatric outpatient care population suffers from ADHD.

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BMJ (Online). 2015;351.

METHYLPHENIDATE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: COCHRANE SYSTEMATIC REVIEW WITH META-ANALYSES AND TRIAL SEQUENTIAL ANALYSES OF RANDOMISED CLINICAL TRIALS.

Storebø OJ, Krogh HB, Ramstad E, et al.

STUDY QUESTION: Is methylphenidate beneficial or harmful for the treatment of attentiondeficit/hyperactivity disorder (ADHD) in children and adolescents?
METHODS: Electronic databases were searched up to February 2015 for parallel and crossover randomised clinical trials comparing methylphenidate with placebo or no intervention in children and adolescents with ADHD. Meta-analyses and trial sequential analyses (TSA) were conducted. Quality was assessed using GRADE. Teachers, parents, and observers rated ADHD symptoms and general behaviour.
STUDY ANSWER AND LIMITATIONS: The analyses included 38 parallel group trials (n=5111, median treatment duration 49 days) and 147 crossover trials (n=7134, 14 days). The average age across all studies was 9.7 years. The analysis suggested a beneficial effect of methylphenidate on teacher rated symptoms in 19 parallel group trials (standardised mean difference (SMD)-0.77, n=1698), corresponding to a mean difference of -9.6 points on the ADHD rating scale. There was no evidence that methylphenidate was associated with an increase in serious adverse events (risk ratio 0.98, nine trials, n=1532; TSA adjusted intervention effect RR 0.91). Methylphenidate was associated with an increased risk of non-serious adverse events (1.29, 21 trials, n=3132; TSA adjusted RR 1.29). Teacher rated general behaviour seemed to improve with methylphenidate (SMD -0.87, five trials, n=668) A change of 7 points on the child health questionnaire (CHQ) has been deemed a minimal clinically relevant difference. The change reported in a meta-analysis of three trials corresponds to a mean difference of 8.0 points on the CHQ (range 0-100 points), which suggests that methylphenidate may improve parent reported quality of life (SMD 0.61, three trials, n=514). 96.8% of trials were considered high risk of bias trials according to the Cochrane guidelines. All outcomes were assessed very low quality according to GRADE.
WHAT THIS STUDY ADDS: The results suggest that among children and adolescents with a diagnosis of ADHD, methylphenidate may improve teacher reported symptoms of ADHD and general behaviour and parent reported quality of life. However, given the risk of bias in the included studies, and the very low quality of outcomes, the magnitude of the effects is uncertain. Methylphenidate is associated with an increased risk of non-serious but not serious adverse events.

FUNDING, COMPETING INTERESTS, DATA SHARING: Region Zealand Research Foundation and Copenhagen Trial Unit. Competing interests are given in the full paper on bmj.com. Full data are available in the version of this review published in The Cochrane Library

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Child Adolesc Ment Health. 2016.

INNOVATIONS IN PRACTICE: AN OBJECTIVE MEASURE OF ATTENTION, IMPULSIVITY AND ACTIVITY REDUCES TIME TO CONFIRM ATTENTION DEFICIT/HYPERACTIVITY DISORDER DIAGNOSIS IN CHILDREN - A COMPLETED AUDIT CYCLE. ***Hall CL, Selby K, Guo B, et al.***

Background: Diagnosing attention deficit/hyperactivity disorder (ADHD) in children and young people typically relies on clinical observation and subjective parent, teacher and self-reports. The subjective nature of reports combined with contradictory or missing data can result in diagnostic uncertainty and delay. The aim of this study was to assess whether the addition of an objective test of attention, impulsivity and activity (QbTest) as an adjunct to standard ADHD assessment could accelerate the diagnostic process in routine National Health Service (NHS) settings.

Method: In a pre vs. post-test audit design, case records were examined in 40 cases diagnosed without the QbTest [pre-QbTest group] and 40 cases diagnosed with the QbTest [QbTest group], recording the number of consultations until a confirmed ADHD diagnosis was reached.

Results: Using Poisson regression, significantly fewer clinician consultations (mean 2.18 vs. 3.05; $p < .02$) were required to confirm the diagnosis of ADHD when the QbTest was used to augment assessment in comparison to standard assessment as usual.

Conclusions: The findings suggest that the addition of the QbTest to standard clinical assessment may reduce time to diagnosis and potentially result in cost savings to the NHS. These preliminary data suggest that there is a potentially clinically meaningful benefit of adding the QbTest to routine clinical ADHD assessment and this should be examined next in the context of a randomised controlled trial

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Child Psychiatry Hum Dev. 2015 Dec;46:951-66.

A DEVELOPMENTAL PSYCHOPATHOLOGY PERSPECTIVE ON ADHD AND COMORBID CONDITIONS: THE ROLE OF EMOTION REGULATION.

Steinberg EA, Drabick DAG.

Research investigating attention-deficit/hyperactivity disorder (ADHD) and co-occurring disorders such as oppositional defiant disorder, conduct disorder, anxiety, and depression has surged in popularity; however, the developmental relations between ADHD and these comorbid conditions remain poorly understood. The current paper uses a developmental psychopathology perspective to examine conditions commonly comorbid with ADHD during late childhood through adolescence. First, we present evidence for ADHD and comorbid disorders. Next, we discuss emotion regulation and its associations with ADHD. The role of parenting behaviors in the development and maintenance of emotion regulation difficulties and comorbid disorders among children with ADHD is explored. An illustrative example of emotion regulation and parenting over the course of development is provided to demonstrate bidirectional relations among these constructs. We then present an integrated conceptual model of emotion regulation as a shared risk process that may lead to different comorbid conditions among children with ADHD. Implications and directions for future research are presented.

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Clin Transl Sci. 2015;8:729-33.
INCORPORATING INFORMATICS FOR INTEGRATING BIOLOGY AND THE BEDSIDE (I2B2) INTO PREDOCTORAL TRAINEE CURRICULUM TO EVALUATE STUDENT-GENERATED HYPOTHESES. *Schieffer KM, Peters DG, Richter CK, et al.*
As part of the Clinical and Translational Science Institute predoctoral TL1 training program at the Pennsylvania State University, a multidisciplinary team of predoctoral trainees representing the Chemistry, Neurosurgery, Nutritional Sciences, and Public Health Sciences departments were introduced to the NIHsponsored Informatics for Integrating Biology and the Bedside (i2b2) database to test the following studentgenerated hypothesis: children with iron deficiency anemia (IDA) are at increased risk of attention deficithyperactivity disorder (ADHD). Children aged 4-12 and 4-17 years were categorized into IDA and control groups. De-identified medical records from the Penn State Milton S. Hershey Medical Center (HMC) and the Virginia Commonwealth University Medical Center (VCUMC) were used for the analysis. Overall, ADHD prevalence at each institution was lower than 2011 state estimates. There was a significant association between IDA and ADHD in the 4-17-year-old age group for all children (OR: 1.902 [95% CI: 1.363-2.656]), Caucasian children (OR: 1.802 [95% CI: 1.133-2.864]), and African American children (OR: 1.865 [95% CI: 1.152-3.021]). Clinical and Translational Science Award (CTSA) infrastructure is particularly useful for trainees to answer de novo scientific questions with minimal additional training and technical expertise. Moreover, projects can be expanded by collaborating within the CTSA network

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Clin Child Psychol Psychiatry. 2016 Jan;21:81-94.
UNCOVERING A CLINICAL PORTRAIT OF SLUGGISH COGNITIVE TEMPO WITHIN AN EVALUATION FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A CASE STUDY. *Becker SP, Ciesielski HA, Rood JE, et al.*
Despite the burgeoning scientific literature examining the sluggish cognitive tempo (SCT) construct, very little is known about the clinical presentation of SCT. In clinical cases where SCT is suspected, it is critical to carefully assess not only for attention-deficit/hyperactivity disorder (ADHD) but also for other comorbidities that may account for the SCT-related behaviors, especially internalizing symptoms and sleep problems. The current case study provides a clinical description of SCT in a 7-year-old girl, offering a real-life portrait of SCT while also providing an opportunity to qualitatively differentiate between SCT and ADHD, other psychopathologies (e.g. depression, anxiety), and potentially related domains of functioning (e.g. sleep, executive functioning [EF]). “Jessica” was described by herself, parents, and teacher as being much slower than her peers in completing schoolwork, despite standardized testing showing Jessica to have above average intelligence and academic achievement. Jessica’s parents completed rating scales indicating high levels of SCT symptoms and daytime sleepiness, as well as mildly elevated EF deficits. More research is needed to determine how to best conceptualize, assess, and treat SCT, and Jessica’s case underscores the importance of further work in this area.

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Clin Pediatr. 2016;55:196-98.
FACIAL PAIN IN A CHILD WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER. *Stolten M, Moak S, Chauhan A, et al.*

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Clin Psychol Rev. 2016;43:162-74. **CHOICE-IMPULSIVITY IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): A META-ANALYTIC REVIEW.**
Patros CHG, Alderson RM, Kasper LJ, et al.
Impulsive behavior is a core DSM-5 diagnostic feature of attention-deficit/hyperactivity disorder (ADHD) that is associated with several pejorative outcomes. Impulsivity is multidimensional, consisting of two

subconstructs: rapid-response impulsivity and reward-delay impulsivity (i.e., choice-impulsivity). While previous research has extensively examined the presence and implications of rapid-response impulsivity in children with ADHD, reviews of choice-impulsive behavior have been both sparse and relatively circumscribed. This review used meta-analytic methods to comprehensively examine between-group differences in choiceimpulsivity among children and adolescents with and without ADHD. Twenty-eight tasks (from 26 studies), consisting of 4320 total children (ADHD = 2360, TD = 1,960), provided sufficient information to compute an overall between-group effect size for choice-impulsivity performance. Results revealed a medium-magnitude between-group effect size (g= .47), suggesting that children and adolescents with ADHD exhibited moderately increased impulsive decision-making compared to TD children and adolescents. Further, relative to the TD group, children and adolescents with ADHD exhibited similar patterns of impulsive decision-making across delay discounting and delay of gratification tasks. However, the use of single-informant diagnostic procedures relative to multiple informants yielded larger between-group effects, and a similar pattern was observed across samples that excluded females relative to samples that included females

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Depression Anxiety. 2016;33:45-55.

METHYLATION OF SEROTONIN RECEPTOR 3A IN ADHD, BORDERLINE PERSONALITY, AND BIPOLAR DISORDERS: LINK WITH SEVERITY OF THE DISORDERS AND CHILDHOOD MALTREATMENT. *Perroud N, Zewdie S, Stenz L, et al.*

Background Serotonin 3A receptor (5-HT3AR) is associated at the genetic and epigenetic levels with a variety of psychiatric disorders and interacts with early-life stress such as childhood maltreatment. We studied the impact of childhood maltreatment on the methylation status of the 5-HT3AR and its association with clinical severity outcomes in relation with a functional genetic polymorphism.

Methods Clinical severity indexes of 346 bipolar, borderline personality, and adult attention deficit hyperactivity disorders patients were tested for association with the DNA methylation status of eight 5-HT3AR gene CpGs. Relationship between the functional variant rs1062613 (C > T) and methylation status on severity of the disorders were also assessed.

Results Childhood maltreatment was associated with higher severity of the disease (higher number of mood episodes, history of suicide attempts, hospitalization, and younger age at onset) across disorders and within each individual disorder. This effect was mediated by two 5-HT3AR CpGs. Compared to T allele carriers, CC carriers had higher methylation status at one CpG located 1 bp upstream of this variant.

Conclusions This study shows that epigenetic modification of the 5-HT3AR is involved in the mechanism underlying the relationship between maltreatment in childhood and the severity of several psychiatric disorders in adulthood

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Dev Neurorehabilitation. 2015;18:317-21.

THE RELATIONSHIP OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER TO ADAPTIVE SKILLS IN YOUNG CHILDREN. *Turygin N, Matson JL, Tureck K.*

Objective: Attention-deficit hyperactivity disorder (ADHD) has been linked to deficits in socialization and communication, similar to those observed in children with ASD. In the present study, we examine the differences in developmental quotient and subscale scores between children with ASD and children with ADHD.

Methods: We compared the developmental scores in a sample of 2990 children who presented to an early intervention program, who met criteria for ASD, inattentive ADHD, hyperactive/impulsive ADHD, combined ASD/ADHD, or are at risk for developmental disorders.

Results: The overall developmental quotient did not significantly differ between those in the ADHD inattentive and hyperactive subtype groups. Adaptive skills differed most greatly between the ASD groups and the ADHD/atypically-developing groups.

Conclusion: The present study represents a first step towards understanding the relationship of ADHD to ASD in early childhood. Young children with ASD symptoms are more greatly impaired than those with symptoms of ADHD

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Drug Alcohol Depend. 2013 Dec;133:607-14.

IMPACT OF ADHD AND CANNABIS USE ON EXECUTIVE FUNCTIONING IN YOUNG ADULTS. ***Tamm L, Epstein JN, Lisdahl KM, et al.***

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) and cannabis use are each associated with specific cognitive deficits. Few studies have investigated the neurocognitive profile of individuals with both an ADHD history and regular cannabis use. The greatest cognitive impairment is expected among ADHD Cannabis Users compared to those with ADHD-only, Cannabis use-only, or neither.

METHODS: Young adults (24.2 +/- 1.2 years) with a childhood ADHD diagnosis who did (n=42) and did not (n=45) report past year >/= monthly cannabis use were compared on neuropsychological measures to a local normative comparison group (LNCG) who did (n=20) and did not (n=21) report past year regular cannabis use. Age, gender, IQ, socioeconomic status, and past year alcohol and smoking were statistical covariates.

RESULTS: The ADHD group performed worse than LNCG on verbal memory, processing speed, cognitive interference, decision-making, working memory, and response inhibition. No significant effects for cannabis use emerged. Interactions between ADHD and cannabis were non-significant. Exploratory analyses revealed that individuals who began using cannabis regularly before age 16 (n=27) may have poorer executive functioning (i.e., decision-making, working memory, and response inhibition), than users who began later (n=32); replication is warranted with a larger sample.

CONCLUSIONS: A childhood diagnosis of ADHD, but not cannabis use in adulthood, was associated with executive dysfunction. Earlier initiation of cannabis use may be linked to poor cognitive outcomes and a significantly greater proportion of the ADHD group began using cannabis before age 16. Regular cannabis use starting after age 16 may not be sufficient to aggravate longstanding cognitive deficits characteristic of ADHD

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Dusunen Adam. 2015;28:319-27. **FACTORS RELATED TO METHYLPHENIDATE RESPONSE IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A RETROSPECTIVE STUDY.**

Say GN, Karabekiroglu K, Yuce M.

Objective: We aimed to explore the predictive value of clinical features and self-concept on methylphenidate (MPH) response in children with attention deficit/hyperactivity disorder (ADHD).

Methods: The study had a naturalistic design where the results were analyzed retrospectively. ADHD and comorbidity were diagnosed by Schedule for Affective Disorders and Schizophrenia for School-Age Children Present Lifetime Version (K-SADS-PL). At the baseline assessment, parents completed Turgay DSM-IV Disruptive Disorders Rating Scale (T-DSM-IV-S) and Child Behavior Check List (CBCL); teachers were given T-DSM-IV-S, CBCL. The children completed Piers-Harris Children's Self-Concept Scale (PHSCS), Children's Depression Inventory (CDI), and Screen for Child Anxiety Related Emotional Disorders (SCARED). Following 4-8 weeks of MPH treatment, the parents completed T-DSM-IV-S and the clinician completed Clinical Global Impression-Improvement scale (CGI-I). This study included 54 children (18 girls, 36 boys; mean age 9.32±0.21 years old). The sample was divided in "good responders" (GR) and "poor responders" (PR) regarding the response criteria defined by authors.

Results: The PR group had significantly higher rates of anxiety disorders, higher internalizing scores and lower PHSCS scores compared to GR. Comorbid anxiety disorders, elimination disorders and negative selfconcept were found to predict poor MPH response by multiple regression analysis.

Conclusions: The results point to the need for additional interventions in the presence of comorbid anxiety, incontinence or poor self-concept in children with ADHD

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Epilepsia. 2015;56:233-34.

EXECUTIVE FUNCTIONS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): COMPARISON WITH ADHD ASSOCIATED WITH ROLANDIC EPILEPSY OR ROLANDIC SPIKES.

Turkdogan D, Zaimoglu S.

Purpose: Attention-deficit/hyperactivity disorder (ADHD) is commonly associated with pediatric epilepsy. Both the high prevalence of epileptiform abnormalities in children with ADHD and prevalent ADHD diagnosis preceding the first seizure in children with epilepsy suggest a bidirectional relationship between these two disorders. We aimed to explore the possible neuropsychological differences between ADHD and ADHD associated with Benign Rolandic Epilepsy (ADHD-BRE) and ADHD associated with Rolandic Spikes (ADHD-RS)

Method: Ninety-eight children (25 female), aged between 6 and 12 (mean age: 8.06 - 1.46) years, diagnosed with ADHD according to the DSM-IV-TR criteria were recruited. The neuropsychological data of children diagnosed as ADHD (n = 52) with normal EEG were compared to children with ADHD-RS (n = 25) and to ADHD-BRE (n = 21). All subjects were given a neuropsychological test battery including Wechsler Intelligence Scale For Children-Revised (WISC-R), Wisconsin Card Sorting Test (WCST), Stroop Task, Visual Span subtests of Wechsler scales, Category Naming Test, and Phonemic Verbal Fluency Task

Results: Total, verbal and performance IQ scores of WISC-R were not statistically different between the groups. Vocabulary (F = 5.10 p = 0.008) and digit span (F = 10.80; p = 0.000) subtests of WISC-R and failure to maintain set score (F = 3.45; p = 0.036) of WCST were different between the groups. ADHD cases had a lower Digit Span score (mean-SD: 8.25 - 2.03) compared to the children with BRE (10.65 - 2.52) and RS (10.33 - 2.82). Children with ADHD had significantly higher vocabulary subtest scores compared to the group with ADHD-RS (mean-SD 11.32 - 2.27; 9.75 - 2.33). Failure to maintain set scores of WCST in ADHD group were higher compared to subjects with ADHD-BRE (mean-¦1.83 - 1.55; 0.84 - 0.96)

Conclusion: We found significantly low digit span score in ADHD group compared to patients with BRE or RS. Digit span performance in ADHD was linked to a locus and low digit span performance was suggested to be an endophenotype. ADHD might have a different pathogenetic process compared to the ADHD associated with BRE or RS

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Eur Child Adolesc Psychiatry. 2015 Feb;24:209-17.

DIFFERENTIAL SUSCEPTIBILITY TO MATERNAL EXPRESSED EMOTION IN CHILDREN WITH ADHD AND THEIR SIBLINGS? INVESTIGATING PLASTICITY GENES, PROSOCIAL AND ANTISOCIAL BEHAVIOUR. *Richards JS, Hartman CA, Franke B, et al.*

The differential susceptibility theory states that children differ in their susceptibility towards environmental experiences, partially due to plasticity genes. Individuals carrying specific variants in such genes will be more disadvantaged in negative but, conversely, more advantaged in positive environments. Understanding geneenvironment interactions may help unravel the causal mechanisms involved in multifactorial psychiatric disorders such as Attention-Deficit/Hyperactivity Disorder (ADHD). The differential susceptibility theory was examined by investigating the presence of interaction effects between maternal expressed emotion (EE; warmth and criticism) and the solitary and combined effects of plasticity genes (DAT1, DRD4, 5-HTT) on prosocial and antisocial behaviour (measured with parent- and self-reports) in children with ADHD and their siblings (N = 366, M = 17.11 years, 74.9% male). Maternal warmth was positively associated with prosocial behaviour and negatively with antisocial behaviour, while maternal criticism was positively associated with antisocial behaviour and negatively with prosocial behaviour. No evidence of differential susceptibility was found. The current study found no evidence for differential susceptibility based on the selected plasticity

genes, in spite of strong EE-behaviour associations. It is likely that additional factors play a role in the complex relationship between genes, environment and behaviour

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Eur Child Adolesc Psychiatry. 2016;25:17-23.

THE DISCRIMINATIVE CAPACITY OF CBCL/1-¢-5-DSM5 SCALES TO IDENTIFY DISRUPTIVE AND INTERNALIZING DISORDERS IN PRESCHOOL CHILDREN.

De La Osa N, Granero R, Trepat E, et al.

This paper studies the discriminative capacity of CBCL/1½-5 (Manual for the ASEBA Preschool-Age Forms & Profiles, University of Vermont, Research Center for Children, Youth, & Families, Burlington, 2000) DSM5 scales attention deficit and hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), anxiety and depressive problems for detecting the presence of DSM5 (DSM5 diagnostic and statistical manual of mental disorders, APA, Arlington, 2013) disorders, ADHD, ODD, Anxiety and Mood disorders, assessed through diagnostic interview, in children aged 3−5. Additionally, we compare the clinical utility of the CBCL/1½-5DSM5 scales with respect to analogous CBCL/1½-5 syndrome scales. A large community sample of 616 preschool children was longitudinally assessed for the stated age group. Statistical analysis was based on ROC procedures and binary logistic regressions. ADHD and ODD CBCL/1½-5-DSM5 scales achieved good discriminative ability to identify ADHD and ODD interview's diagnoses, at any age. CBCL/1½-5-DSM5 Anxiety scale discriminative capacity was fair for unspecific anxiety disorders in all age groups. CBCL/1½-5DSM5 depressive problems' scale showed the poorest discriminative capacity for mood disorders (including depressive episode with insufficient symptoms), oscillating into the poor-to-fair range. As a whole, DSM5oriented scales generally did not provide evidence better for discriminative capacity than syndrome scales in identifying DSM5 diagnoses. CBCL/1½-5-DSM5 scales discriminate externalizing disorders better than internalizing disorders for ages 3−5. Scores on the ADHD and ODD CBCL/1½-5-DSM5 scales can be used to screen for DSM5 ADHD and ODD disorders in general populations of preschool children

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Eur Child Adolesc Psychiatry. 2016;1-9.

DIAGNOSTIC EFFICIENCY OF THE SDQ FOR PARENTS TO IDENTIFY ADHD IN THE UK: A ROC ANALYSIS. *Algorta GP, Dodd AL, Stringaris A, et al.*

Early, accurate identification of ADHD would improve outcomes while avoiding unnecessary medication exposure for non-ADHD youths, but is challenging, especially in primary care. The aim of this paper is to test the Strengths and Difficulties Questionnaire (SDQ) using a nationally representative sample to develop scoring weights for clinical use. The British Child and Adolescent Mental Health Survey (N = 18,232 youths 5Γ Çô15 years old) included semi-structured interview DSM-IV diagnoses and parent-rated SDQ scores. Areas under the curve for SDQ subscales were good (0.81) to excellent (0.96) across sex and age groups. Hyperactivity/inattention scale scores of 10+ increased odds of ADHD by 21.3+ù. For discriminating ADHD from other diagnoses, accuracy was fair (<0.70) to good (0.88); Hyperactivity/inattention scale scores of 10+ increased odds of ADHD by 4.47+ù. The SDQ is free, easy to score, and provides clinically meaningful changes in odds of ADHD that can guide clinical decision-making in an evidence-based medicine framework

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Eur Neuropsychopharmacol. 2015;25:S252-S253.

ATTENTION DEFICIT AND HYPERACTIVITY DISORDER - THE PHARMACOLOGICAL APPROACH IN OUR CLINIC. *Irimie-Ana A, Militaru M, Turtoi I, et al.*

Purpose: Our main interest was to look at the therapeutic handling of attention deficit and hyperactivity disorder diagnosed in children and adolescents in our clinic, in order to have a descriptive overview of this aspect to stand at the basis of a future standardized conduct.

Method: We conducted a case-series observational study for which we reviewed all patients' medical files from 2005 until present from "TITAN Dr. Constantin Gorgos" Psychiatry Hospital in Bucharest and extracted those with the diagnosis of interest. Using data from the selected records we enrolled 257 patients in our study and conceived a data base which contained: patients' age, sex, date of their last admission, intelligence coefficient for children older than 5 years old measured with Raven's test, scores from the ADHD-rating scale for parents, number of co morbidities and doses of the drugs we used. The mentioned doses were the minimal effective doses that controlled the symptoms and were reached through a progressive accretion followed by a gradual decrease during the patients' hospitalization. We used Microsoft Excel 2007 to organize our data and computed the descriptive statistics with the help of Analyses Tool Pack. In order to test our assumptions and make comparisons we used Wilcoxon rank sum test or Pearson correlation coefficient with a level of significance $p<0.05$.
Results: Out of a total 257 patients 209 (81.32%) were males and only 48 (18.68%) were female patients, leading us to a ratio male/femaleofapproximately4/1.Ourpatientswereagedbetween 2 and 17 years old with a mean (±SD) of 9.19 ±3.10. The pharmacological agents used in our clinic were: Atomoxetine in 56.60% of cases and Methylphenidate in 28.93 while 14.47% were given Risperidone. 148 patients had no other psychiatric or neurologic comorbidities associated while the rest of 109 had one or more of the following: pervasive developmental disorder, tics, conduct disorder, epilepsy. The average dose of Atomoxetine in patients with zero comorbidities was 31.78mg while for the patients in the latter category it was 33.12mg. For Methylphenidate the average dose was 17.25mg when ADHD was the sole diagnosis and 18.72mg when other pathologies were associated. These differences were not statistically significant. Between the score of ADHD measured on the ADHD rating scale for parents and their intelligence quotient we found only a weak negative correlation ($R=-0.1179$). For patients with an intelligence quotient lower than 70 the average dose of Atomoxetine and Methyphenidat was 26.33mg, respectively 18.57mg while for those with higher quotients the average doses were 29mg and 15.66, the differences were not statistically significant.
Conclusions: The majority of our patients were males. Atomoxetine was the most frecquently used pharmacological agent. The lowest doses that controlled the symptoms and with which our patients checked out from the hospital didn't correlate with their intelligence quotient. We obtained a weak negative correlation between the score of ADHD and their intelligence quotient.

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Eur Neuropsychopharmacol. 2015;25:S201-S202.

EVALUATION OF ACUTE CARDIOVASCULAR EFFECTS OF IMMEDIATE-RELEASE METHYLPHENIDATE IN CHILDREN WITH ADHD: A NEW ELECTROCARDIOGRAPHIC T-WAVES MARKER.

Lamberti M, Guerriero L, Italiano D, et al.

Introduction: Attention deficit/hyperactivity disorder (ADHD) is a common behavioural disorder characterized by symptoms of inattention, impulsivity and hyperactivity that impact several domains of the life of patients, their family, and society. Treatments and interventions for ADHD are different and include psychological therapies and pharmacological treatment, especially for severe clinical cases. Immediate release (IR) MPH is considered the gold-standard of psychopharmacotherapy for patients ADHD. Stimulants have been associated with increased cardiovascular risk, due to rise in blood pressure and heart rate (HR). Furthermore, immediate release IR-MPH has raised concerns about potential cardiovascular adverse effects within a few hours after administration. This study was carried out to investigate acute effects of IR-MPH on ECG in a pediatric population and in particular by measuring the acute effects of IR-MPH on the ventricular repolarization through TpTe and TpTe/QT intervals, along with QTc and QTd. Recent studies indicate that prolongation of the interval between the peak and the end of the T wave (T-peak to T-end, TpTe) on the 12lead ECG can represent a new marker of ventricular arrhythmogenesis. The prolongation of the TpTe interval, measured in lead V5, is considered independently associated with sudden cardiac death, and it can be a suitable risk indicator even when the QTc is within range or not measurable due to prolonged QRS duration.
Methods: A total of 60 consecutive patients with ADHD (54 males and 6 females; mean age= 11.9 years DS + 3.3, range 6-19 years), receiving a new prescription of MPH, underwent a standard ECG 2 hours before and after the administration of IR-MPH 10 mg per os. Basal and post-treatment ECG parameters, including mean QT (QTc), QT dispersion (QTd) interval duration, Tp-Te intervals and TpTe/QT ratio were compared.

Results: No clinically significant changes were observed using our cardiological parameters after methylphenidate treatment. Significant modifications of both QTc and QTd values were not found after drug administration. A significant variation in blood pressure (BP) (Systolic BP 105.7±10.1mmHg vs 109.9±11.1 mmHg; p<0.1; Diastolic BP 59.1±7.3mmHg vs 63.8±8.5 mmHg; p<0.01) was observed, but all the data were within normal range. Also in HR and in TpTe values was found a statistically significant increase from T0 to T1. HR moved from 81.1 + 15.4 bpm to 88.4+ 18.1 bpm. TpTe/QTc intervals were changed with respect to basal values (0.209 +0.016 ms vs 0.215 +0.019 ms; p<0.01). No patient exhibited values exceeding the clinical intervals.
Conclusions: The findings of this study show no significant changes in ECG parameters within 2 hours after IR-MPH administration. TpTe values can be an additional parameter to evaluate borderline cases. It's important to investigate the cardiac effects of stimulants when associated with other concomitant drugs, especially in patients with high burden of cardiovascular disease

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Eur Neuropsychopharmacol. 2015;25:S651-S652.
PUBLIC PERSPECTIVES ON PHARMACOLOGICAL TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER. *Nam B, Shon I, Kim MH, et al.*
About half of children who were diagnosed attention-deficit hyperactivity disorder (ADHD) got treatment for ADHD, and the number of medicated ADHD children was smaller than the estimated ADHD children based the prevalence rate of ADHD. This undertreatment phenomenon might be based on public misconceptions about ADHD and its treatment. It is important to investigate public knowledge and beliefs about ADHD and its treatment. The aim of this study was to examine 1) public knowledge and perceptions about ADHD and 2) factors influencing the public's decisions to adhere to ADHD pharmacotherapy. In this study, 396 participants who were members of the child care internet blog for non professional parents, responded to the internet survey. The questionnaires were about their experiences, beliefs and treatment preferences about ADHD and it was made by Google Docs. They use their personal computer or smart phone to reply it. 390 of 396 participants (98.5%) were female and mean age was 33.9±4.1 years. 372 respondents (93.9%) have child(ren) and mean age of their child(ren) was 4.2±3.2 years. 217 respondents (54.8%) were housewifves by occupation. 376 respondents (95.0%) graduated college or higher. 145 respondents (36.6%) chose caregiver's attitude as the main cause of ADHD. Subsequent responses were innate temperament (24.2%), brain dysfunction (20.7%), violent environment (16.7%), inappropriate diet (1.0%), and overexposure to multimedia device (0.5%). 248 respondents (62.6%) preferred non pharmacological treatment only for ADHD, 141 respondents (35.6%) chose both pharmacological and non pharmacological treatment, and 3 respondents (0.8%) chose pharmacological treatment only. Knowledge scores of ADHD were 9.4-1.8 (of 13). The respondents who chose the functional impairment of the brain as the main cause of ADHD were favorable to pharmacological treatment and scored 10.2-1.7 (of 13) on the ADHD Knowledge Questionnaire. It was significantly higher than the score of group who chose others as the main cause (p<0.001). On the other hand, the respondents who regarded ADHD as an overly active personality were skeptical to pharmacotherapy and scored 8.7±1.8 (of 13) on the ADHD Knowledge Questionnaire. It significantly lower than the score of the group who regard ADHD as a disease (p<0.001). The respondents who were acquainted with someone who had been diagnosed with ADHD perceived themselves relatively well informed about ADHD (p<0.001). However, the subjective perception of the degree of knowledge of ADHD was not correlated with the objective score of the ADHD Knowledge Questionnaire. The public is not well informed about ADHD and its treatments. Culturally appropriate psychoeducational strategies based on the media and the internet are needed. Providing biomedical conceptualization of ADHD to the public may aid in treatment decisions and promote adherence to pharmacological treatment

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Eur Neuropsychopharmacol. 2015;25:S321-S322.

EFFECTS OF NOREPINEPHRINE TRANSPORTER GENE VARIANTS ON PROTEIN BINDING IN PATIENTS WITH ADHD USING PET.

Sigurdardottir H, Kranz G, Rami-Mark C, et al.

Purpose of the study: Attention Deficit Hyperactivity Disorder (ADHD) is one of the most prevalent disorders in children as well as in many cases they persist well into adulthood. ADHD is characterized by inattention, hyperactivity and impulsiveness which frequently leads to severe social, academic and vocational dysfunction. The norepinephrine (NE) system has long been implicated in the pathophysiology of ADHD. A recent study investigating the norepinephrine transporter (NET) in ADHD using PET did however not detect any differences in protein binding between groups. Since ADHD has a strong heritability factor it is therefore of high interest to examine whether genetic variants in the NE system serve as possible modulators of ADHD pathophysiology. The objective of this study was to examine whether single nucleotide polymorphisms (SNPs) in the NET modulate the NET binding in regions that have been implicated as faulty in ADHD and whether they differ from controls and ADHD subjects [3]. Furthermore, it was also tested whether behavioural subscales correlated with these areas and whether they differ between genotypes.
Methods: 20 adult non-medicated ADHD patients (age SD: 30.8±10.9, 14 males) and 20 healthy controls (age SD: 30.4±10.9, 14 males) were recruited through ADHD outpatient clinic at the Department of Psychiatry and Psychotherapy, Medical University of Vienna and from the local community via advertisement. Each subject underwent a (S,S)-[18F]FMeNER-D2 PET scan using a full-ring scanner (General Electric Medical Systems, Milwaukee, WI, USA) in 3D acquisition mode. DNA was extracted using the QiaAmp DNA blood maxi kit and genotyping of NET SNPs with the Sequenom iPLEX assay. NET binding potential was quantified using the caudate as a reference region. Statistical analysis was calculated in SPSS using linear mixed models analysis with genotypes, status and ROIs as fixed factors and NET BPND as the dependent variable.
Results: Differences were detected between groups in the cerebellum and thalamus depending on genotype. For the cerebellum, two 3' untranslated region SNPs (3'UTR) showed higher binding in healthy controls for major allele group then the major allele group of ADHD subjects ($p<0.05$, corrected). In the thalamus, a functional promotor SNP showed lower binding in healthy controls compared to ADHD subjects in the major allele group ($p <0.05$, corrected). Additionally, CAARS Hyperactivity/Impulsivity and CAARS total scores were correlated with BPND in the cerebellum for the 3'UTR SNPs.
Conclusions: These findings indicate that SNPs in the SLC6A2 gene regulate NET binding up to a certain extent in ADHD. Moreover, they are located within areas that have been shown to be altered in ADHD. Interestingly, the subscale for CAARS Hyperactivity/Impulsivity correlated with BPND in the cerebellum, which has been implicated in impulsivity control as well as being dysregulated in ADHD. Limitations to this study is that BPND cannot be assessed properly in the cortex due to spill over from the bone from this radioligand as well as sample size is rather small, at least for some of the analyses. While these results look very promising, further replications are needed

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Eur Neuropsychopharmacol. 2015;25:S189.

SUBCORTICAL VOLUMES ACROSS THE LIFE SPAN IN ADHD: AN ENIGMA COLLABORATION . *Hoogman M, Bralten J, Mennes M, et al.*

Objectives: Neuroimaging studies in ADHD show structural alterations of various brain regions in affected children and adults [1-3]. In part due to inconsistencies in published results, it remains unclear, however, how these differences develop across the lifespan, and whether effects are brain-wide or localized to particular neurological structures and pathways. To clarify brain changes in ADHD, an ADHD Working Group was formed within the ENIGMA consortium (http://enigma.ini.usc.edu/). Within the working group, we are sharing brain imaging data from children and adults with ADHD and healthy comparison subjects. Our first aim is to study subcortical brain differences in ADHD across the lifespan. Our second aim is to study the potential effects of sex and medication.
Methods: Within the ENIGMA-ADHDWorking Group cohorts from around the world analyzed MRI scans using fully automated and validated neuroimaging segmentation software (FreeSurfer), for which protocols are available on our website. The working group comprises 23 international sites including 1544 patients with ADHD and 1729 healthy controls. This pooled sample has an age-range of 4 to 63 years and includes 66%

males. Volumetric summaries of subcortical regions were pooled together and shared across the consortium. Meta- and Mega-analysis for the casecontrol volume differences of hippocampus, nucleus accumbens, amygdala, caudate nucleus, putamen, pallidum, and thalamus were carried out. Effects of age, sex and medication were studied.
Results: Our case-control meta-analysis showed subtle but significantly smaller volumes for the amygdala (d: 0.15, p = 0.004), caudate nucleus (d: 0.11, p = 0.007), and putamen (d: 0.11, p = 0.003) for cases compared to controls. The results of the megaanalysis appeared to be more powerful and also found casecontrol differences for the nucleus accumbens (d: 0.11, p = 0.0001), and hippocampus (d: 0.08, p = 0.005). The hippocampus showed agedependent effects that were different in patients with ADHD compared with healthy controls. Also for nucleus accumbens, amygdala and putamen it seems there is a delay of maturation in childhood and a delay of degeneration later in life in patients with ADHD. The factor sex did not interact with diagnostic status, thus the volume decrease in male and female patients are similar. Patients who were currently taking stimulant medication showed reduced effects of volume decrease in the striatal volumes, but the volume decrease in the amygdala was unaffected by stimulant medication.
Conclusions: Brain structure differences related to ADHD across the lifespan remain largely unexplored. As large, wellpowered longitudinal studies are still scarce, the ENIGMA-ADHD Working Group, with a large cross-sectional sample across six decades of the lifespan, is beginning to address this gap. By sharing individual brain data, we are able to perform both metaanalysis as well as a more powerful mega-analysis, which also has the benefit of studying individual factors such as age, sex and medication in more detail

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Eur Neuropsychopharmacol. 2015;25:S199-S200.

ACCESS TO DIAGNOSIS, TREATMENT AND SUPPORTIVE SERVICES: RESULTS FROM THE CAREGIVER PERSPECTIVE ON PEDIATRIC ADHD STUDY IN EUROPE.

Fridman M, Quintero J, Chen K, et al.

Purpose: To evaluate the access to obtain a diagnosis for attention-deficit/hyperactivity disorder (ADHD), behavioural therapy (BT) and ADHD supportive care for European children/ adolescents with ADHD from the caregiver's prespective.
Methods: Caregiver Perspective on Pediatric ADHD (CAPPA) is a cross-sectional online survey completed between 2012 and 2013 by caregivers of children/adolescents aged 6-17 years with ADHD in 10 European countries: Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden and the UK. Data from Denmark, Finland and Norway were pooled because of small sample sizes. Responses from caregivers of children/ adolescents receiving ADHD pharmacological treatment at the time of survey or within the previous 6 months were analysed. Caregivers were asked about their experiences with obtaining an ADHD diagnosis, access to BT, and the level of support from social services, healthcare providers and schools. Responses were summarized and compared across countries using chi-square and t-tests for categorical and continuous measures, respectively.
Results: Among 3616 respondents, 81% were married/ partnered; 64% of caregivers were the child/adolescent's mother, 30% their father and the rest had other relation to the child/ adolescent. Children's mean (SD) age was 11.5 (3.2) years and 80% were male. Pan-EU and the individual country range summaries are presented in the table. Thirty-one percent (range: 21-43%) of caregivers reported difficulty in obtaining a diagnosis and 44% (range: 23-77%) received no BT. Only 47% of caregivers were satisfied with availability of resources, 44% with quality of medical care and 50% with healthcare provider's support. Mainstream schools were attended by 82% of children. Of those, 48% received extra help or special accommodations and 64% of caregivers thought schools could do more. Comparisons of reported results were significantly different across countries ($p<0.001$). (Table presented)
Conclusions: A large percentage of caregivers reported difficulty and prolonged time to obtain a diagnosis for their child/ adolescent with ADHD, and suboptimal supportive care from medical and school systems. These unmet needs may increase the burden on families. Additionally, there is a wide variation across countries in practice and care patterns. These findings suggest a need for improved access to diagnosis, provision of supportive services and adherence to BT established guidelines

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Eur Neuropsychopharmacol. 2015;25:S200-S201.

OPEN-LABEL STUDY COMPARING THE EFFICACY AND TOLERABILITY OF ARIPIPRAZOLE AND RISPERIDONE IN THE TREATMENT OF CHILDREN WITH AUTISM SPECTRUM DISORDER AND ADHD. Lamberti M, Siracusano R, Italiano D, et al.

Introduction: Autism Spectrum Disorders (ASD) and Attention- Deficit/Hyperactivity Disorder (ADHD) are frequently overlap ping severe neurodevelopmental disorders. Individuals with cooccurring ASD and ADHD symptoms are more severely impaired, with relevant deficits of social processing, adaptive functioning and executive control. Despite not FDA-approved for treatment of ADHD, atypical antipsychotic medications such as risperidone (2006) and aripiprazole (2009) are FDA-approved for treatment of disruptive behavior disorder including aggression and severe behavioral problems in ASDs. Among atypical antipsychotics, risperidone and aripiprazole, seem to be effective in reducing irritability, stereotypy and hyperactivity in patients with ASDs. The aim of the study is to evaluate and compare the efficacy and tolerability of these two drugs on ASD and ADHD comorbid patients after 6 months of treatment.

Method: 23 children (18 boys and 5 girls) were included in the study. The mean age was 8.9 years (SD ±2.8) in the aripiprazole group and 7.2 years (SD ±2.0) in the risperidone group. Children were evaluated before starting treatment (T0), and after 3 months (T1) and 6 months of treatment (T2). Conners' Parent Rating Scales-Revised (CPRS-R), Attention- Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS), Clinical Global Impression-Severity (CGI-S), Clinical Global Impression- Improvement (CGI-I), and Children's Global Assessment Scale (C-GAS) were administered at each step of treatment to assess the effectiveness of medication, as primary outcomes. The secondary outcomes were: QT-interval prolongation on Electrocardiography (ECG), blood pressure, pulse, body weight, height, body mass index, abdominal circumference, fasting blood glucose, insulin and lipid levels, prolactin, and other general blood tests). Further, the Abnormal Involuntary Movement Scale (AIMS) was administered to assess drug-related dyskinetic adverse effects. Results were compared between Risperidone and Aripiprazole groups and within the single groups. Both groups showed significantly lower scores on hyperactivity/inattention rating scales (ADHDRS, CPRS-H and CPRS-D) after 24 weeks of treatment.

Results: After the first 12 weeks of treatment, both groups had a significant reduction of the CGI - severity global (CGI-S $p<0.001$). Aripiprazole and risperidone appeare to have similar benefits in terms of efficacy and tolerability. Compared to risperidone, the benefit of aripiprazole treatment seems significantly greater at 12 weeks but this difference doesn't persist at 24 weeks. This could indicate a faster positive effect of Aripiprazole compared to Risperidone. Both drugs were well tolerated with no serious adverse events detected. In our sample we found an average weight gain of 4 kg for patients treated with risperidone and 1.6 kg for patients treated with aripiprazole.

Conclusions: Our research confirms the efficacy of Aripiprazole and Risperidone in ameliorating symptoms of children with complex co-morbidities such as ASD and ADHD, even if the two drugs have shown slight differences in efficacy and tolerability. It's required an accurate knowledge of comorbidity between the two disorders in order to plan appropriate treatments that can be effective on both the specific symptoms and the overall functioning

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Eur Neuropsychopharmacol. 2015 Dec;25:2300-10.

DIFFERENTIAL THERAPEUTIC EFFECTS OF 12-WEEK TREATMENT OF ATOMOXETINE AND METHYLPHENIDATE ON DRUG-NAÏVE CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A COUNTING STROOP FUNCTIONAL MRI STUDY.

Chou TL, Chia S, Shang CY, et al.

Methylphenidate and atomoxetine are effective in treating attention-deficit/hyperactivity disorder (ADHD) with underlying distinct pharmacological mechanisms. To relate neural mechanisms to clinical response, we conducted a comparative trial to differentiate the changes in brain activation of drug-naïve children with ADHD when performing neuropsychological tasks after 12 weeks of pharmacotherapy. We randomized 50 drug-naïve children with ADHD, aged 7–17, to treatment with methylphenidate (n = 25) or atomoxetine (n = 25). These children were scanned twice with functional magnetic resonance imaging (fMRI) during the counting Stroop task before and after treatment. Focused attention and impulsivity were assessed twice by using the Conner's Continuous Performance Test (CCPT). The final sample for fMRI analysis comprised 20

in the methylphenidate group and 22 in the atomoxetine group. Atomoxetine decreased activations in the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex, which correlated with improvement in focused attention assessed by the CCPT. In contrast, methylphenidate increased activations in the inferior frontal gyrus, which correlated with the decreasing severity of impulsivity assessed by the CCPT. The current findings suggest that differential therapeutic effects on neuronal changes induced by 12-week treatment atomoxetine and methylphenidate may contribute to behavioral improvement.

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Eur Neuropsychopharmacol. 2015;25:S360.

CORRELATION BETWEEN ADHD AND DEPRESSION AMONG UNIVERSITY STUDENTS IN MACEDONIA. ***Sushevska PL, Richter K, Niklewski G.***

Introduction: Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral developmental disorder usually diagnosed in children, with appearance of the first symptoms before the age of seven years. The disorder is characterized by inattention and/or impulsivity and hyperactivity that can seriously affect many aspects of behavior and performance at school. ADHD may significantly affect an individual through childhood as well as in adulthood, especially if it is not optimally managed, has been associated with lower professional status, crime, and substance abuse ADHD can be associated with comorbidities, such as oppositional defiant disorder, conduct disorder, anxiety or depression. The aim of our research was to determine the prevalence and gender distribution of ADHD as well as to determine the subtypes and conditions (in this case depression) associated with it.

Material and Methods: The study design was cross sectional. There were 127 boys and 251 girls. The target group consists of university students from the Faculty of Medical Sciences in Stip, a town in Macedonia. The number of participants in the survey is 500 respondents (in order to make better screening), from all years of study and from all four study programs (general medicine, dentistry, pharmacy and vocational studies). It represents 25% of the total number of students of medical sciences and every fourth student who attends the lectures will be included in the research.

Inclusion criteria: research concerns the students of the Faculty of Medical Sciences who agree to participate in research.

Exclusion criteria: the research will not participate students who refuse to participate because of personal reasons.

Results: The research results show that the ADHD is highly significant associated with gender ($p = 0.0004$). Men more often than women have this kind of disorder. Female examinees are significantly ($p = 0.028$) more often depressed compared to male examinees. The existence of depression can be recognised in 76 (30.3%) persons from the group of female students compared to 25 (29.7%) male students who suffer from depression according to the scale results. The Pearson's linear correlation coefficient value is $r = 0.173$ for the examined connection between depression and attention deficit, and $r = 0.148$ for the examined connection between depression and hyperactivity/impulsiveness. These values show that the examined correlations are positive ones or direct, meaning that by increasing the values of the scores from both subscales from the Evaluation ADHD Scale one also increases the scores from the Depression Scale, and vice versa. For a value of $p = 0.001$ and $p = 0.004$ these correlations are statistically highly significant, in other words highly important.

Conclusion and Discussion: Our results are similar with the results from the studies worldwide. The research results show that the ADHD is highly associated with gender. Men more often than women have this kind of disorder. Female students have deficit of attention subtype, while man student have often hyperactivity/impulsivity disorder and combined subtype due to psychological, temperament and character gender differences among boys and girls

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Eur Neuropsychopharmacol. 2015;25:S178-S179.

THE EEG SPECIFICITY IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD). ***Khachidze I, Maloletnev V, Gugushvili M, et al.***

Purpose: To find out the distinctive topographic EEG profiles of children with attention deficit hyperactivity disorder (ADHD) should have predictive value. A comprehensive study of this syndrome has an essential significance in Neuropsychopharmacology since it has been demonstrated that in 40-60% of patients ADHD syndrome continues to manifest itself in mature age as well. The present study aimed to study and compare peculiarities of EEG characteristics in children with ADHD using procedures qEEG analysis.

Methods: The EEG of 20 children aged 6 to 9 years with ADHD (10 boys and 10 girls) and EEG of 20 healthy ones of the same age and gender served as a control group was studied. EEG signals were digitally recorded using a set of 19 scalp electrodes according to the International 10-20 system. EEG Recording in all patients was carried out in the morning during of quiet wakefulness. Mean duration of EEG recording was 20-25 minutes. For each child, 10 sec artifact-free EEG epochs were selected (at rest, with open and closed eyes, during functional exertion). 8 EEG fragments for each patient were performed and Fourier transformed to provide absolute (AP) and relative power (RP) estimates for the delta, theta, alpha and beta bands.

Summary: The analysis of data to reveal a few types of EEG changes 1. Disorganization of basic EEG' rhythmicity with single sharp alpha waves - 52.5%. 2. Increase of indices of AP in the low frequency bands on the all cortex. Authentic increase of RP values in the low frequency manifested only in fronto-central region ($p<0.05$). The Power of activity of Beta frequency band appeared to be higher in the occipital records from the control group and this difference manifested both in AP and RP indices. In the fronto-central leads significantly higher values were manifested in the control group only by AP indices ($p <0.05$). In girls group of AP indices beta frequency were higher in control group ($p<0.05$). RP analysis also displayed higher values of beta activity in the fronto-central and right temporal recordings in the control group. Special attention deserves the fact that both in boys and girls with ADHD we have revealed decline in AP and RP activity within beta range 3. Presence paroxysms during hyperventilation - 37.4%. The basic patterns of EEG disturbances in different combination may be found in a same patient.

Conclusions: The results shown increase of AP in slow-wave activity (predominantly of theta range) and declined of RP in the fast (predominantly of beta) domain of spectrum in ADHD children. It should be related with different neurophysiological and psychopharmacologycal mechanisms, and patients with ADHD by EEG indices do not constitute a homogenous group. Different EEG rhythms reflect function of a variety of intracerebral feature. The comparison of different EEG rhythms maturation in normal ontogenesis and ADHD patients' one can detect the most vulnerable links in pathogenic mechanism of this syndrome. Detection of such loci and clinical role of computerized EEG perhaps contribute to a more beneficial treatment in children with ADHD

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Eur Neuropsychopharmacol. 2015;25:S641-S642.

A SYSTEMATIC REVIEW OF LISDEXAMFETAMINE VERSUS PLACEBO IN THE TREATMENT OF CHILD AND ADOLESCENT ADHD.

Maneeton B, Maneeton N, Likhitsatian S, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common behavioral problem in children and adolescents with a worldwide prevalence rate of five to ten percent in children and adolescents. Several studies have shown that stimulants, including lisdexamfetamine (LDX), are efficacious in child and adolescent ADHD.

Objectives: Aims of this study were to systematically review the efficacy, acceptability and tolerability of LDX in child and adolescent ADHD. All randomized controlled trials (RCTs) of LDX compared with placebo conducted in children and adolescents with ADHD were included.

Data sources: The searches of the SCOPUS, MEDLINE, CINHAL and Cochrane Controlled Trials Register were performed in September, 2014. Additional searches in the ClinicalTrials.gov and EU Clinical Trials Register database were conducted.

Study eligibility criteria, participants and interventions: This review included all RCTs of LDX vs. placebo which were performed in children and adolescents up to 18 years. Additionally, the included studies must

have reported the final outcomes of: i) severity of ADHD symptoms with standardized scales, ii) rates of improvement iii) rates of discontinuation. The languages of such RCTs were not limited.
Study appraisal and synthesis methods: The abstracts from databases were examined. After irrelevant studies were discarded, the full text versions of relevant trials were assessed and extracted for interest outcomes. According to the Cochrane bias assessment, an assessment of risk of bias was also carried out. The efficacy of outcome was determined by either the pooled mean end-point or changed scores of ADHD rating scales, and the rate of improvement. The acceptability and tolerability were measured by the pooled overall discontinuation rate and the pooled discontinuation rate due to adverse events. A random effect model technique was applied for synthesizing the mean differences [either standardized mean differences (SMDs) or weighted mean differences (WMDs] and relative risks (RRs) with 95% confidence intervals (CIs). **Results**: A total of 1,016 children and adolescents with ADHD were included. The doses of LDX were 30 to 70 mg/day. The pooled mean change scores between LDX-treated group was significantly higher than that of the placebo [WMD (95% CI) of -15.20 (-19.95, -10.46), I2 = 94%]. The pooled improvement rate of the LDX-treated group was also significantly greater than that of the placebo [RR (95% CI) of 0.34 (0.24, 0.47), I2 = 80%]. The pooled overall discontinuation rate between the two groups had no significant difference [RR (95% CI) of 0.78 (0.46, 1.31), I2 = 63%]. Similarly, the pooled discontinuation rate due to adverse events between the two groups was not significantly different [RR (95% CI) of 1.99 (0.70, 5.64), I2 = 0%].
Limitations: The number of included studies was limited (five RCTs).
Conclusions: Based on this review, LDX was efficacious and well-tolerated in the treatment of child and adolescent ADHD. Unfortunately, the acceptability of LDX was not better than the placebo. Since the number of included studies was limited, the findings from this review should be carefully interpreted and considered as preliminary. Further studies, therefore, should be carried out to verify these outcomes

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Eur Neuropsychopharmacol. 2015;25:S642.

A SYSTEMATIC REVIEW OF DEXMETHYLPHENIDATE VERSUS PLACEBO IN CHILD AND ADOLESCENT ADHD: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS.

Maneeton N, Maneeton B, Woottiluk P, et al.

Background: Dexmethylphenidate (d-MPH) have shown its efficacy in the treatment of children and adolescents with attentiondeficit hyperactivity disorder (ADHD).
Objectives: Aims of this systematic review determined the efficacy, acceptability and tolerability of d-MPH in child and adolescent ADHD. This review included all randomized controlled trials (RCTs) of d-MPH vs. placebo conducted in child and adolescent groups with diagnosis of ADHD.
Data sources: The searches of SCOPUS, MEDLINE, CINHAL, Cochrane Controlled Trials Register, ClinicalTrials.gov, EU Clinical Trials Register and Norvatis clinical trial databases were performed in February, 2015.
Study eligibility criteria, Participants and Interventions: There were included all RCTs of d-MPH vs. placebo which were performed in children and adolescent with ADHD, aged up to 18 years. Those studies must report the final results of: i) severity of ADHD symptoms with standardized scales, ii) response rates iii) rates of discontinuation.
Study appraisal and synthesis methods: The tittles and abstracts of articles gathered from such databases were assessed. After the irrelevant studies removed, the full text version of relevant clinical studies was thoroughly inspected and extracted for interest findings. Additionally, risks of bias were examined by using the Cochrane bias assessment method. The efficacy was measured by using the pooled mean end-point or changed scores of ADHD rating scales and the response rate. Acceptability and tolerability were measured by using the pooled overall discontinuation rate and the pooled discontinuation rate due to adverse events, respectively. A random effect model technique was applied in synthesis of the weighted mean differences (WMDs), standardized mean differences (SMDs) and relative risks (RRs) with 95% confidence intervals (CIs).
Results: A total number of 1,124 children and adolescents diagnosed in ADHD were included in this review. Doses of d-MPH were 2.5-10 mg for single dose and 5 to 30 mg/day. Based on the laboratory school setting, the pooled mean-changed and meanend point scores of child and adolescent ADHD in d-MPH-treated group were significantly greater than that of placebo-treated group [SMD (95% CI) of -1.2 (-1.73, -0.67), I2=95%].

Additionally, the mean-changed scores of ADHD rating scales for teachers in regular classroom for d-MPHtreated group had also a greater significance than that of placebo-treated group [WMD (95% CI) of -13.01 (15.97, -10.05), I2=0%]. Similarly, the mean-changed scores of ADHD rating scales for parents in d-MPHtreated group were significantly greater than that of placebo-treated group [WMD (95% CI) of -12.99 (-15.57, -10.42), I2=0%]. The pooled response rate of child and adolescent ADHD in d-MPH-treated groups had a higher significance than that of placebo-treated group [RR (95% CI) of 0.45 (0.27, 0.76), I2=91%]. The pooled overall discontinuation rate in child and adolescent ADHD between d-MPH- and placebo-treated groups was not significantly different [RR (95% CI) of 0.75 (0.46, 1.24), I2=0%]. The pooled discontinuation rate due to adverse events between two group had also no significant difference [RR (95% CI) of 0.92 (0.33, 2.57), I2=0%].

Conclusions: Based on the findings in this review, d-MPH medication is efficacious and tolerable in child and adolescent ADHD. However, the acceptability of d-MPH is not greater than the placebo. Further systematic studies may confirm these findings

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Eur Neuropsychopharmacol. 2015;25:S644.

EFFECTS OF METHYLPHENIDATE ON HEIGHT IN ADHD CHILDREN. THE MONITORING OF BONE AGE WITHIN THE ADDUCE PROJECT.

Carucci S, Caddeo M, Romaniello R, et al.

Background: CNS stimulants represent the most effective medication in improving the core symptoms of ADHD, however in the last 30 years, there has been increasing concern about the risks associated with these medications in particular with respect possible growth deficits. Although poor growth is a common concern, especially with children already on the lower growth percentiles, the impact of medication on growth and pubertal maturation has remained somehow unclear and stimulants effects at different ages have not been extensively investigated. Many unanswered questions remain about the biological mechanism underlying the growth deficit in medicated ADHD subjects, some of the hypothesis considering that the condition of ADHD per se is associated to an impaired growth condition.

Objectives: To evaluate, within the prospective, longitudinal, pharmacovigilance, EU funded project ADDUCE, whether ADHD children exhibit an abnormal pattern of growth per se before starting stimulant medication, whether methylphenidate (MPH) interferes with growth in medicated ADHD children and finally to explore the application of monitoring of bone age as a helpful tool in order to study adverse developmental effects of MPH.

Methods: Height, Weight, BMI, Target Height, pubertal stage and X-ray of left wrist were collected from 36 drug naÏve ADHD children, aged 6-12, at three time points of the ADDUCE longitudinal protocol: baseline visit and after 12 and 24 months.

Results: Baseline data analysis revealed normal growth parameters for the ADHD population: height Z-score was 0.33±1.19, weight Z-score 0.52±1.97, BMI Z-score 1.57±2.68 and the Target Height Z-score -0.82±0.88, resulting even slightly taller than expected. The bone age calculated by comparing each of 20 bones of an X-ray of the left hand with the Tanner and Whitehouse II method showed no significant differences between the bone age (8.11±2.19) and the chronological age (8.85±1.77) although about the 61% of subjects reported a slightly lower bone age than expected (7.23±1.61). Same results have been evidenced by the analysis of carpal bone (CB 8.51±2.10) and radio ulna and short bones (RUS 7.67±2.29). Only one subject has presented a Tanner pubertal stage G4 with a testicular volume of 12 cc, with no significant abnormalities of the bone age. No significant differences have been found by further dividing the sample for gender, age (610 vs 10-12 years old) or bone age (normal, low or increased). Analysis of the growth parameters and bone age collected at the follow up visits are in due course and will be presented during the conference.

Discussion: Results from the present sample reveal that ADHD children presents with a normal growth pattern before starting medication confirming that a possible impact on growth, in particular with respect to height, could be related more to stimulant medication than to the ADHD condition per se. The study of bone age and pubertal stage at follow up will allow to get more information about the growth outcome helping to clarify the effect of MPH with regards to height and pubertal maturation

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Expert Rev Neurother. 2016;1-12.

GENETICS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: AN UPDATE. *Akutagava-Martins GC, Rohde LA, Hutz MH*.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder affecting children, adolescents, and adults. The prevalence is estimated at 5 to 7% of school-aged children and 2.5 to 5% of adults. The phenotype is complex and heterogeneous, presenting variable clinical features, developmental course, and outcome. The genetic susceptibility to ADHD is attributed to both common and rare variants from a broad range of genes related mainly to neurotransmission and neurodevelopment pathways. However, it has been difficult to identify the genetic risk variants that account for the high heritability of this disorder. In this paper, we present recent findings from molecular genetics studies on both child and adult ADHD. Challenges and future directions for ADHD genetic studies are reviewed and discussed

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Fortschritte der Neurologie Psychiatrie. 2015;83:676-85.

LISDEXAMFETAMINE DIMESYLATE: A TREATMENT OPTION FOR CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN GERMANY AND ACROSS EUROPE. *Häge A, Banaschewski T, Dittmann RW.*

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder - which may persist into adolescence and adulthood. Psychostimulants and atomoxetine (ATX) are frequently prescribed to treat ADHD in Germany. Lisdexamfetamine dimesylate (LDX) is the most recently approved ADHD medication in Germany and other European countries. Data used to support the European registration of LDX is summarised from three phase-3/3b studies in children and adolescents with ADHD. Short-term efficacy (study SPD489-325), maintenance of efficacy (study SPD489-326) and efficacy in patients who had previously responded inadequately to methylphenidate (MPH) treatment (study SPD489-317) were demonstrated. The safety and tolerability profile of LDX in all three European studies was shown to be in line with that of other psychostimulants used to treat patients with ADHD

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Games for Health. 2015 Dec;4:502-12.

DEVELOPMENT AND USER SATISFACTION OF 'PLAN-IT COMMANDER,' A SERIOUS GAME FOR CHILDREN WITH ADHD. *Bul KCM, Franken IHA, van der Oord S, et al*.

The need for engaging treatment approaches within mental health care has led to the application of gaming approaches to existing behavioral training programs (i.e., gamification). Because children with attention deficit/hyperactivity disorder (ADHD) tend to have fewer problems with concentration and engagement when playing digital games, applying game technologies and design approaches to complement treatment may be a useful means to engage this population in their treatment. Unfortunately, gamified training programs currently available for ADHD have been limited in their ability to demonstrate in-game behavior skills that generalize to daily life situations. Therefore, we developed a new serious game (called “Plan-It Commander”) that was specifically designed to promote behavioral learning and promotes strategy use in domains of daily life functioning such as time management, planning/organizing, and prosocial skills that are known to be problematic for children with ADHD. An interdisciplinary team contributed to the development of the game. The game's content and approach are based on psychological principles from the Self-Regulation Model, Social Cognitive Theory, and Learning Theory. In this article, game development and the scientific background of the behavioral approach are described, as well as results of a survey (n = 42) to gather user feedback on the first prototype of the game. The findings suggest that participants were satisfied with this game and provided the basis for further development and research to the game. Implications for developing serious games and applying user feedback in game development are discussed.

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Genes Brain Behav. 2016.

THE DIVERGENT IMPACT OF COMT VAL158MET ON EXECUTIVE FUNCTION IN CHILDREN WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER. ***Jin J, Liu L, Gao Q, et al.***

Children with attention-deficit/hyperactivity disorder (ADHD) usually display deficits in executive function (EF), which are primarily mediated by prefrontal cortex (PFC). The functional polymorphism of catechol-Omethyltransferase (COMT), Val158Met (rs4680), leads to observed polymorphic differences in the degradation of dopamine within PFC. This study aimed to explore the effect of rs4680 on EF using casecontrol design. In addition, considering the dynamic development of EF, we also attempted to investigate whether this genetic influence changes during development or not. A total of 597 ADHD children and 154 unaffected controls were recruited. The EF was evaluated using Rey-Osterrieth complex figure test (RCFT), trail making test (TMT) and Stroop color and word test for working memory, shifting and inhibition. Association between genotype and EF was analyzed using analysis of covariance (ancova). The results showed significant interaction effect of genotype and ADHD diagnosis on RCFT performance (P<0.001). However, the associated genotypes between ADHD and controls were divergent. In ADHD, the Met carriers performed better than the Val homozygotes on detail immediate [(10.38±6.90) vs. (9.33±6.92), P=0.007] and detail delay [(9.96±6.86) vs. (8.86±6.89), P=0.004], while Val homozygotes showed better performance compared with Met carrier controls [for detail immediate (14.55±6.18) vs. (11.10±6.45), P<0.001; for detail delay (14.31±5.96) vs. (11.31±6.96), P=0.001]. We did not find significant interaction between genetic variant and development. COMT Val158Met (rs4680) may have divergent effect on working memory in ADHD children compared with healthy controls

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Hum Psychopharmacol. 2016.

EFFECTS OF METHYLPHENIDATE ON BODY INDEX AND PHYSICAL FITNESS IN KOREAN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kang KD, Yun SW, Chung U, et al.

Objective: The side effects of methylphenidate (MPH) on growth remain a controversial concern. This study aimed to investigate the effect of MPH on clinical symptoms, growth, and physical fitness in Korean children.
Methods: Fifty male children with attention deficit hyperactivity disorder (ADHD) treated with methylphenidate (MPH-ADHD), 69 MPH-na+»ve male children with ADHD (Naï-ADHD), and 60 agematched and sex-matched healthy control subjects were recruited. Intelligence quotient (IQ), clinical symptoms of ADHD, body index (height, weight, and body mass index [BMI]), and physical fitness (muscular strength, endurance, flexibility, agility, speed, and balance) were assessed.
Results: Total IQ and performance IQ scores were significantly different among the three groups, as were mean Korean Attention Deficit Hyperactivity Disorder (K-ARS)-total, K-ARS-inattention, and K-ARShyperactivity scores. There was no significant difference in height, weight, or BMI among the three groups. There were significant differences in skill-related fitness scores for balance (healthy controls>MPHADHD>Na+»ve-ADHD) and agility shuttle test time (healthy controls<MPH-ADHD<Naïve-ADHD).
Conclusions: Our findings support the effectiveness of MPH treatment for improving IQ, attention, and balance and agility measures of skill-related fitness in Korean children with ADHD. MPH was not associated with growth delays in height, weight, and BMI

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Int J Dev Neurosci. 2012 May;30:207-15.

INHIBITORY CONTROL AFTER TRAUMATIC BRAIN INJURY IN CHILDREN. ***Sinopoli KJ, Dennis M.***

Inhibitory control describes a number of distinct processes. Effortless inhibition refers to acts of control that are automatic and reflexive. Effortful inhibition refers to voluntary, goal-directed acts of control such as response flexibility, interference control, cancellation inhibition, and restraint inhibition. Disruptions to a

number of inhibitory control processes occur as a consequence of childhood traumatic brain injury (TBI). This paper reviews the current knowledge of inhibition deficits following childhood TBI, and includes an overview of the inhibition construct and a discussion of the specific deficits shown by children and adolescents with TBI and the factors that mediate the expression of these deficits, including injury-related variables and the expression of pre- and post-injury attention-deficit/hyperactivity disorder. The review illustrates that inhibitory control processes differ in terms of measurement, assessment, and neurological underpinnings, and also that childhood TBI may selectively disrupt particular forms of inhibition

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Int J Behav Dev. 2016;40:53-57.

COGNITIVE AND REACTIVE CONTROL PROCESSES: ASSOCIATIONS WITH ADHD SYMPTOMS IN PRESCHOOLERS.
Jarrett MA, Gilpin AT, Pierucci JM, et al.

Attention-deficit/hyperactivity disorder (ADHD) can be identified in the preschool years, but little is known about the correlates of ADHD symptoms in preschool children. Research to date suggests that factors such as temperament, personality, and neuropsychological functioning may be important in understanding the development of early ADHD symptomatology. The current study sought to extend this research by examining how cognitive and reactive control processes predict ADHD symptoms. Data were drawn from a larger study that measured the cognitive, social, and emotional functioning of preschool children. Eighty-seven children (aged 4-6 years) were evaluated using teacher report and laboratory task measures relevant to cognitive control (i.e., conscientiousness, working memory) and reactive control (i.e., neuroticism, delay of gratification) processes. In multiple regression analyses, cognitive control variables added unique variance in the prediction of both inattention and hyperactivity, but only reactive control variables added unique variance in the prediction of hyperactivity. The current findings align with past research suggesting that cognitive control processes (e.g., conscientiousness) are related to both inattention and hyperactivity/impulsivity, while reactive control processes (e.g., neuroticism) are more strongly related to hyperactivity/impulsivity in preschool children. Future longitudinal research utilizing various methods and measures is needed to understand how cognitive and reactive control processes contribute to ADHD symptom development

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Ir J Psychol Med. 2016;1-15.

REVIEW OF INTERNATIONAL CLINICAL GUIDELINES FOR ADOLESCENTS ON TRANSITION TO ADULT MENTAL HEALTH SERVICES AND ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND THEIR APPLICATION TO AN IRISH CONTEXT.

Hughes GC, OΓÇÖHanrahan S, Kavanagh G, et al.

Objectives: To review the available clinical guidelines from Canada, North America, Europe and the United Kingdom for the diagnosis and management of attention-deficit hyperactivity disorder (ADHD) for adolescents previously diagnosed in Child and Adolescent Mental Health Services (CAMHS) on transition to Adult Mental Health Services (AMHS) and for adults presenting with a diagnostic query re-ADHD. This article seeks to apply the available guidelines to an Irish context.

Method: Various clinical guidelines and consensus statements were identified by a literature search of PubMed, incorporating literature from the past 10 years from English speaking countries and inclusion of any additional guidelines of clinical relevance. A clinical guideline with specific reference for Irish clinicians was proposed for the diagnosis and management of adults presenting for the first time with a diagnostic query reADHD and also to include those young adults previously diagnosed in CAMHS on transition to AMHS.

Conclusions: ADHD is a lifelong disorder, which if undiagnosed or untreated can lead to significant impairment resulting in a high economic cost for society. Stimulant medication is a first-line treatment option for adults with ADHD; however, some formulations are unlicensed in Ireland. Recent licensing of Atomoxetine, for both adolescents on transition and for adults with newly diagnosed ADHD is a welcome development. Third-line agents are rarely prescribed due to their side effect profiles and are prescribed

offlabel: It is important to establish clinical guidelines for an Irish context incorporating a biopsychosocial approach. Further discussion amongst clinicians and stakeholders is needed to plan service development

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J Atten Disord. 2013 May;17:279-90.

EXERCISE: APPLICATIONS TO CHILDHOOD ADHD.

Wigal SB, Emmerson N, Gehricke JG, et al.

ADHD is the most common neurobehavioral disorder of childhood, presenting with pervasive and impairing symptoms of inattention, hyperactivity, impulsivity, or a combination. The leading hypothesis of the underlying physiology of this disorder of inattention and/or hyperactivity-impulsivity is based on catecholamine dysfunction. Pharmacotherapy research indicates that psychostimulants, which are catecholamine agonists, show the greatest efficacy for treating the core symptoms of ADHD. Exercise affects the same dopaminergic and noradrenergic systems that stimulant medications target and is a stressor, which elicits measurable physiological changes. The magnitude of these peripheral alterations is posited as a potential biomarker of ADHD. The hypothesis that exercise training alters the underlying physiology present in ADHD and other medical conditions as well as conceptual issues behind its potential clinical utility is reviewed

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J Atten Disord. 2015 Feb;19:125-37.

CANINE-ASSISTED THERAPY FOR CHILDREN WITH ADHD: PRELIMINARY FINDINGS FROM THE POSITIVE ASSERTIVE COOPERATIVE KIDS STUDY.

Schuck SE, Emmerson NA, Fine AH, et al.

OBJECTIVE: The objective of this study was to provide preliminary findings from an ongoing randomized clinical trial using a canine-assisted intervention (CAI) for 24 children with ADHD.

METHOD: Project Positive Assertive Cooperative Kids (P.A.C.K.) was designed to study a 12-week cognitive-behavioral intervention delivered with or without CAI. Children were randomly assigned to group therapy with or without CAI. Parents of children in both groups simultaneously participated in weekly parent group therapy sessions.

RESULTS: Across both treatment groups, parents reported improvements in children's social skills, prosocial behaviors, and problematic behaviors. In both groups, the severity of ADHD symptoms declined during the course of treatment; however, children who received the CAI model exhibited greater reductions in the severity of ADHD symptoms than did children who received cognitive-behavioral therapy without CAI.

CONCLUSION: Results suggest that CAI offers a novel therapeutic strategy that may enhance cognitivebehavioral interventions for children with ADHD

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J Atten Disord. 2015 Feb;19:158-66.

EFFECTS OF AN 8-SESSION BEHAVIORAL PARENT TRAINING GROUP FOR PARENTS OF CHILDREN WITH ADHD ON CHILD IMPAIRMENT AND PARENTING CONFIDENCE. *Loren*

RE, Vaughn AJ, Langberg JM, et al.

OBJECTIVE: This study examined the feasibility and effectiveness of a behavioral parent training (BPT) group intervention implemented in an outpatient mental health setting in reducing child impairments and increasing parenting confidence in managing child behavior.

METHOD: Parents of 241 children with ADHD participated in the eight-session parent group program, completing the Impairment Rating Scale (IRS) and a measure of parenting confidence at the first and last session.

RESULTS: Parents reported improvements in child behavior across all domains of the IRS, with the largest improvements in terms of overall impairment, parent-child relationship, and impact of child behavior on the family. Parents also reported increased confidence in managing their child's behavior.

CONCLUSION: These findings suggest that brief BPT group programs administered to a diverse range of attendees in a typical outpatient setting result in improvements in functional impairments comparable with those produced in controlled studies, as well as improved parenting confidence

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J Child Psychol Psychiatry. 2012 May;53:558-74.

ANNUAL RESEARCH REVIEW: EMBRACING NOT ERASING CONTEXTUAL VARIABILITY IN CHILDREN'S BEHAVIOR-THEORY AND UTILITY IN THE SELECTION AND USE OF METHODS AND INFORMANTS IN DEVELOPMENTAL PSYCHOPATHOLOGY.

Dirks MA, De Los RA, Briggs-Gowan M, et al.

This paper examines the selection and use of multiple methods and informants for the assessment of disruptive behavior syndromes and attention deficit/hyperactivity disorder, providing a critical discussion of (a) the bidirectional linkages between theoretical models of childhood psychopathology and current assessment techniques; and (b) current knowledge concerning the utility of different methods and informants for key clinical goals. There is growing recognition that children's behavior varies meaningfully across situations, and evidence indicates that these differences, in combination with informants' unique perspectives, are at least partly responsible for inter-rater discrepancies in reports of symptomatology. Such data suggest that we should embrace this contextual variability as clinically meaningful information, moving away from models of psychopathology as generalized traits that manifest uniformly across situations and settings, and toward theoretical conceptualizations that explicitly incorporate contextual features, such as considering clinical syndromes identified by different informants to be discrete phenomena. We highlight different approaches to measurement that embrace contextual variability in children's behavior and describe how the use of such tools and techniques may yield significant gains clinically (e.g., for treatment planning and monitoring). The continued development of a variety of feasible, contextually sensitive methods for assessing children's behavior will allow us to determine further the validity of incorporating contextual features into models of developmental psychopathology and nosological frameworks

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J Clin Exp Neuropsychol. 2014;36:930-43.

RELATIONS BETWEEN FINE MOTOR SKILL AND PARENTAL REPORT OF ATTENTION IN YOUNG CHILDREN WITH NEUROFIBROMATOSIS TYPE 1.

Casnar CL, Janke KM, van der Fluit F, et al.

Neurofibromatosis type 1 (NF1) is one of the most common genetic disorders presenting in approximately 1 in 3,500 live births. NF1 is a highly variable condition with a large number of complications. A common complication is neuropsychological problems, including developmental delays and learning difficulties that affect as many as 60% of patients. Research has suggested that school-aged children with NF1 often have poorer fine motor skills and are at greater risk for attention difficulties than the general population. Thirtyeight children with NF1 and 23 unaffected children between the ages of 4 and 6 years, who are enrolled in a study of early development in NF1, were included in the present study. Varying levels of fine motor functioning were examined (simple to complex fine motor tasks). For children with NF1, significant difficulties were demonstrated on lab-based mid-level and complex fine motor tasks, even after controlling for nonverbal reasoning abilities, but not on simple fine motor tasks. Parental report also indicated difficulties in everyday adaptive fine motor functioning. No significant correlations were found between complex fine motor ability and attention difficulties. This study provides much needed descriptive data on the early emergence of fine motor difficulties and attention difficulties in young children with NF1

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J Pediatr. 2015 Jan;166:132-38.

PREDICTORS OF HEALTH-RELATED QUALITY OF LIFE IN ADOLESCENTS WITH TETRALOGY OF FALLOT. Neal AE, Stopp C, Wypij D, et al.

OBJECTIVE: To assess health-related quality of life (HRQoL) of adolescents with repaired tetralogy of Fallot (TOF) and whether impairments in HRQoL domains are associated with neurocognitive and medical factors.

STUDY DESIGN: Parents of subjects with TOF and healthy referents 13-16 years of age completed the Child Health Questionnaire-Parent Form 50, generating psychosocial (PsS) and physical (PhS) health summary scores. Adolescents completed the Child Health Questionnaire-Child Form 87 and concurrent in-person neurocognitive testing. We analyzed relationships of PsS and PhS scores with neurocognitive performance and medical factors.

RESULTS: Compared with referents (n = 85), adolescents with TOF without a genetic diagnosis (n = 66) had lower PsS (50.9 +/- 9.4 vs 57.2 +/- 4.2, P < .001) and PhS scores (49.4 +/- 9.5 vs 55.8 +/- 4.9; P < .001). Compared with a normative sample, these adolescents with TOF had similar PsS scores (P = .52) but significantly lower PhS scores (P = .01). Within adolescents with TOF without genetic disorders, lower PsS scores were highly associated with worse neurocognitive measures, particularly the parent-reported Behavior Rating Inventory of Executive Function composite (r = -0.66, P < .001) and Parent Conners' attention deficit-hyperactivity disorder Index T score (r = -0.54, P < .001), whereas associations of PhS scores with neurocognitive measures were weaker.

CONCLUSIONS: Psychosocial health status in adolescents with TOF without genetic disorders was worse than in healthy referents without risk factors for brain injury but similar to a normative sample; physical health status was worse in these adolescents than in either comparison group. Within these subjects with TOF, worse psychosocial health status was most highly associated with concurrent executive dysfunction and attention deficit-hyperactivity disorder. Optimizing HRQoL constitutes another indication for attention to neurodevelopment in children with congenital heart disease

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J Abnorm Psychol. 2016.

DO ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SHOW RISK SEEKING? DISENTANGLING PROBABILISTIC DECISION MAKING BY EQUALIZING THE FAVORABILITY OF ALTERNATIVES. *Pollak Y, Oz A, Neventsal O, et al*.

The clinical literature provides evidence for increased risk taking by individuals with attentiondeficit/hyperactivity disorder (ADHD). Most of the experimental tasks used to measure risk taking, confounded risky and disadvantageous alternatives, and therefore did not disentangle increased risk seeking from suboptimal decision making. The aim of the study was to examine whether adolescents with ADHD show risk seeking by equalizing the expected value of both certain and risky alternatives. In 3 different samples, adolescents with and without ADHD performed gambling tasks, in which they had to choose between certain and risky alternatives. Notably, the expected values of both alternatives were equal. Various personal and contextual intervening factors were controlled for. The rate of risky choices was compared across groups. In addition, participants reported on risk taking in real-life. We found that adolescents with ADHD did not choose the risky alternative more often than controls, but reported higher engagement in reallife risky behavior. These findings suggest that risky behavior shown by people with ADHD in daily life and on some experimental tasks may not be accounted for by increased risk seeking, but rather may reflect suboptimal decision making.

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J Abnorm Psychol. 2016 Jan;125:125-37.

GENERAL AND SPECIFIC ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FACTORS OF CHILDREN 4 TO 6 YEARS OF AGE: AN EXPLORATORY STRUCTURAL EQUATION MODELING APPROACH TO ASSESSING SYMPTOM MULTIDIMENSIONALITY.

Arias VB, Ponce FP, Martínez-Molina A, et al.

We tested first-order factor and bifactor models of attention-deficit/hyperactivity disorder (ADHD) using confirmatory factor analysis (CFA) and exploratory structural equation modeling (ESEM) to adequately summarize the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, (DSM–IV–TR) symptoms observed in a Spanish sample of preschoolers and kindergarteners. Six ESEM and CFA models were estimated based on teacher evaluations of the behavior of 638 children 4 to 6 years of age. An ESEM bifactor model with a central dimension plus 3 specific factors (inattention, hyperactivity, and impulsivity) showed the best fit and interpretability. Strict invariance between the sexes was observed. The bifactor model provided a solution to previously encountered inconsistencies in the factorial models of ADHD in young children. However, the low reliability of the specific factors casts doubt on the utility of the subscales for ADHD measurement. More research is necessary to clarify the nature of G and S factors of ADHD.

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J Affective Disord. 2016 Jan;189:321-28.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND SUICIDE IDEATION AND ATTEMPTS: FINDINGS FROM THE ADULT PSYCHIATRIC MORBIDITY SURVEY 2007. *Stickley*

A, Koyanagi A, Ruchkin V, et al.

Background: Adults with attention-deficit/hyperactivity disorder (ADHD) may have an increased risk of engaging in suicidal behavior. This study examined this association in the general adult population where there has been little research.

Methods: Data came from the Adult Psychiatric Morbidity Survey 2007. This was a representative sample of the English adult household population aged =16 years (N = 7403). The Adult ADHD Self-Report Scale (ASRS) was used to obtain information on ADHD symptoms. The Clinical Interview Schedule Revised (CISR) was used to assess six forms of common mental disorder (CMD). Information was also obtained on the lifetime and past 12-month occurrence of suicide ideation and attempts. Logistic regression analysis was used to examine these associations.

Results: After adjusting for comorbid disorders, adults with more ADHD symptoms had significantly higher odds for suicidal behavior. When a single cut-off point was used to classify ADHD (ASRS score =14), odds ratios ranged from 1.62 (lifetime suicide attempt) to 2.43 (past 12-month suicide ideation). When ADHD symptoms were categorized by strata (I: a score of 0–9; II: 10–13; III: 14–17; IV: 18–24), compared to adults in stratum I, those in stratum IV had odds ratios ranging from 2.16 (lifetime suicide ideation) to 3.68 (past 12month suicide attempt).

Limitations: ADHD and suicide data came from self-reports which may have been affected by socially desirable responding.

Conclusions: ADHD symptoms were linked to suicidal behavior after controlling for comorbid conditions. Health care professionals should be alerted to the increased suicide risk among adults with ADHD symptoms.

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J Child Adolesc Psychopharmacol. 2015;25:783-98.

CLINICALLY SIGNIFICANT SYMPTOM REDUCTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATED WITH MICRONUTRIENTS: AN OPEN-LABEL REVERSAL DESIGN STUDY. *Gordon*

HA, Rucklidge JJ, Blampied NM, et al.

Objective: The purpose of this study was to investigate the clinical effect and safety of a broad spectrum, 36 ingredient micronutrient (vitamins and minerals) in treating children with attention-deficit/hyperactivity disorder (ADHD).

Methods: This open-label, on-off-on-off (reversal design) study followed 14 participants (8-12 years of age) with ADHD, diagnosed using standardized instruments, for 6 months with no dropouts. Following baseline

assessment, including hematology and biochemistry screening, participants began an 8 week treatment phase with micronutrients titrated up to maximum dose (15 capsules/day). Treatment was withdrawn for 4 weeks, reinstated for a further 8 weeks, and then withdrawn for 4 weeks. Primary outcomes included the Conners' Parent Rating Scale, the Clinical Global Impressions Scale (CGI), and the Strengths and Difficulties Questionnaire-Parent version (SDQ). Secondary outcomes were mood and global functioning.
Results: Modified Brinley plots revealed a reduction in ADHD symptoms, improved mood, and improved overall functioning during intervention phases, and deterioration in ADHD symptoms, mood, and overall functioning during the withdrawal phases. Reliable change analyses, Cohen's d and percent superiority effect sizes, 95% confidence intervals and t tests confirmed clinically and statistically significant change between the intervention and withdrawal phases, with large effect sizes observed pre-to post-exposure of micronutrients (d = 1.2-2.2) on ADHD symptoms during intervention phases. Seventy-one percent of participants showed at least a 30% decrease in ADHD symptoms by the end of the second treatment phase, and 79% were identified as "much improved" or "very much improved" at the end of the second phase (5 months) based on the clinician-rated CGI when considering functioning generally. The SDQ showed that these benefits occurred across other areas of functioning including emotional symptoms, conduct problems, and prosocial behaviours. The children's self-reports confirmed the improvements. Excellent adherence to treatment occurred throughout, side effects were mild and transitory, and no safety issues were identified through blood analyses.
Conclusions: This study demonstrates the clinical benefit, feasibility, and safety of broad-spectrum micronutrients in the treatment of childhood ADHD. Replications utilizing double-blind placebo-controlled studies are warranted

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J Child Adolesc Psychopharmacol. 2015;25:799-809.
EFFICACY AND SAFETY EXTRAPOLATION ANALYSES FOR ATOMOXETINE IN YOUNG CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Upadhyaya H, Kratochvil C, Ghuman J, et al.
OBJECTIVES: This extrapolation analysis qualitatively compared the efficacy and safety profile of atomoxetine from Lilly clinical trial data in 6-7-year-old patients with attention-deficit/hyperactivity disorder (ADHD) with that of published literature in 4-5-year-old patients with ADHD (two open-label [4-5-year-old patients] and one placebo-controlled study [5-year-old patients]).
METHODS:
The main efficacy analyses included placebo-controlled Lilly data and the placebo-controlled external study (5-year-old patients) data. The primary efficacy variables used in these studies were the ADHD Rating ScaleIV Parent Version, Investigator Administered (ADHD-RS-IV-Parent:Inv) total score, or the Swanson, Nolan and Pelham (SNAP-IV) scale score. Safety analyses included treatment-emergent adverse events (TEAEs) and vital signs. Descriptive statistics (means, percentages) are presented.
RESULTS: Acute atomoxetine treatment improved core ADHD symptoms in both 6-7-year-old patients (n=565) and 5-year-old patients (n=37) (treatment effect: -10.16 and -7.42). In an analysis of placebocontrolled groups, the mean duration of exposure to atomoxetine was ~7 weeks for 6-7-year-old patients and 9 weeks for 5-year-old patients. Decreased appetite was the most common TEAE in atomoxetine-treated patients. The TEAEs observed at a higher rate in 5-year-old versus 6-7-year-old patients were irritability (36.8% vs. 3.6%) and other mood-related events (6.9% each vs. <3.0%). Blood pressure and pulse increased in both 4-5-year-old patients and 6-7-year-old patients, whereas a weight increase was seen only in the 6-7year-old patients.
CONCLUSIONS: Although limited by the small sample size of the external studies, these analyses suggest that in 5-year-old patients with ADHD, atomoxetine may improve ADHD symptoms, but possibly to a lesser extent than in older children, with some adverse events occurring at a higher rate in 5-year-old patients.

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J Child Adolesc Psychopharmacol. 2015;25:749-53.

AN ALTERNATIVE APPROACH TO SCORING THE MTA-SNAP-IV TO GUIDE ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MEDICATION TREATMENT TITRATION TOWARDS SYMPTOM REMISSION: A PRELIMINARY CONSIDERATION.

Wagner DJ, McLennan JD.

Objective: The Multimodal Treatment Study for Attention-Deficit/Hyperactivity Disorder Swanson, Nolan, and Pelham, Version IV (MTA-SNAP-IV) is a common rating scale to measure attention-deficit/hyperactivity disorder (ADHD) symptoms during medication treatment. Relying on the traditional scoring approach for this instrument to identify symptom remission, however, may leave a child with significant residual symptoms. The objective of this study was to examine an alternative scoring approach for this instrument to identify the extent of residual symptoms for children completing ADHD medication treatment.

Methods: Parent and teacher ratings on the ADHD symptom component of the MTA-SNAP-IV were extracted from medical records of 80 children completing medication treatment at a specialty clinic in Canada. Data were scored in two ways. 1) Traditional scoring based on assigning a value ranging from 0 to 3 for response options: "Not at all," "Just a little," "Pretty much," or "Very much," for each symptom and then determining a mean across items, and 2) alternative scoring based on assigning values of 0, 0, 0.5, and 1 across the same response options and summing the total across items. Symptom remission based on the former is defined as a mean value Γëñ1, and for the latter it is defined as a summed value equal to 0.

Results: Children were significantly less likely to be classified as symptom remitted under the alternative scoring method based on parent, teacher, and combined parent-teacher ratings. Using the alternative scoring approach, residual symptoms were identified for 25%, 39%, and 70% of children classified as symptom remitted (under traditional scoring rules) by parents, teachers, and parents/teachers combined, respectively.

Conclusions: Potential "residual" ADHD symptoms were identified in many children attaining symptom remission using the traditional scoring approach; however, further scrutiny of this alternative scoring approach is required. Although it may improve the ability to detect residual symptoms that could signal the need for further intervention to achieve symptom remission, it may increase the risk of over treatment

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J Child Adolesc Psychopharmacol. 2015;25:775-82.

BIOCHEMICAL AND PSYCHOLOGICAL EFFECTS OF OMEGA-3/6 SUPPLEMENTS IN MALE ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED, PLACEBO-CONTROLLED, CLINICAL TRIAL.

Matsudaira T, Gow RV, Kelly J, et al.

Background: An abnormality in long chain-polyunsaturated fatty acid (LC-PUFA) levels has been implicated in attention-deficit/hyperactivity disorder (ADHD). Studies evaluating LC-PUFA supplementation for therapeutic efficacy in ADHD have shown mixed and, therefore, inconclusive results.

Methods: Seventy-six male adolescents (age 12-16 years, mean = 13.7) with ADHD were assessed for the effects of 12 weeks omega-3 and omega-6 supplements on biochemical and psychological outcomes in a randomized, placebo-controlled, clinical trial. The primary outcome measure was change in the Conners' Teacher Rating Scales (CTRS) following 12 weeks of supplementation of LC-PUFA or placebo. At baseline, the placebo and treatment groups had comparable levels of LC-PUFA as measured by red blood cell phosphatidylcholine. In the treatment group, supplementation enhanced eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and total omega-3 fatty acid levels.

Results: No superiority of LC-PUFAs to placebo was observed on the primary outcome. Further, there were no reliable treatment effects on aggression, impulsivity, depression, and anxiety.

Conclusions: Future studies should use larger sample sizes and longer supplementation period to detect small-modest effects for clinical recommendations in ADHD

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J Child Neurol. 2016;31:131-33.

ASSOCIATION OF ATTENTION DEFICIT DISORDER WITH BEDSIDE ANTI-SACCADES IN SURVIVORS OF CHILDHOOD LEUKEMIA.

Khan RB, Hudson MM, Ness KK, et al.

Impaired attention is well recognized in childhood cancer survivors. We prospectively evaluated 162 longterm survivors of childhood acute lymphoblastic leukemia to study an association between presence of neurologic soft signs as measured by Zurich Neuromotor Scale, bedside evaluation of anti-saccades, and attention deficit disorder. Attention deficit disorder was recognized in 10.5% of the study cohort. We did not find an association of attention deficit with presence of any soft sign. However, there was an association between presence of abnormal anti-saccades and attention deficit (P =.04). These results will require further validation and if confirmed may introduce a quick bedside method of assessing impaired attention in cancer survivors

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Journal of Child Psychology and Psychiatry. 2015 Dec;56:1316-26.

DEVELOPMENTAL DIFFERENCES IN INTRA-INDIVIDUAL VARIABILITY IN CHILDREN WITH ADHD AND ASD. *van Belle J, van Hulst BM, Durston S*.

Background: Intra-individual variability reflects temporal variation within an individual's performance on a cognitive task. Children with developmental disorders, such as ADHD and ASD show increased levels of intraindividual variability. In typical development, intra-individual variability decreases sharply between the ages 6 and 20. The tight link between intra-individual variability and age has led to the suggestion that it may be marker of neural development. As there is accumulating evidence that ADHD and ASD are characterised by atypical neurodevelopmental trajectories, we set out to explore developmental changes in intra-individual variability in subjects with ADHD and ASD.

Method: We used propensity score matching to match a cross-sectional sample of children with ADHD, ASD and control subjects (N = 405, aged 6–19 years old) for age, IQ and gender. We used ex- Gaussian distribution parameters to characterise intra-individual variability on fast responses (sigma) and slow responses (tau).

Result: Results showed that there was a similar decrease in mean response times with age across groups, and an interaction between age and group for measures of variability, where there was a much lower rate of change in the variability parameters (sigma and tau) for subjects with ASD compared with the other two groups. Subjects with ADHD had higher intra-individual variability, reflected by both sigma and tau, but the rate of decrease in variability with age was similar to that of the controls.

Conclusion: These results suggest that subjects with ADHD, ASD and controls differ in the rate at which intra-individual variability decreases during development, and support the idea that intra-individual variability may be a marker of neural development, mimicking the neurodevelopmental changes in these disorders.

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Journal of Child Psychology and Psychiatry. 2015 Dec;56:1380-88.

SEX DIFFERENCES IN THE ASSOCIATION BETWEEN FOETAL GROWTH AND CHILD ATTENTION AT AGE FOUR: SPECIFIC VULNERABILITY OF GIRLS.

***Murray E, Matijasevich A, Santos IS, et al*.**

Background: Recent evidence suggests that impaired foetal growth may provide an early indication of increased risk of child attention problems. However, despite both foetal growth and child attention problems differing by sex, few studies have examined sex differences in this association. Furthermore, no studies have been conducted in low- and middle-income countries, where there are higher rates of perinatal problems. This study aimed to test for sex differences in the association between foetal growth indices and attention problems at age four, in a large, prospective birth cohort from a middle-income country.

Methods: A total of 3,749 neonates from the 2004 Pelotas birth cohort (Brazil) with foetal growth indices collected at birth [low birthweight (LBW), small-for-gestational age (SGA), head circumference (HC), head circumference-to-abdominal circumference ratio (HC/AC) and ponderal index (PI)], were assessed for attention problems using the Child Behaviour Checklist at age four. Ordinal logistic regression with

successive adjustment for maternal, demographic, gestational, perinatal and child nutrition/mother–child morbidity, was conducted separately for girls and boys.
Results: In girls, attention difficulties were associated with being born SGA (OR = 1.40, CI = 1.08–1.82, p = .012), with a small HC (OR = 1.52, CI = 1.11–2.08, p = .009), or with a low PI (OR = 1.29, CI = 1.08–1.54, p = .005). There were no associations identified between attention difficulties and any foetal growth indices in boys.
Conclusions: Our results show that girls with impaired foetal growth may be particularly at risk of attention difficulties in childhood. This is consistent with emerging research that female foetuses may be more vulnerable to certain suboptimal intrauterine environments, inducing epigenetic changes that lead to disturbed growth and long-term developmental impairment.

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Journal of Child Psychology and Psychiatry. 2015 Dec;56:1298-313.
DOES INTENSIVE MULTIMODAL TREATMENT FOR MATERNAL ADHD IMPROVE THE EFFICACY OF PARENT TRAINING FOR CHILDREN WITH ADHD? A RANDOMIZED CONTROLLED MULTICENTER TRIAL. ***Jans T, Jacob C, Warnke A, et al.***
Background: This is the first randomized controlled multicenter trial to evaluate the effect of two treatments of maternal attention-deficit hyperactivity disorder (ADHD) on response to parent–child training targeting children's external psychopathology.
Methods: Mother–child dyads (n = 144; ADHD according to DSM-IV; children: 73.5% males, mean age 9.4 years) from five specialized university outpatient units in Germany were centrally randomized to multimodal maternal ADHD treatment [group psychotherapy plus open methylphenidate medication; treatment group (TG): n = 77] or to clinical management [supportive counseling without psychotherapy or psychopharmacotherapy; control group (CG): n = 67]. After 12 weeks, the maternal ADHD treatment was supplemented by individual parent–child training for all dyads. The primary outcome was a change in the children's externalizing symptom scores (investigator blinded to the treatment assignment) from baseline to the end of the parent–child training 6 months later. Maintenance therapy continued for another 6 months. An intention-to-treat analysis was performed within a linear regression model, controlling for baseline and center after multiple imputations of missing values.
Results: Exactly, 206 dyads were assessed for eligibility, 144 were randomized, and 143 were analyzed (TG: n = 77; CG: n = 66). After 6 months, no significant between-group differences were found in change scores for children's externalizing symptoms (adjusted mean TG-mean CG = 1.1, 95% confidence interval 0.5–2.7; p = .1854), although maternal psychopathology improved more in the TG. Children's externalizing symptom scores improved from a mean of 14.8 at baseline to 11.4 (TG) and 10.3 (CG) after 6 months and to 10.8 (TG) and 10.1 (CG) after 1 year. No severe harms related to study treatments were found, but adverse events were more frequent in TG mothers than in CG mothers.
Conclusions: The response in children's externalizing psychopathology did not differ between maternal treatment groups. However, multimodal treatment was associated with more improvement in maternal ADHD. Child and maternal treatment gains were stable (CCT-ISRCTN73911400).

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Journal of Child Psychology and Psychiatry. 2015 Dec;56:1289-97.
WHITE MATTER MICROSTRUCTURE AND DEVELOPMENTAL IMPROVEMENT OF HYPERACTIVE/IMPULSIVE SYMPTOMS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER. ***Francx W, Zwiers MP, Mennes M, et al.***
[Correction Notice: An Erratum for this article was reported in Vol 57(1) of Journal of Child Psychology and Psychiatry (see record [rid]2015-56742-008[/rid]). In the original article, there were some errors in the coordinates provided in Table 3. Voxel coordinates were provided rather than Montreal Neurological Institute (MNI) coordinates. The corrected MNI coordinates in Table 3 are present in the erratum.]
Background A developmental improvement of symptoms in Attention-Deficit/Hyperactivity Disorder (ADHD) is frequently reported, but the underlying neurobiological substrate has not been identified. The aim of this

study was to determine whether white matter microstructure is related to developmental improvement of ADHD symptoms.
Methods A cross-sectional Magnetic Resonance Imaging (MRI) analysis was embedded in a prospective follow-up of an adolescent cohort of ADHD and control subjects (NeuroIMAGE). Mean age at baseline was 11.9 years, mean interval of follow-up was 5.9 years. About 75.3% of the original cohort was retained successfully. Data of 101 participants with ADHD combined type at baseline and 40 healthy controls were analysed. ADHD symptoms were measured with semistructured, investigator-based interviews and Conners' questionnaires, on the basis of DSM-IV criteria. Fractional anisotropy (FA) and mean diffusivity (MD) indices of white matter microstructure were measured using whole brain diffusion tensor imaging at follow-up only. In a dimensional analysis FA and MD were related to change in ADHD symptoms. To link this analysis to DSM-IV diagnoses, a post hoc categorical group analysis was conducted comparing participants with persistent (n = 59) versus remittent (n = 42) ADHD and controls.
Results Over time, participants with ADHD showed improvement mainly in hyperactive/impulsive symptoms. This improvement was associated with lower FA and higher MD values in the left corticospinal tract at followup. Findings of the dimensional and the categorical analysis strongly converged. Changes in inattentive symptoms over time were minimal and not related to white matter microstructure.
Conclusions The corticospinal tract is important in the control of voluntary movements, suggesting the importance of the motor system in the persistence of hyperactive/impulsive symptoms.

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J Consult Clin Psychol. 2016 Jan;84:1-14.
MEDIATORS OF CHANGE IN THE CHILD/ADOLESCENT ANXIETY MULTIMODAL TREATMENT STUDY. *Kendall PC, Cummings CM, Villabø MA, et al.*
Objective: Test changes in (a) coping efficacy and (b) anxious self-talk as potential mediators of treatment gains at 3-month follow-up in the Child/Adolescent Anxiety Multimodal Treatment Study (CAMS).
Method: Participants were 488 youth (ages 7–17; 50.4% male) randomized to cognitive-behavioral therapy (CBT; Coping cat program), pharmacotherapy (sertraline), their combination, or pill placebo. Participants met Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (DSM–IV) criteria for generalized anxiety disorder, social phobia, and/or separation anxiety disorder. Coping efficacy (reported ability to manage anxiety provoking situations) was measured by youth and parent reports on the Coping Questionnaire, and anxious self-talk was measured by youth report on the Negative Affectivity Self-Statement Questionnaire. Outcome was measured using the Pediatric Anxiety Rating Scale (completed by Independent Evaluators blind to condition). For temporal precedence, residualized treatment gains were assessed at 3month follow-up.
Results: Residualized gains in coping efficacy mediated gains in the CBT, sertraline, and combination conditions. In the combination condition, some unique effect of treatment remained. Treatment assignment was not associated with a reduction in anxious self-talk, nor did anxious self-talk predict changes in anxiety symptoms.
Conclusions: The findings suggest that improvements in coping efficacy are a mediator of treatment gains. Anxious self-talk did not emerge as a mediator.

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J Dev Behav Pediatr. 2015 Nov;36:717-23.
SLEEP DIFFICULTIES ARE ASSOCIATED WITH PARENT REPORT OF SLUGGISH COGNITIVE TEMPO. *Koriakin TA, Mahone EM, Jacobson LA.*
Objective: Sleep disturbance is considered both a behavioral symptom of and a contributor to functional difficulties in children with attention-deficit/hyperactivity disorder (ADHD). The construct of sluggish cognitive tempo (SCT) has also been linked to ADHD; however, little is known regarding the effects of sleep specifically on SCT symptoms. This study examined the association between parent-reported sleep disturbance and parent- and teacher-reported SCT, while controlling for the effects of ADHD and mood symptoms.

Method: Participants included 746 clinically referred children (65% male, age range: 5–18 years) with both parent and teacher ratings assessing symptoms of ADHD, mood symptoms (depression, anxiety), and SCT. Parents/caregivers also rated their child's sleep problems with regard to 4 core concerns: falling asleep, sleep restlessness, difficulty waking, and breathing difficulties. The SCT scale included three empirically derived subscales: sleepy/sluggish, low initiation/persistence, and daydreamy.
Results: After accounting for age, medication status, ADHD symptoms, depressive symptoms, and anxiety, sleep problems accounted for a small but significant proportion of additional variance in the prediction of parent-reported sleepy/sluggish SCT. Difficulty waking showed the strongest associations with parentreported SCT. There were no significant relationships found between parent-reported sleep difficulties and teacher-reported SCT.
Conclusions: Some elements of sluggishness and lethargy inherent to the SCT construct may be associated with sleep difficulties, even after accounting for ADHD and mood symptoms; however, these associations are not consistent across SCT subscales and sleep problem domains.

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Journal of Iranian Psychologists. 2015;11:209-18.
DEVELOPMENT OF EXECUTIVE FUNCTIONING IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND NORMAL CHILDREN: FROM PRESCHOOL TO THE END OF PRIMARY SCHOOL. *Karamshaii A, Abedi A, Yarmohamadian A*.
This study aimed to investigate the development of executive functioning in children with Attention Deficit/Hyperactivity Disorder (ADHD) and normal children. Four hundred and twenty children (210 normal children, 210 ADHD children) were selected using multistage cluster random sampling .The participants completed the Connors Parental Questionnaire (Connors, 1997) and the NEPSY Tower Test (Korkman, Kirk, & Kemp, 1998). The results of two ways analysis of variance indicated significant differences in executive functioning between normal children and ADHD children in different age groups. The ADHD children performances were significantly lower than normal children. The findings suggest that the developmental trend of executive functioning in normal children increase with age

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J Neuroimmunol. 2015 Nov;288:87-91.
PARANEOPLASTIC SYNDROME-ASSOCIATED NEURONAL ANTIBODIES IN ADULT ADHD. *Haukanes BI, Hegvik TA, Eichler T, et al*.
A high seroprevalence of Yo antibodies targeting cerebellar Purkinje cells was recently reported in children with attention deficit/hyperactivity disorder (ADHD). We investigated the presence of 8 paraneoplastic neurological syndrome (PNS)-associated antibodies including anti-Yo in 169 adult ADHD patients. No associations between ADHD and serum Yo antibodies or other antibodies associated with PNS were found. However, 10 out of 48 ADHD patient sera analyzed by immunofluorescence presented antibodies targeting cerebellar Purkinje cells. This reactivity probably represents the presence of low levels of antibodies against multiple cellular hitherto unknown antigens with little to no clinical significance

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J Paediatr Child Health. 2015;51:1232-34.
TRICYCLIC ANTIDEPRESSANTS - THIRD-LINE TREATMENT FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN SCHOOL-AGED CHILDREN. *Bell G, Efron D*.

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J Psychosom Res. 2015;79:443-50.

CIRCADIAN RHYTHM DISRUPTION AS A LINK BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND OBESITY?

Vogel SWN, Bijlenga D, Tanke M, et al.

Objective: Patients with Attention-Deficit/Hyperactivity Disorder (ADHD) have a high prevalence of obesity. This is the first study to investigate whether circadian rhythmdisruption is a mechanismlinking ADHD symptoms to obesity.

Methods: ADHD symptoms and two manifestations of circadian rhythmdisruption: sleep problems and an unstable eating pattern (skipping breakfast and binge eating later in the day) were assessed in participants with obesity (n= 114), controls (n= 154), and adult ADHD patients (n= 202).

Results: Participants with obesity had a higher prevalence of ADHD symptoms and short sleep on free days as compared to controls, but a lower prevalence of ADHD symptoms, short sleep on free days, and an unstable eating pattern as compared to ADHD patients.We found that participants with obesity had a similar prevalence rate of an unstable eating pattern when compared to controls. Moreover,mediation analyses showed that both sleep duration and an unstable eating pattern mediated the association between ADHD symptoms and body mass index (BMI).

Conclusion: Our study supports the hypothesis that circadian rhythm disruption is a mechanism linking ADHD symptoms to obesity. Further research is needed to determine if treatment of ADHD and circadian rhythm disruption is effective in the prevention and treatment of obesity in patients with obesity and/or ADHD

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J Sleep Res. 2016.

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

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

Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous psychiatric disorder with three different presentations and high levels of psychiatric comorbidity. Serious sleep complaints are also common, but the role of the presentations and comorbidity in sleep is under-investigated in ADHD. Consequently, the goal of the study was to investigate sleep problems in medicine-naive school-aged children (mean age = 9.6 years) with ADHD compared to controls using objective methods and to examine the role of comorbidity and presentations. Ambulatory polysomnography results suggested that children with ADHD (n = 76) had significantly more sleep disturbances than controls (n = 25), including a larger percentage of rapid eye movement (REM) sleep and more sleep cycles, as well as lower mean sleep efficiency, mean non-REM (NREM) sleep stage 1 and mean NREM sleep stage 3. No significant between-group differences were found on the multiple sleep latency test. Stratifying for comorbidity in the ADHD group did not reveal major differences between groups, but mean sleep latency was significantly longer in children with ADHD and no comorbidity compared to controls (36.1 min; SD = 30.1 versus 22.6 min; SD = 15.2). No differences were found between ADHD presentations

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J Int Neuropsychol Soc. 2016 Jan;22:1-11.

GOOD HOLDERS, BAD SHUFFLERS: AN EXAMINATION OF WORKING MEMORY PROCESSES AND MODALITIES IN CHILDREN WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER. *Simone AN, Bédard AC, Marks DJ, et al.*

The aim of this study was to examine working memory (WM) modalities (visual-spatial and auditory-verbal) and processes (maintenance and manipulation) in children with and without attention-deficit/hyperactivity disorder (ADHD). The sample consisted of 63 8-year-old children with ADHD and an age- and sex-matched non-ADHD comparison group (N = 51). Auditory-verbal and visual-spatial WM were assessed using the Digit Span and Spatial Span subtests from the Wechsler Intelligence Scale for Children Integrated—Fourth Edition. WM maintenance and manipulation were assessed via forward and backward span indices, respectively. Data were analyzed using a 3-way Group (ADHD vs. non-ADHD) × Modality (Auditory-Verbal

vs. Visual-Spatial) × Condition (Forward vs. Backward) Analysis of Variance (ANOVA). Secondary analyses examined differences between Combined and Predominantly Inattentive ADHD presentations. Significant Group × Condition (p = .02) and Group × Modality (p = .03) interactions indicated differentially poorer performance by those with ADHD on backward relative to forward and visual-spatial relative to auditoryverbal tasks, respectively. The 3-way interaction was not significant. Analyses targeting ADHD presentations yielded a significant Group × Condition interaction (p = .009) such that children with ADHD-Predominantly Inattentive Presentation performed differentially poorer on backward relative to forward tasks compared to the children with ADHD-Combined Presentation. Findings indicate a specific pattern of WM weaknesses (i.e., WM manipulation and visual-spatial tasks) for children with ADHD. Furthermore, differential patterns of WM performance were found for children with ADHD-Predominantly Inattentive versus Combined Presentations

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J Int Neuropsychol Soc. 2016 Jan;22:12-23.

INCREASED DELAY DISCOUNTING ON A NOVEL REAL-TIME TASK AMONG GIRLS, BUT NOT BOYS, WITH ADHD. ***Rosch KS, Mostofsky SH.***

The aim of this study was to examine delay discounting in girls and boys with ADHD-Combined type (ADHDC) relative to typically developing (TD) children on two tasks that differ in the extent to which the rewards and delays were experienced by participants. Children ages 8–12 years with ADHD-C (n = 65; 19 girls) and TD controls (n = 55; 15 girls) completed two delay discounting tasks involving a series of choices between smaller, immediate and larger, delayed rewards. The classic delay discounting task involved choices about money at delays of 1–90 days and only some of the outcomes were actually experienced by the participants. The novel real-time discounting task involved choices about an immediately consumable reward (playing a preferred game) at delays of 25–100 s, all of which were actually experienced by participants. Participants also provided subjective ratings of how much they liked playing the game and waiting to play. Girls with ADHD-C displayed greater delay discounting compared to boys with ADHD-C and TD girls and boys on the real-time discounting task. Diagnostic group differences were not evident on the classic discounting task. In addition, children with ADHD-C reported wanting to play the game more and liking waiting to play the game less than TD children. This novel demonstration of greater delay discounting among girls with ADHD-C on a discounting task in which the rewards are immediately consumable and the delays are experienced in realtime informs our understanding of sex differences and motivational processes in children with ADHD

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Molecular Autism. 2016.

PARENT-REPORTED AND CLINICIAN-OBSERVED AUTISM SPECTRUM DISORDER (ASD) SYMPTOMS IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD): IMPLICATIONS FOR PRACTICE UNDER DSM-5. ***Grzadzinski R, Dick C, Lord C, et al.***

Background: Children with attention deficit/hyperactivity disorder (ADHD) often present with social difficulties, though the extent to which these clearly overlap with symptoms of autism spectrum disorder (ASD) is not well understood.

Methods: We explored parent-reported and directly-observed ASD symptoms on the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) in children referred to ASD-specialty clinics who received diagnoses of either ADHD (n = 48) or ASD (n = 164).

Results: Of the ADHD sample, 21 % met ASD cut-offs on the ADOS and 30 % met ASD cut-offs on all domains of the ADI-R. Four social communication ADOS items (Quality of Social Overtures, Unusual Eye Contact, Facial Expressions Directed to Examiner, and Amount of Reciprocal Social Communication) adequately differentiated the groups while none of the items on the ADI-R met the criteria for adequate discrimination.

Conclusions: Results of this work highlight the challenges that clinicians and researchers face when distinguishing ASD from other disorders in verbally fluent, school-age children

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Neuropsychiatr Dis Treat. 2015 Nov;11.
ATOMOXETINE TREATMENT MAY DECREASE STRIATAL DOPAMINERGIC TRANSPORTER AVAILABILITY AFTER 8 WEEKS: PILOT SPECT REPORT OF THREE CASES. *Akay AP, Kaya GC, Baykara B, et al.*
Attention deficit/hyperactivity disorder is one of the most common neurodevelopmental disorders. The pathophysiology is thought to involve noradrenaline and dopamine. The role of dopamine transporter (DAT) was evaluated in imaging studies using mostly dopamine reuptake inhibitors. Atomoxetine is a selective noradrenaline reuptake inhibitor. Here we report the results of a pilot study conducted to evaluate changes in striatal DAT after 8 weeks of atomoxetine treatment. Our results suggest that 8 weeks of atomoxetine treatment may change striatal DAT bioavailability as measured via SPECT but that change was not correlated with genotype or clinical improvement.

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Neuropsychiatr Dis Treat. 2015 Nov;11.
COMPARATIVE EFFICACY, ACCEPTABILITY, AND TOLERABILITY OF DEXMETHYLPHENIDATE VERSUS PLACEBO IN CHILD AND ADOLESCENT ADHD: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. *Maneeton N, Maneeton B, Woottiluk P, et al.*
Background: The efficacy of dexmethylphenidate (d-MPH) has been proven in the treatment of children and adolescents with attention-deficit hyperactivity disorder (ADHD).
Objective: The aim of this systematic review is to determine the efficacy, acceptability, and tolerability of dMPH in child and adolescent ADHD.
Methods: The searches of SCOPUS, MEDLINE, CINAHL, and Cochrane Controlled Trials Register were performed in February 2015. All randomized controlled trials of d-MPH versus placebo that were performed in children and adolescents with ADHD up to 18 years of age were included in the study. The efficacy was measured by using the pooled mean-endpoint or mean-changed scores of ADHD rating scales and the response rate. Acceptability and tolerability were measured by using the pooled rates of overall discontinuation and discontinuation due to adverse events, respectively.
Results: A total of 1,124 children and adolescents diagnosed as having ADHD were included in this review. In a laboratory school setting, the pooled mean-change and mean-endpoint scores in the d-MPH-treated group were significantly greater than those of the placebo-treated group with standardized mean difference (95% confidence interval [CI]) of -1.20 (-1.73, -0.67), I^2 = 95%. Additionally, the pooled mean-changed scores of the ADHD rating scales for teachers and parents in the d-MPH-treated group were significantly greater than that of the placebotreated group with weighted mean difference (95% CI) of -13.01 (-15.97, -10.05), I^2 = 0% and (95% CI) of -12.99 (-15.57, -10.42), I^2 = 0%, respectively. The pooled response rate in the d-MPHtreated groups had a significance higher than that of the placebo-treated group. The rates of pooled overall discontinuation and discontinuation due to adverse events between the two groups were not significantly different.

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Neuropsychiatr Enfance Adolesc. 2015 Nov;63:463-67. **LE NEUROFEEDBACK DANS LE TROUBLE DÉFICIT DE L'ATTENTION/HYPERACTIVITÉ DE L'ENFANT EST-IL EFFICACE? DEPUIS LES ÉTUDES RIGOUREUSES JUSQU'AUX BONNES PRATIQUES CLINIQUES. = IS NEUROFEEDBACK AN EFFICACIOUS TREATMENT FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN? FROM RIGOROUS STUDIES TO CLINICAL GOOD PRACTICE. *Micoulaud-Franchi JA, Lopez R, Bioulac S, et al.***
Background: Neurofeedback, based on the concept of creating a retroactive psychophysiological loop, has advantages compared with other cognitive therapeutic techniques in the treatment of children with attentiondeficit/hyperactivity disorder (ADHD). However, although this technique has been used for almost 20 years in ADHD, the level of evidence for its efficacy remains debated. This debate has recently been brought into focus in the literature following a published meta-analysis.
Aims: This article aims to review and classify existing literature on the efficacy of neurofeedback in ADHD.

Methods: Publications were identified through a literature search of the electronic database PubMed using the Medical Subject Headings (Mesh) terms "Neurofeedback" and "Attention-Deficit/Hyperactivity Disorder". All relevant papers published in English or French were reviewed by the authors. These were separated into 2 groups: published before and after 2011.
Results: Prior to 2011, studies are characterized by low sample size and are often non-randomized and uncontrolled. In addition these are most often performed by practitioners who participated in the development of the first neurofeedback equipment and who have electrophysiological expertise, essential for effective training during sessions. In 2009 Arns et al. published the first meta-analysis on the efficacy of neurofeedback in ADHD. They found a large effect size, 1.02 (0.84 to 1.21) and 0.94 (0.76 to 1.12) respectively for the inattention and impulsivity dimensions, and a moderate effect size of 0.71 (0.54 to 0.87) on the hyperactivity dimension. Improved inattention dimension was proportional to the number of sessions and maintained in randomized trials, which was not the case for the hyperactivity dimension. After 2011, studies are characterized by larger samples, and methodology including randomized, controlled trials and blinded assessments. In 2013, Sonuga-Barke et al. published the second meta-analysis on the efficacy of neurofeedback in ADHD (Am J Psych). They found a smaller effect size of 0.59 (0.31 to 0.87) compared to the first meta-analysis of 2009. The effectiveness of neurofeedback was not confirmed in studies with blinded assessment. The effect size was 0.29 (-0.02 to 0.61) (P = 0.07; NS). However the effectiveness of the training during neurofeedback sessions in some of the included studies has been called into question.
Conclusion: Methodological issues are likely to have a large impact on results obtained in studies of neurofeedback. Thus, it is critical that future trials implement adequately randomized, controlled, blinded designs that do not compromise the quality of neurofeedback session itself.

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Neurosci Behav Physiol. 2016;1-6.
RESULTS OF PHARMACOTHERAPY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: ASSESSMENT USING NEUROPSYCHOLOGICAL METHODS.
Zavadenko NN, Suvorinova NY.
Study aim. To investigate the dynamics of measures of behavior, attention, and memory during treatment with Noofen (250-mg capsules) in children with attention deficit hyperactivity disorder (ADHD).
Materials and methods. A total of 50 patients taking part in an open study were divided into two groups of 25 patients: patients of group 1 received Noofen while patients of group 2 (controls) received only low doses of multivitamins. Treatment lasted one month. Noofen was given at doses of 15-20 mg/kg (500Γ Çô750 mg) per day using 250-mg capsules, as two or three doses.
Results and conclusions. Neuropsychological test results at the end of one month of treatment demonstrated improvements in cognitive functions, including measures of self-control, sustained, focused, and distributed attention, and auditory verbal memory. It is suggested that the initial positive changes may provide a base for attaining more significant clinical outcomes with longer-lasting treatment

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Neurotoxicol Teratol. 2015 Nov;52:143-50.
PRENATAL EXPOSURE TO POLYBROMINATED DIPHENYL ETHERS AND CHILD ATTENTION PROBLEMS AT 3–7YEARS.
Cowell WJ, Lederman SA, Sjödin A, et al.
Introduction: Polybrominated diphenyl ethers (PBDEs) comprise a class of halogenated compounds used extensively as flame retardant chemicals in consumer products resulting in nearly ubiquitous human exposure. Mounting evidence suggests that PBDEs are developmental neurotoxicants; however, associations between early life exposure and child behavior have been largely limited to a single developmental time point.
Methods: The study population consists primarily of white, black and Chinese women who were pregnant on 11 September 2001 and delivered at 1 of 3 downtown New York City hospitals. Maternal–child pairs were followed through age 7years. Cord blood was collected at delivery and PBDE plasma levels for 210 samples were analyzed by the U.S. Centers for Disease Control and Prevention. The Child Behavior Checklist, a

validated maternal-report instrument used for assessing child behavior, was administered annually between the ages of 3 and 7years. We analyzed the association between natural log-transformed and dichotomized (low vs. high) PBDEs and attention problems using multivariable adjusted negative binomial regression.
Results: We detected 4 PBDE congeners in more than 50% of samples, with concentrations highest for BDE-47 (median ± IQR: 11.2 ± 19.6ng/g). In adjusted analyses, we detected associations between BDE-47 (1.21, 95% CI: 1.00, 1.47), and BDE-153 (1.18, 95% CI: 1.00, 1.39) in cord plasma and increased attention problems among children at age 4 (n = 109) but not 6 (n = 107) years.
Conclusions: Our findings demonstrate a positive trend between prenatal PBDE exposure and early childhood attention problems, and are consistent with previous research reporting associations between prenatal PBDE exposure and disrupted child behaviors.

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Paediatr Perinat Epidemiol. 2016.
GESTATIONAL AGE AT TERM, DELIVERY CIRCUMSTANCE, AND THEIR ASSOCIATION WITH CHILDHOOD ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS. ***Talge NM, Allswede DM, Holzman C.***
Background: Perinatal characteristics may identify subgroups of term-born children at risk for academic and behavioural difficulties. Using follow-up data from the Pregnancy Outcomes and Community Health Study, we subdivided term births according to two potential markers of perinatal risk (gestational age, delivery circumstance) and evaluated their association with attention deficit hyperactivity disorder (ADHD) symptoms.
Methods: We included children born at term whose mothers completed the Conners' Parent Rating ScalesRevised-Short Form (CPRS-R-S) (n=610; ages: 3-9 years). The CPRS-R-S yields age and sex-referenced T-scores for the two primary dimensions of ADHD (inattention, hyperactivity) and an ADHD Index that reflects both dimensions. Using general linear models, we evaluated whether: (1) term delivery defined by gestational week (reference: 39-40 weeks), or (2) term delivery circumstance defined by labour onset type and mode of delivery (reference: spontaneous labour, vaginal delivery) was associated with these problems.
Results: Following adjustment for parity, sociodemographics, and maternal mental health both during pregnancy and at the child follow-up survey, the induced labour plus caesarean group exhibited higher inattention and ADHD Index scores relative to the spontaneous labour, vaginal delivery group (inattention: mean difference=5.1, 95% CI 0.6, 9.7; ADHD Index: mean difference=4.1, 95% CI 0.5, 7.8). Findings were primarily driven by male children.
Conclusions: Among term-born children, only those whose mothers experienced induction of labour that culminated in caesarean delivery exhibited higher levels of ADHD symptoms. Prenatal, antepartum, and/or postnatal factors associated with this delivery profile may reflect increased risk for such problems

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Pharmacoepidemiol Drug Saf. 2015;24:206-07.
ATTENTION DEFICIT HYPERACTIVITY MEDICATIONS DURING PREGNANCY AND THE RISK OF CONGENITAL CARDIAC MALFORMATIONS: A COHORT STUDY.
Bateman BT, Huybrechts KF, Patorno E, et al.
Background: Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric disorder in children, which is increasingly being recognized as having the potential to extend into adulthood. As such, it is important to understand the teratogenic risk of drugs commonly used to treat ADHD.
Objectives: The aim of this study was to define the risk of cardiac malformation associated with first trimester exposure to two of the most commonly used ADHD medications: amphetamine-dextroamphetamine and methylphenidate.
Methods: We used a cohort of 1356514 completed pregnancies linked to liveborn infants of women enrolled in Medicaid from 2000 to 2010. We examined the risk of major cardiac malformations associated with first trimester exposure to amphetamine-dextroamphetamine and methylphenidate, which was defined based on a filled prescription during this exposure window. The reference group consisted of women without exposure to these medications during the first trimester. Propensity score stratification (100 strata of fixed score

interval) was used to control for potential confounders including maternal demographics, obstetric and medical conditions, and exposure to other medications.
Results: There were 3068 (0.2%) women dispensed amphetamine-dextroamphetamine and 1437 (0.1%) dispensed methylphenidate during the first trimester. The risk of cardiac malformations in the amphetamine-dextroamphetamine exposed was 1.92% and 2.78% in the methylphenidate exposed compared with 1.53% in the non-exposed. After controlling for confounders, the relative risk for cardiac malformations was 0.81 (95%CI 0.44 to 1.50) for amphetaminedextroamphetamine and 2.08 (95%CI 1.26 to 3.44) for methylphenidate.
Conclusions: The results of this preliminary analysis suggest that maternal use of methylphenidate in the first trimester may be associated with an approximately twofold increase in the risk of major cardiac malformations, independent of measured confounders. Amphetamine-dextroamphetamine was not associated with elevated risk

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Pharmacoepidemiol Drug Saf. 2015;24:235-36.
CARDIAC RISK ASSOCIATED WITH METHYLPHENIDATE IN PEDIATRIC PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): SELFCONTROLLED CASE SERIES STUDY IN KOREA. *Shin J-Y, Lee SH, Shin HN, et al.*
Background: Since the cases of serious cardiac adverse event associated with methylphenidate was reported, many epidemiology studies have been performed. However, previous studies reported conflicting findings with limited statistical power and low absolute risk of an event.
Objectives: The aim of this study was to evaluate the association between methylphenidate use and adverse cardiac outcomes using the self-controlled case series study design.
Methods: We used the Korea Health Insurance Review and Assessment (HIRA) claims database between 1 January 2009 and 31 December 2012. Pediatrics patients 18 years of age and younger with attention deficit hyperactivity disorder (ADHD) (ICD-10 code F90) who had records of a cardiac outcome (sudden cardiac death (ICD-10 code I46.1, I46.9), myocardial infarction (I29), stroke (I63), hypertensive disease (I10-I15), or arrhythmias (I44-I49 except I46.1, I46.9)) and at least one prescription for methylphenidate before the end of 2012 were identified. Incident rate ratios (IRR) for cardiac outcomes in periods of methylphenidate exposure compared with unexposed periods were calculated. We estimated the IRR and their 95% confidence intervals (CI) using conditional Poisson regression.
Results: The total number of 2945 eligible participants were identified and included in the final analysis. The median period of exposure was 2.5 years with follow- up (Q1-Q3, 1.3-3.8). The study population consisted of 77% boys, whose median age was 15 years (Q1-Q3, 12-17). An increased risk was observed in the 1-30 days post initiation (IRR=2.08, 95%CI: 1.98-2.18), 31-60 days (IRR=1.84, 95%CI: 1.70-1.99), and post 60 days (IRR=1.39, 95%CI: 1.27-1.51).
Conclusions: Our self-controlled case series study suggests an increased risk of cardiac events associated with methylphenidate use

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Pharmacoepidemiol Drug Saf. 2015;24:501-02.
PERSISTENCE OF STIMULANTS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A LONGITUDINAL STUDY.
Sura S, Chatterjee S, Kamble P, et al.
Background: Treatment persistence with stimulants is critical for long-term disease state management of attention deficit hyperactivity disorder (ADHD) in children and adolescents.
Objectives: To evaluate the persistence of long acting stimulant (LAS) use among children and adolescents with ADHD and to examine the factors associated with LAS persistence.
Methods: This retrospective longitudinal study used 2004-2007 IMS LifeLink data and included patients aged 6-19 years with ADHD diagnosis. Children continuously enrolled 6 months before and 12 months after the index date were included in the cohort. The index date was defined as the first claim date for LAS prescription.

Patients were considered concurrent users if they used short-acting stimulants (SAS) or intermediate- acting stimulants (IAS) during the follow-up. All patients were followed for 12 months to measure persistence. Persistence was defined as the time from index date to discontinuation of LAS therapy with allowable gap of than 30 days. Accelerated failure time (AFT) model using Weibull distribution was constructed to determine the predictors of LAS persistence.
Results: A total of 40 385 patients were diagnosed with ADHD and used LAS. Among them, 14.8% and 1.58% patients were concurrently taking SAS and IAS, respectively. The mean persistence of LAS was 154±129 days. Analysis of AFT model found that patients aged 13-19 years had 35% lower persistence (survival time ratio (STR), 0.65; 95%CI, 0.63-0.66) compared to those aged 6-12 years. Concurrent SAS users had higher persistence (STR, 1.18; 95%CI, 1.14-1.22) whereas concurrent IAS users had lower persistence (STR, 0.62; 95%CI, 0.57-0.68) compared to LAS users. Comorbidities such as depression, oppositional disruptive disorder and conduct disorder, and use of medications such as non-stimulants, agonists, antidepressants, antipsychotics, and mood stabilizers were also associated with longer LAS persistence.
Conclusions: The study identified several predictors of LAS persistence among children and adolescents with ADHD. There is a strong need to target factors that influence treatment persistence for long-term disease management of ADHD

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Pharmacoepidemiol Drug Saf. 2015;24:374.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND SOCIOECONOMIC STATUS IN CHILDREN AND ADOLESCENTS IN THE UK.

Hire AJ, Ashcroft DM, Springate DA, et al.
Background: Research has suggested that an individual's chance of being diagnosed with ADHD may be influenced by his or her socioeconomic status. Prescription analysis has identified geographical variations in spending for ADHD in England; it is unclear if this is associated with regional variations in diagnostic rates and deprivation levels.
Objectives: This study aimed to assess the geographical distribution of ADHD in the UK and discern if there were differences in diagnostic rates between regions. It also examined if there was an association between ADHD and socioeconomic deprivation on a national scale.
Methods: The study used data from the Clinical Practice Research Datalink (CPRD). The study population comprised patients diagnosed with ADHD before the age of 19 years, between 1 January 2004 and 31 December 2013. Patients with a diagnosis of ADHD were identified by the presence of codes relating to the disorder in their medical records. Using CPRD data, patients were stratified according to the region in which their general practice was based. Each practice has an Index of Multiple Deprivation (IMD) score based on the locality in which it is sited; this relative measure of deprivation provided a surrogate measure of patients' deprivation status.
Results: Between 2004 and 2013, there were 10 284 new diagnoses of ADHD. Most patients were diagnosed between the ages of 7 and 12 years (56.67%, n=5828), and 81.75% (n=8407) of those diagnosed were male. The South East England region had the highest incidence of ADHD [1.59 cases per 1000 personyears at risk/PY (95%CI 1.51-1.67). Yorkshire had the lowest incidence of ADHD [0.81 cases per 1000 PY (95%CI 0.71-0.93)]. There appeared to be a linear association between socioeconomic deprivation and ADHD incidence in England. In the other three nations of the UK, evidence for an association was somewhat weaker.
Conclusions: There were notable differences in ADHD incidence between UK regions. In England, incidence of diagnosed ADHD was highest amongst the most deprived patients and lowest in patients from the least deprived areas

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Pharmacoepidemiol Drug Saf. 2015;24:234-35.

USE OF ADHD DRUGS IN CHILDREN AND ADOLESCENTS IN THE NORDIC COUNTRIES 2008-2012-A POPULATION-BASED STUDY.

Furu K, Karlstad +, Zoega H, et al.

Background: Hyperkinetic disorder or attentiondeficit hyperactivity disorder (ADHD) is one of the most common psychiatric conditions of childhood and is estimated to affect 3-6% of children. Use of stimulants to treat ADHD has increased several-fold over the past two decades throughout the world. We use the Nordic prescription databases to examine the individual use of ADHD drugs in children and adolescents.

Objectives: The aim of this study was to assess the annual prevalence and incidence of use of ADHD drugs during 2008-2012 in the entire Nordic child population aged 6-17 years comprising about 3.5 million inhabitants.

Methods: Data on ADHD drugs dispensed from pharmacies were retrieved from the nationwide prescription registers in each of the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) with complete coverage of prescribed drug use in the outpatient setting for all inhabitants. ADHD drugs were methylphenidate (N06BA04), atomoxetine (N06BA09), amphetamine (N06BA01) and dexamphetamine (N06BA02). Data were pooled in one database and analysed as annual cross sections for 2008-2012. Period prevalence was defined as the number of users of ADHD drugs per year, while incidence was defined as the number of new users per year (730 days run-in). The denominator was the gender-specific and age-specific population in each country of the same year.

Results: In 2008, 47 226 individuals (1.3% of all Nordic children aged 6-17 years) were dispensed a stimulant at least once, increasing further to 76 363 (2.1%) in 2012. The annual prevalence increased from 1.9% to 3.1% for boys and from 0.6% to 1.1% in girls during the study period. Methylphenidate was the predominant stimulant used in all years. The proportion of extended release formulation of methylphenidate increased during the study period. The incidence was 0.55% for boys and 0.21% for girls in 2008, increasing to 0.69% and 0.33% in 2012, respectively.

Conclusions: In the Nordic countries, both the prevalence and the incidence of use of ADHD drugs increased in both gender during the 5-year period 2008-2012. The male/female prevalence ratio declined slightly from 2008 to 2012

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Pharmacoepidemiol Drug Saf. 2015;24:382-83.

INCREASING ATOMOXETINE AND DECREASING METHYLPHENIDATE USE FOR PEDIATRIC PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN KOREA. *Shin*

J-Y, Shin SM, Lee SH, et al.

Background: Increasing prevalence of attention deficit hyperactivity disorder (ADHD) and methylphenidate use worldwide were reported. However, the changing patterns of drug use have not been investigated after the introduction of a newer drug, atomoxetine, in 2006.

Objectives: The aim of this study was to investigate the prevalence of methylphenidate and atomoxetine use in Korean pediatric patients with ADHD.

Methods: We used Korea National Health Insurance Corporation (NHIC) claims database between 1 January 2007 and 31 December 2011. Study subjects consisted of pediatrics younger than 18 years old who were diagnosed with ADHD (ICD-10, F90) with prescriptions of methylphenidate or atomoxetine. Monthly proportion was calculated according to the prescribed ADHD medication. All analyses were performed for boys and girls. Cochrane-Armitage test was performed to calculate the p for its trend.

Results: The total number of 75 377 ADHD patients/year was identified from 2007 to 2011 (boys - 79.7%, girls - 20.3%; p-value<0.05). Approximately three-quarters of the ADHD patients were prescribed methylphenidate or atomoxetine (total - 72.2%, boys - 73.0%, girls - 69.2%; p-value<0.05). We found an increasing prevalence of ADHD medication use among pediatric patients with ADHD (boys - 74, 83% in 2007 to 78.38% in 2011, p for trend <0.05; girls - 70.31% in 2007 to 73.50% in 2011, p for trend <0.05). The increasing pattern was observed in atomoxetine use since September 2009 (boys - 6.09% in 2009 to 13.74% in 2011, p for trend <0.05; girls - 4.50% in 2009 to 10.67% in 2011, p for trend <0.05), whereas a decreasing pattern was observed in methylphenidate use (boys - 74.83% in 2007 to 71.09% in 2011, p for trend <0.05; girls - 70.31% in 2007 to 67.47% in 2011, p for trend <0.05).

Conclusions: The pattern of increased atomoxetine use was observed since September 2009, whereas methylphenidate use decreased in both boys and girls with ADHD. More research would be needed to show how the change in epidemiology of ADHD medication use affected the safety and efficacy of ADHD treatments

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Pharmacoepidemiol Drug Saf. 2015;24:234.

PRENATAL ANTIDEPRESSANT EXPOSURE AND THE RISK OF AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

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

Background: Recent studies suggested that prenatal exposure of selective serotonin reuptake inhibitors (SSRIs) may be associated with increased risk of autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD). However, confounding has not been comprehensively excluded.
Objectives: The aim of this study was to investigate the association between SSRIs and ASD and ADHD in a large healthcare system.
Methods: 429 645 children who were delivered in public hospital were identified using the Hong Kong population-based electronic medical records on the Clinical Data Analysis & Reporting System (2001- 2014). Using a case-control study design, we evaluated the association between ASD or ADHD and prenatal exposure of SSRIs. Further analyses using disease risk score (DRS) matching (1:10) and withinpatient study design, case-time-control (CTC), were conducted to address residual confounding. The risks of ASD and ADHD were estimated using odds ratios (ORs) from logistic regression.
Results: Among 429 645 children identified, 299 672 were included in the analysis; 4208 and 2706 children were diagnosed with ASD and ADHD, respectively. 0.88% of ASD and 1.22% of ADHD children were having prenatal SSRIs exposure compared with 0.6% in controls. The adjusted ORs of ASD and ADHD are 1.35 (95%CI 0.94-1.93) and 2.12 (95%CI 1.44- 3.11), respectively. The findings were similar in DRS matched model. In contrasts, no association was found in CTC analysis (OR=1.12, 95%CI 0.83-1.53 for ASD; OR=0.81, 95%CI 0.58-1.12 for ADHD). Alternative analyses using non-SSRI antidepressant as exposure showed similar results. The CTC ORs for ASD and ADHD were 1.08 (95%CI 0.81-1.44) and 1.02 (95%CI 0.75-1.39), respectively. In validation analysis using insulin as negative control, no association was found in CTC analyses (OR=1.13, 95%CI 0.31-4.04 for ASD; OR=1.15, 95%CI 0.25-5.28 for ADHD).
Conclusions: This study does not support the hypothesis that prenatal SSRIs exposure increased the risk of ASD or ADHD in children. These results suggest that the risk of ASD and ADHD observed with prenatal SSRI exposure is likely confounded by maternal underlying medical conditions and genetic factors

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Pharmacoepidemiol Drug Saf. 2015;24:277-78.

STATE-LEVEL VARIATION OF PSYCHOTROPIC DRUG UTILIZATION IN CHILDREN WITH ADHD IN THE UNITED STATES USING MULTIPLE DISPARITY MEASURES. *Liu*

X, Kubilis P, Bussing R, et al.

Background: Children with attention deficit/hyperactivity disorder (ADHD) represent the largest pediatric population with high likelihood of psychotropic treatment (PT). Geographic variation of PT in children with ADHD deserves investigation to detect disparities in following evidence-based practice guidelines.
Objectives: The aim of this study was to evaluate state-level variation of PT utilization in children with ADHD using Medicaid Analytic eXtract (MAX) data in 26 US states from 1999 to 2006.
Methods: For each study year, we followed children aged 4-18 years from their first ADHD diagnosis for 1 year to ascertain filled prescriptions for the three most commonly used psychotropic drug classes: stimulants, antidepressants, and antipsychotics. We extended the follow-up time to 2 years to evaluate psychotropic polypharmacy defined as using than 2 psychotropic drugs concomitantly. We used extremal quotient (EQ), 2-test, boot strapping of coefficients of variation (CV), and logistic regression to evaluate state-level variation.
Results: We identified 235 432 to 449 408 patients from 1999 to 2005 for the 1-year cohort and 195 933 to 360 782 patients from 1999 to 2004 for the 2-year cohort. The highest and lowest state-level annual

prevalence and the range of EQ of PT across years were 88.4%, 57.7%, and 1.3-1.4 for stimulants; 16.0%, 48.1%, and 2.3-2.6 for antidepressants; 24.1%, 63.5%, and 2.0-2.6 for psychotropic polypharmacy; and 7.1%, 46.5%, and 3.3-4.3 for antipsychotics. Both 2-test and boot strapping of CV rejected the null hypothesis that the prevalence of each drug class or polypharmacy was the same across 26 US states ($p<0.001$). In the logistic regression, state of residence had significant impact on psychotropic treatment after the adjustment for age, gender, race/ethnicity, foster care, disability, poverty, and year ($p<0.001$).
Conclusions: There is a significant state-level variation in psychotropic drug and psychotropic polypharmacy prescribing in children with ADHD. Further research is needed to investigate the reasons leading to the variation

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Pharmacoepidemiol Drug Saf. 2015;24:285-86.
THE ASSOCIATION BETWEEN ATOPIC DISEASES AND CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RETROSPECTIVE MATCHED CASE-CONTROL STUDY. *van der Schans J, Pleiter JC, De Vries TW, et al.*
Background: Data on the association between attention- deficit/hyperactivity disorder (ADHD) and atopic diseases have been inconclusive.
Objectives: We assessed whether children with ADHD are more likely to have a history of atopy like asthma, allergic rhinitis or eczema than children without ADHD.
Methods: A retrospective nested case-control study among children (6-12 years) using the IADB.nl prescription database was preformed. Medication proxies were used for the identification of ADHD and atopy. Cases were defined as children with at least two prescriptions of methylphenidate within 12months. Cases were matched to four controls: patients without ADHD medication, on age, sex and area code. For each case and control, we recorded the presence of asthma, allergic rhinitis and eczema in the 3 years prior to the inclusion. Asthma was defined as having at least three prescriptions of an inhaled corticosteroid or a short working betamimetic, allergic rhinitis was defined as having at least three prescriptions of a corticosteroid for nasal use and eczema was defined as having at least three prescriptions of ointments containing steroids or at least three prescriptions of calcineurin inhibitors, all within 12months. We further assessed the parental ADHD and atopic diseases as a predicting parameter on developing ADHD in childhood. Conditional logistic regression analysis was applied to obtain odds ratios (OR) and corresponding 95% confidence intervals (CI).
Results: We identified 4257 cases and 17 028 controls. Asthma, allergic rhinitis and eczema were more common in cases than controls with odds ratios of 1.4 (95%CI: 1.3-1.6), 1.4 (95%CI: 1.1-1.8) and 1.3 (95%CI: 1.1-1.5), respectively. Association of parental use of medication for atopy on receiving ADHD medication in the offspring (OR: 1.1; 95%CI: 1.0- 1.2) was higher in cases compared to controls.
Conclusions: This study suggests that atopic diseases are associated with the development of ADHD. Future studies should focus on the genetic component of the association to clarify the possible underlying mechanism

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Pharmacoepidemiol Drug Saf. 2015;24:396.
FACTORS ASSOCIATED WITH PHARMACOLOGICAL TREATMENT INITIATION IN ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER PATIENTS: FINDINGS FROM A PUBLICLY INSURED POPULATION. *Li Y, Liu W, Kubilis P, et al.*
Background: Attention-deficit/hyperactivity disorder (ADHD)in adulthood adversely affects occupational, academic, and social functioning but can be effectively managed by medications. Factors associated with ADHD pharmacological treatment initiation in children and adolescents arewell described,while little is known for adults.
Objectives: The aim of this study was to explore how patient socio-demographic and clinical characteristics affect ADHD pharmacological treatment initiation.
Methods: Using the US Medicaid eXtract Files of 29 states from 1999 and 2010, we assembled a retrospective cohort of adult patients with new ADHD episodes. The outcome of interest was initiation of stimulants or atomoxetine within 6 months after the index diagnosis. Treatment initiators and non-initiators

were compared with respect to their baseline socio-demographics, mental comorbidities, history of psychotropic use, and diabetes and cardiovascular conditions using multivariable logistic regression.
Results: Of the 32 622 eligible ADHD patients, 8601 (26.4%) started pharmacological treatment within 6 months of diagnosis. Female (OR 1.46; 95%CI 1.38-1.54), White (OR 1.61; 95%CI 1.51-1.71), and patients aged >25 years (OR 1.61; 95%CI 1.51-1.71) were more likely to initiate therapy. More than 70% of the study population had one or more diagnoses for mental disorders in the year prior to the new ADHD episode. The presence of more severe conditions including schizophrenia (OR 0.61; 95%CI 0.54-0.69) and bipolar disorders (OR 0.90; 95%CI 0.84-0.97) decreased the probability of initiation, while the presence of anxiety (OR 1.17; 95%CI 1.09-1.25) and substance use disorders (OR 1.17; 95%CI 1.08-1.27) increased the probability. Preexisting cardiovascular disease (OR 0.79; 95%CI 0.73-0.86) and diabetes (OR 0.66; 95%CI 0.58- 0.74) were adversely associated with treatment initiation.
Conclusions: Several socio-demographic and clinical characteristics were associated with the initiation of ADHD medications in adult patients. The findings provide valuable information to future efforts of providing timely and appropriate pharmacological treatment to these patients

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Prev Sci. 2015 Feb;16:242-53.

THE EFFECTIVENESS OF THE STOP NOW AND PLAN (SNAP) PROGRAM FOR BOYS AT RISK FOR VIOLENCE AND DELINQUENCY.

Burke JD, Loeber R.

Among the available treatments for disruptive behavior problems, a need remains for additional service options to reduce antisocial behavior and prevent further development along delinquent and violent pathways. The Stop Now and Plan (SNAP) Program is an intervention for antisocial behavior among boys between 6 and 11. This paper describes a randomized controlled treatment effectiveness study of SNAP versus standard behavioral health services. The treatment program was delivered to youth with aggressive, rule-breaking, or antisocial behavior in excess of clinical criterion levels. Outcomes were measured at 3, 9, and 15 months from baseline. Youth in the SNAP condition showed significantly greater reduction in aggression, conduct problems, and overall externalizing behavior, as well as counts of oppositional defiant disorder and attention deficit hyperactivity disorder symptoms. Additional benefits for SNAP were observed on measures of depression and anxiety. Further analyses indicated that the SNAP program was more effective among those with a higher severity of initial behavioral problems. At 1 year follow-up, treatment benefits for SNAP were maintained on some outcome measures (aggression, ADHD and ODD, depression and anxiety) but not others. Although overall juvenile justice system contact was not significantly different, youth in SNAP had significantly fewer charges against them relative to those standard services. The SNAP Program, when contrasted with standard services alone, was associated with greater, clinically meaningful, reductions in targeted behaviors. It may be particularly effective for youth with more severe behavioral problems and may result in improvements in internalizing problems as well

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Proc Natl Acad Sci U S A. 1998 Nov;95:14494-99.

SELECTIVE EFFECTS OF METHYLPHENIDATE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER: A FUNCTIONAL MAGNETIC RESONANCE STUDY.

Vaidya CJ, Austin G, Kirkorian G, et al.

Functional MRI revealed differences between children with Attention Deficit Hyperactivity Disorder (ADHD) and healthy controls in their frontal-striatal function and its modulation by methylphenidate during response inhibition. Children performed two go/no-go tasks with and without drug. ADHD children had impaired inhibitory control on both tasks. Off-drug frontal-striatal activation during response inhibition differed between ADHD and healthy children: ADHD children had greater frontal activation on one task and reduced striatal activation on the other task. Drug effects differed between ADHD and healthy children: The drug improved response inhibition in both groups on one task and only in ADHD children on the other task. The drug modulated brain activation during response inhibition on only one task: It increased frontal activation to an

equal extent in both groups. In contrast, it increased striatal activation in ADHD children but reduced it in healthy children. These results suggest that ADHD is characterized by atypical frontal-striatal function and that methylphenidate affects striatal activation differently in ADHD than in healthy children

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Psychiatr Serv. 2016;67:101-06.

SCHOOL-BASED BEHAVIORAL HEALTH SERVICE USE AND EXPENDITURES FOR CHILDREN WITH AUTISM AND CHILDREN WITH OTHER DISORDERS.

Kang-Yi CD, Locke J, Marcus SC, et al.

Objective: This study compared use of and associated expenditures for Medicaid-reimbursed school-based and out-of-school services for children with autism spectrum disorder (ASD) and those with other psychiatric disorders.

Methods: Philadelphia County Medicaid claims were used to identify children ages five to 17 who received behavioral health services through Medicaid any time between October 2008 and September 2009 (N=24,271). Children were categorized into four diagnostic groups: autism spectrum disorder (ASD), conduct disorder or oppositional defiant disorder (conduct-ODD), attention-deficit hyperactivity disorder (ADHD), and other psychiatric disorders. Logistic regression analysis compared use of in-school and out-ofschool behavioral health services between children with ASD and children with other psychiatric disorders. Generalized linear models with gamma distribution were used to estimate differences in Medicaid expenditures for in-school and out-of-school services and total Medicaid expenditures for both service types by disorder, with adjustments for age, sex, and race-ethnicity.

Results: The most common diagnosis was ADHD (40%); 35% had other psychiatric disorders, 21% had conduct-ODD, and 4% had ASD. A significantly greater proportion of children with ASD (52%) received inschool behavioral health services (conduct-ODD, 5%; ADHD, 8%; and other psychiatric disorders, 1.7%) Per-child expenditures for both school-based and outofschool behavioral health services were significantly higher for children with ASD than for children in the other groups.

Conclusions: Medicaid represents an important source of inschool and out-of-school care for childrenwith ASD and their families. States that expand Medicaid under the Affordable Care Act should give careful consideration to covering school-based mental health services for children with ASD

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Psychiatry Res. 2007 May;155:75-82.

ASSESSMENT AND PREVENTION OF HEAD MOTION DURING IMAGING OF PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Epstein JN, Casey BJ, Tonev ST, et al.

The present study serves to detail the specific procedures for a mock scanner protocol, report on its use in the context of a multi-site study, and make suggestions for improving such protocols based on data acquired during study scanning. Specifically, a mock scanner compliance training protocol was used in a functional imaging study with a group of adolescents and adults with Attention Deficit Hyperactivity Disorder (ADHD) and a matched sample of healthy children and adults. Head motion was measured during mock and actual scanning. Participants across groups exhibited excess motion (>2 mm) on 43% of runs during the mock scanner. During actual scanning, excessive motion was limited to 10% of runs. There was a clear taskcorrelated head motion during a go/no-go task that occurred even after the compliance training: participants had a tendency to respond with increased head motion immediately after committing an error. This study illustrates the need to (1) report data attrition due to head motion, (2) assess task-related motion, and (3) consider mock scanner training in functional imaging protocols

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Psychiatry Res Neuroimaging. 2015.

INCREASED WHITE MATTER CONNECTIVITY IN TRAUMATIZED CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Park S, Lee J-M, Kim J-W, et al.

To distinguish between the consequences of trauma exposure and those of attention deficit hyperactivity disorder (ADHD), we compared brain diffusion tensor imaging (DTI) of children according to the diagnosis and the presence of a potentially traumatic event (PTE). The Early Trauma Inventory Self Report-Short Form (ETISR-SF) was used for the assessment of PTEs. Subjects who experienced any traumatic event were placed in the PTE group, and subjects who did not experience such a traumatic event were placed in the non-PTE group. We examined the interactions between ADHD and PTEs in brain [fractional anisotropy (FA) values and mean diffusivity (MD) values] in 54 children with ADHD (29 with PTEs and 25 without PTEs) and 41 controls (18 with PTEs and 23 without PTEs). Analysis of covariance (ANCOVA) revealed main effects of ADHD for FA and MD values in several white matter tracts in the absence of main effects for PTEs. In addition, there was a significant ADHD-PTEs interaction in relation to FA and MD values in several white matter tracts. Further longitudinal studies in a larger sample are warranted to evaluate the neurobiological sequelae related to childhood trauma, ADHD, and interaction between the two

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Psychiatry Res. 2015.

IMPAIRED INHIBITION AND WORKING MEMORY IN RESPONSE TO INTERNET-RELATED WORDS AMONG ADOLESCENTS WITH INTERNET ADDICTION: A COMPARISON WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER. *Nie J, Zhang W, Chen J, et al.*

Impairments in response inhibition and working memory functions have been found to be closely associated with internet addiction (IA) symptoms and attention-deficit/hyperactivity disorder (ADHD) symptoms. In this study, we examined response inhibition and working memory processes with two different materials (internetrelated and internet-unrelated stimuli) among adolescents with IA, ADHD and co-morbid IA/ADHD. Twentyfour individuals with IA, 28 individuals with ADHD, 17 individuals with IA/ADHD, and 26 matched normal controls (NC) individuals were recruited. All participants were measured with a Stop-Signal Task and 2-Back Task under the same experimental conditions. In comparison to the NC group, subjects with IA, ADHD and IA/ADHD demonstrated impaired inhibition and working memory. In addition, in comparison to internetunrelated conditions, IA and co-morbid subjects performed worse on the internet-related condition in the Stop trials during the stop-signal task, and they showed better working memory on the internet-related condition in the 2-Back Task. The findings of our study suggest individuals with IA and IA/ADHD may be impaired in inhibition and working memory functions that might be linked to poor inhibition specifically related to internetrelated stimuli, which will advance our understanding of IA and contribute to prevention and intervention strategies

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Psychological Research. 2015;17:112-27.

EFFECTIVENESS OF COGNITIVE BEHAVIOR THERAPY ON ANGER MANAGEMENT IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Moodi M, Alizadeh H, Bonab BG, et al.

In cognitive-behavior therapy for children suffering from ADHD, the focus is on reducing aggression signs through failure anger control training. These sings are due lo mistaken attributions about the goal or their partial selection of aggression signs. This study has been conducted to evaluate this approach. To do so, 32 students with ADHD in the third, fourth, and fifth grades of primary school have been randomly divided into two groups of 16 members each. Prior to the intervention, a questionnaire about anger decline has been distributed among students a.s a pretest. Then, the experimental group participated in 9 sessions of cognitive-behavior therapy. Following this intervention, again the same questionnaire was distributed among both groups, During the follow up phase, the same questionnaire was used one month later. The results showed a significant difference between the groups in post test and follow up phases. Cognitive-behavior

therapy seems to be effective on anger and its subscales such as failure and aggression, and also leads to alleviate them. It also improved the relationship between these children with their peers and superiors.

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Revista Brasileira de Psiquiatria. 2015;37:289-95.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND INTELLECTUAL GIFTEDNESS: A STUDY OF SYMPTOM FREQUENCY AND MINOR PHYSICAL ANOMALIES. *Minahim D, Rohde LA*.

To evaluate the presence of symptoms of attention deficit and hyperactivity disorder (ADHD) in intellectually gifted adults and children.

Methods: Two cross-sectional studies were performed in children and adults whose intelligence quotient (IQ) had been previously evaluated using Raven's Progressive Matrices (RPM) test. Seventyseven adults displaying IQ scores above the 98th percentile were assessed using the Adult Self- Report Scale (ASRS-18) for signs of ADHD and a modified Waldrop scale for minor physical anomalies (MPAs). Thirty-nine children (grades 1-5) exhibiting IQ scores above the 99th percentile, as well as an equally matched control group, were assessed for ADHD by teachers using the Swanson, Nolan and Pelham IV Rating Scale (SNAP-IV) as used in the NIMH Collaborative Multisite Multimodal Treatment Study of Children with AttentionDeficit/Hyperactivity Disorder (MTA-SNAP-IV).

Results: In gifted adults, the frequency of ADHD-positive cases was 37.8%, and the total MPA score was significantly associated with ADHD ($p<0.001$). In children, the ADHD-positive case frequency was 15.38% in the gifted group and 7.69% in the control group (odds ratio [OR] = 2.18, $p = 0.288$).

Conclusions: The high frequency of ADHD symptoms observed, both in gifted adults and in gifted (and nongifted) children, further supports the validity of this diagnosis in this population. Furthermore, the significant association between MPAs and ADHD suggests that a neurodevelopmental condition underlies these symptoms

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Semin Fetal Neonatal Med. 2015 Feb;20:52-57.

IMPACT OF BILIRUBIN-INDUCED NEUROLOGIC DYSFUNCTION ON NEURODEVELOPMENTAL OUTCOMES. *Wusthoff CJ, Loe IM*.

Bilirubin-induced neurologic dysfunction (BIND) is the constellation of neurologic sequelae following milder degrees of neonatal hyperbilirubinemia than are associated with kernicterus. Clinically, BIND may manifest after the neonatal period as developmental delay, cognitive impairment, disordered executive function, and behavioral and psychiatric disorders. However, there is controversy regarding the relative contribution of neonatal hyperbilirubinemia versus other risk factors to the development of later neurodevelopmental disorders in children with BIND. In this review, we focus on the empiric data from the past 25 years regarding neurodevelopmental outcomes and BIND, including specific effects on developmental delay, cognition, speech and language development, executive function, and the neurobehavioral disorders, such as attention deficit/hyperactivity disorder and autism

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Sleep Med. 2015;16:S108.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND NARCOLEPSY IN CHILD. Qu S, Xu L.

Introduction: To explore the co-occurrence of narcolepsy and attention deficit hyperactivity disorder (ADHD) symptoms and compare the damage of cognitive function and improvement after treatment of methylphenidate hydrochloride for 8-16weeks between narcolepsy with and without ADHD.

Materials and methods: Three hundred eight child narcolepsy patients (232 males and 76 females, with a range between 5 and 17 years old) were selected from outpatients at the People's Hospital, Peking University, from February 2011 to July 2013. All of them underwent polysomnography (PSG) followed by the

multiple sleep latency test (MSLT). Epworth Sleepiness Scale (ESS) was completed. All patients were interviewed by a psychiatrist according to DSM-IV diagnostic criteria through Mini International Neuropsychiatric Interview for children and adolescents (MINI Kid). Meanwhile, we compared ecological executive function between narcolepsy with and without ADHD through Behavior Rating Inventory of Executive Function - Parents Version (BRIEF-P). Narcolepsy with ADHD symptoms were treated with 9-18 mg methylphenidate hydrochloride for 16 weeks and completed ADHD rating scale (ADHDRS) and ESS. **Results**: Narcolepsy with ADHD symptoms was 27.92% (86/ 308). Subtype: ADHD-I: 94% (81/86), ADHDC: 6% (5/86), ADHDH: 0% (0/86). It was much higher than the prevalence of ADHD in Mainland China (3.17.8%). There were no difference between narcolepsy with and without ADHD in performance in MSLT and the number of SOREM. In ecological executive function, BRIEF-P after Bonferroni testing correction, narcolepsy with ADHD had a higher score than without ADHD in total scale, Behavioral Regulation Index and Metacogniton Index, as well as all eight factors of inhibition, shift, emotion control, initiation, work memory, plan, self monitoring and organization ($p < 0.05$). Fifty-six of 86 (65%) insisted methylphenidate hydrochloride for 16 weeks. After treatment, score of ESS was lower (13 ± 2) than before (17 ± 2) (t: 7.951, $p < 0.001$) but no change before and after therapy in ADHD-RS ($p > 0.05$).
Conclusion: ADHD is very common in children with narcolepsy, and the overlap of two disorders, results in more severe deterioration in executive functiony. Treatment strategies need to be adjusted for narcolepsy with ADHD

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Social Neuroscience. 2015 Nov;10:583-91.

PROCESSING OF AFFECTIVE PROSODY IN BOYS SUFFERING FROM ATTENTION DEFICIT HYPERACTIVITY DISORDER: A NEAR-INFRARED SPECTROSCOPY STUDY.

Köchel A, Schöngaßner F, Feierl-Gsodam S, et al.

Neurobiological studies on facial affect recognition have demonstrated reduced response amplitudes to anger cues in patients suffering from attention deficit hyperactivity disorder (ADHD). It is still unclear whether a similar deficit exists in the auditory domain. Therefore, this near-infrared spectroscopy study focused on neuronal correlates of affective prosody processing. Fourteen boys suffering from ADHD and fourteen healthy boys were exposed to emotionally intoned, standardized sentences of the categories anger, sadness, happiness, and to affectively neutral sentences. Relative to controls, the patients displayed a diminished activation of the right superior temporal gyrus (STG) when processing anger prosody, which was correlated with aggressive behavior. There were no group differences for the other emotions. Additionally, the ADHD group showed increased supramarginal gyrus (SMG) activation in the anger condition. This might mirror compensatory attention allocation. In summary, we identified a selectively lowered STG activation to auditory anger cues in ADHD patients. Consequently, STG recruitment during anger exposure might be used for evaluation of psychotherapy effects.

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Soc Sci Med. 2016;150:248-55.

SELF-PATHOLOGIZING, SELF-CONDEMNING, SELF-LIBERATING: YOUTHS' ACCOUNTS OF THEIR ADHD-RELATED BEHAVIOR.

Honkasilta J, Vehmas S, Vehkakoski T.

This study analyzes the discursive construction of attention deficit hyperactivity disorder (ADHD) and self in relation to a socioculturally shared understanding of moral norms. Thirteen Finnish youth aged 11 to 16 diagnosed with ADHD were interviewed during this discourse analysis study. The youth accounted for their culturally undesirable behavior, performance and traits through three different types of accounts: (1) externalizing personal responsibility due to a compelling medical condition, (2) internalizing personal responsibility through moral self-condemnation, and (3) distancing oneself from the socially imposed stereotypes and stigmas related to ADHD. This study challenges dominant understanding of young people with a diagnosis of ADHD and contributes to our understanding of how ADHD is constructed in their lives

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Transl Psychiatry. 2016;6.

ABSENCE OF EVIDENCE FOR INCREASE IN RISK FOR AUTISM OR ATTENTION-DEFICIT HYPERACTIVITY DISORDER FOLLOWING ANTIDEPRESSANT EXPOSURE DURING PREGNANCY: A REPLICATION STUDY. *Castro VM, Kong SW, Clements CC, et al.*

Multiple studies have examined the risk of prenatal antidepressant exposure and risk for autism spectrum disorder (ASD) or attention-deficit hyperactivity disorder (ADHD), with inconsistent results. Precisely estimating such risk, if any, is of great importance in light of the need to balance such risk with the benefit of depression and anxiety treatment. We developed a method to integrate data from multiple New England health systems, matching offspring and maternal health data in electronic health records to characterize diagnoses and medication exposure. Children with ASD or ADHD were matched 1:3 with children without neurodevelopmental disorders. Association between maternal antidepressant exposure and ASD or ADHD liability was examined using logistic regression, adjusting for potential sociodemographic and psychiatric confounding variables. In new cohorts of 1245 ASD cases and 1701 ADHD cases, along with age-, sex- and socioeconomic status matched controls, neither disorder was significantly associated with prenatal antidepressant exposure in crude or adjusted models (adjusted odds ratio 0.90, 95% confidence interval 0.50-1.54 for ASD; 0.97, 95% confidence interval 0.53-1.69 for ADHD). Pre-pregnancy antidepressant exposure significantly increased risk for both disorders. These results suggest that prior reports of association between prenatal antidepressant exposure and neurodevelopmental disease are likely to represent a falsepositive finding, which may arise in part through confounding by indication. They further demonstrate the potential to integrate data across electronic health records studies spanning multiple health systems to enable efficient pharmacovigilance investigation

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Trials. 2015;16.

COGNITIVE REHABILITATION FOR ATTENTION AND MEMORY IN PEOPLE WITH MULTIPLE SCLEROSIS: STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL (CRAMMS). *Lincoln NB, das NR, Bradshaw L, et al.*

Background: People with multiple sclerosis have problems with memory and attention. Cognitive rehabilitation is a structured set of therapeutic activities designed to retrain an individual's memory and other cognitive functions. Cognitive rehabilitation may be provided to teach people strategies to cope with these problems, in order to reduce the impact on everyday life. The effectiveness of cognitive rehabilitation for people with multiple sclerosis has not been established.

Methods: This is a multi-centre, randomised controlled trial investigating the clinical and cost-effectiveness of a group-based cognitive rehabilitation programme for attention and memory problems for people with multiple sclerosis. Four hundred people with multiple sclerosis will be randomised from at least four centres. Participants will be eligible if they have memory problems, are 18 to 69 years of age, are able to travel to attend group sessions and give informed consent. Participants will be randomised in a ratio of 6:5 to the group rehabilitation intervention plus usual care or usual care alone. Intervention groups will receive 10 weekly sessions of a manualised cognitive rehabilitation programme. The intervention will include both restitution strategies to retrain impaired attention and memory functions and compensation strategies to enable participants to cope with their cognitive problems. All participants will receive a follow-up questionnaire and an assessment by a research assistant at 6 and 12 months after randomisation. The primary outcome is the Multiple Sclerosis Impact Scale (MSIS) Psychological subscale at 12 months. Secondary outcomes include the Everyday Memory Questionnaire, General Health Questionnaire-30, EQ5D and a service use questionnaire from participants, and the Everyday Memory Questionnaire-relative version and Carer Strain Index from a relative or friend. The primary analysis will be based on intention to treat. A mixed-model regression analysis of the MSIS Psychological subscale at 12 months will be used to estimate the effect of the group cognitive rehabilitation programme.

Discussion: The study will provide evidence regarding the clinical and cost-effectiveness of a group-based cognitive rehabilitation programme for attention and memory problems in people with multiple sclerosis.

Trial registration:ISRCTN09697576. Registered 14 August 2014

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Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie. 2015 Nov;43:425-31.

EXPRESSED EMOTION, MUTTER-KIND-BEZIEHUNG UND ADHS-SYMPTOME IM VORSCHULALTER: EINE STUDIE ZUR VALIDITÄT DES DEUTSCHSPRACHIGEN PRESCHOOL FIVEMINUTE SPEECH SAMPLE. = EXPRESSED EMOTION, MOTHER-CHILD RELATIONSHIP, AND ADHD SYMPTOMS IN PRESCHOOL—A STUDY ON THE VALIDITY OF THE GERMAN PRESCHOOL FIVE MINUTE SPEECH SAMPLE.

Schloß S, Schramm M, Christiansen H, et al.

An inadequate parent-child relationship with hostility, low warmth, and a lack of responsiveness/sensitivity on the part of the primary caregiver often accompanies a child's externalizing disorders and predicts a negative developmental course. The Preschool Five Minute Speech Sample (PFMSS) was developed to enable an economic assessment of components of an inadequate parent-child relationship. In this article we investigate aspects of the validity of the German version of the PFMSS. We analyze whether the PFMSS scales are associated with observed maternal sensitivity, symptoms of attention deficit-/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and maternal depressive symptoms. The sample consists of n = 114 families with 4- to 5-year-old children, whereof n = 65 (57%) show heightened ADHD-symptoms. The families were recruited from local kindergardens. Maternal sensitivity was assessed by observing the motherchild interaction at home. ADHD, ODD, and maternal depressive symptoms were measured by clinical interviews and questionnaires. Most of the PFMSS scales showed the expected associations with maternal sensitivity, ADHD, and ODD symptoms of the child. The German PFMSS thus validly captures significant components of an inadequate mother-child relationship within the context of preschool externalizing behavior problems

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P.1.c.012 Open-label study comparing the efficacy and tolerability of aripiprazole and risperidone in the treatment of children with autism spectrum disorder and ADHD

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Introduction: Autism Spectrum Disorders (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are frequently overlap-

ping severe neurodevelopmental disorders. Individuals with co-occurring ASD and ADHD symptoms are more severely impaired, with relevant deficits of social processing, adaptive functioning and executive control [1]. Despite not FDA-approved for treatment of ADHD, atypical antipsychotic medications such as risperidone (2006) and aripiprazole (2009) are FDA-approved for treatment of disruptive behavior disorder including aggression and severe behavioral problems in ASDs. Among atypical antipsychotics, risperidone and aripiprazole, seem to be effective in reducing irritability, stereotypy and hyperactivity in patients with ASDs [2]. The aim of the study is to evaluate and compare the efficacy and tolerability of these two drugs on ASD and ADHD comorbid patients after 6 months of treatment.

Method: 23 children (18 boys and 5 girls) were included in the study. The mean age was 8.9 years (SD ±2.8) in the aripiprazole group and 7.2 years (SD ±2.0) in the risperidone group. Children were evaluated before starting treatment (T0), and after 3 months (T1) and 6 months of treatment (T2). Conners' Parent Rating Scales–Revised (CPRS-R), Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS), Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), and Children's Global Assessment Scale (C-GAS) were administered at each step of treatment to assess the effectiveness of medication, as primary outcomes. The secondary outcomes were: QT-interval prolongation on Electrocardiography (ECG), blood pressure, pulse, body weight, height, body mass index, abdominal circumference, fasting blood glucose, insulin and lipid levels, prolactin, and other general blood tests). Further, the Abnormal Involuntary Movement Scale (AIMS) was administered to assess drug-related dyskinetic adverse effects. Results were compared between Risperidone and Aripiprazole groups and within the single groups. Both groups showed significantly lower scores on hyperactivity/inattention rating scales (ADHD-RS, CPRS-H and CPRS-D) after 24 weeks of treatment.

Results: After the first 12 weeks of treatment, both groups had a significant reduction of the CGI – severity global (CGI-S $p < 0.001$). Aripiprazole and risperidone appeare to have similar benefits in terms of efficacy and tolerability. Compared to risperidone, the benefit of aripiprazole treatment seems significantly greater at 12 weeks but this difference doesn't persist at 24 weeks. This could indicate a faster positive effect of Aripiprazole compared to Risperidone. Both drugs were well tolerated with no serious adverse events detected. In our sample we found an average weight gain of 4 kg for patients treated with risperidone and 1.6 kg for patients treated with aripiprazole [3].

Conclusions: Our research confirms the efficacy of Aripiprazole and Risperidone in ameliorating symptoms of children with complex co-morbidities such as ASD and ADHD, even if the two drugs have shown slight differences in efficacy and tolerability. It's required an accurate knowledge of comorbidity between the two disorders in order to plan appropriate treatments that can be effective on both the specific symptoms and the overall functioning [4–5].

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P.1.c.013 Evaluation of acute cardiovascular effects of immediate-release methylphenidate in children with ADHD: A new electrocardiographic T-waves marker

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Introduction: Attention deficit/hyperactivity disorder (ADHD) is a common behavioural disorder characterized by symptoms of inattention, impulsivity and hyperactivity that impact several domains of the life of patients, their family, and society [1]. Treatments and interventions for ADHD are different and include psychological therapies and pharmacological treatment, especially for severe clinical cases. Immediate release (IR) MPH is considered the gold-standard of psychopharmacotherapy for patients ADHD [2]. Stimulants have been associated with increased cardiovascular risk, due to rise in blood pressure and heart rate (HR) [3]. Furthermore, immediate release IR-MPH has raised concerns about potential cardiovascular adverse effects within a few hours after administration.

This study was carried out to investigate acute effects of IR-MPH on ECG in a pediatric population and in particular by measuring the acute effects of IR-MPH on the ventricular repolarization through TpTe and TpTe/QT intervals, along with QTc and QTd. Recent studies indicate that prolongation of the interval between the peak and the end of the T wave (T-peak to T-end, TpTe) on the 12-lead ECG can represent a new marker of ventricular arrhythmogenesis [4]. The prolongation of the TpTe interval, measured in lead V5, is considered independently associated with sudden cardiac death, and it can be a suitable risk indicator even when the QTc is within range or not measurable due to prolonged QRS duration [5].

Methods: A total of 60 consecutive patients with ADHD (54 males and 6 females; mean age= 11.9 years DS + 3.3, range 6–19 years), receiving a new prescription of MPH, underwent a standard ECG 2 hours before and after the administration of IR-MPH 10 mg per os. Basal and post-treatment ECG parameters, including mean QT (QTc), QT dispersion (QTd) interval duration, Tp-Te intervals and TpTe/QT ratio were compared.

Results: No clinically significant changes were observed using our cardiological parameters after methylphenidate treatment. Significant modifications of both QTc and QTd values were not found after drug administration. A significant variation in blood pressure (BP) (Systolic BP 105.7±10.1 mmHg vs 109.9±11.1 mmHg; $p<0.1$; Diastolic BP 59.1±7.3 mmHg vs

63.8±8.5 mmHg; $p < 0.01$) was observed, but all the data were within normal range. Also in HR and in TpTe values was found a statistically significant increase from T0 to T1. HR moved from 81.1 + 15.4 bpm to 88.4+ 18.1 bpm. TpTe/QTc intervals were changed with respect to basal values (0.209 +0.016 ms vs 0.215 +0.019 ms; $p < 0.01$). No patient exhibited values exceeding the clinical intervals.

Conclusions: The findings of this study show no significant changes in ECG parameters within 2 hours after IR-MPH administration. TpTe values can be an additional parameter to evaluate borderline cases. It's important to investigate the cardiac effects of stimulants when associated with other concomitant drugs, especially in patients with high burden of cardiovascular disease.

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P.7.d.005 Effects of methylphenidate on height in ADHD children. The monitoring of bone age within the ADDUCE project

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Background: CNS stimulants represent the most effective medication in improving the core symptoms of ADHD, however in the last 30 years, there has been increasing concern about the risks associated with these medications in particular with respect possible growth deficits [1]. Although poor growth is a common concern, especially with children already on the lower growth percentiles, the impact of medication on growth and pubertal maturation has remained somehow unclear and stimulants effects at different ages have not been extensively investigated. Many unanswered questions remain about the biological mechanism underlying the growth deficit in medicated ADHD subjects, some of the hypothesis considering that the condition of ADHD per se is associated to an impaired growth condition [2].

Objectives: To evaluate, within the prospective, longitudinal, pharmacovigilance, EU funded project ADDUCE, whether ADHD children exhibit an abnormal pattern of growth per se before starting stimulant medication, whether methylphenidate (MPH) interferes with growth in medicated ADHD children and finally to explore the application of monitoring of bone age as a helpful tool in order to study adverse developmental effects of MPH.

Methods: Height, Weight, BMI, Target Height, pubertal stage and X-ray of left wrist were collected from 36 drug naïve ADHD children, aged 6–12, at three time points of the ADDUCE longitudinal protocol: baseline visit and after 12 and 24 months.

Results: Baseline data analysis revealed normal growth parameters for the ADHD population: height Z-score was 0.33 ± 1.19, weight Z-score 0.52 ± 1.97, BMI Z-score 1.57 ± 2.68 and the Target Height Z-score -0.82 ± 0.88, resulting even slightly taller than expected. The bone age calculated by comparing each of 20 bones of an X-ray of the left hand with the Tanner and Whitehouse II method showed no significant differences between the bone age (8.11 ± 2.19) and the chronological age (8.85 ± 1.77) although about the 61% of subjects reported a slightly lower bone age than expected (7.23 ± 1.61). Same results have been evidenced by the analysis of carpal bone (CB 8.51 ± 2.10) and radio ulna and short bones (RUS 7.67 ± 2.29). Only one subject has presented a Tanner pubertal stage G4 with a testicular volume of 12 cc, with no significant abnormalities of the bone age. No significant differences have been found by further dividing the sample for gender, age (6–10 vs 10–12 years old) or bone age (normal, low or increased).

Analysis of the growth parameters and bone age collected at the follow up visits are in due course and will be presented during the conference.

Discussion: Results from the present sample reveal that ADHD children presents with a normal growth pattern before starting medication confirming that a possible impact on growth, in particular with respect to height, could be related more to stimulant medication than to the ADHD condition per se. The study of bone age and pubertal stage at follow up will allow to get more information about the growth outcome helping to clarify the effect of MPH with regards to height and pubertal maturation.

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24 ORE Sanità

26 gen.-1 feb. 2016

LA TRANSIZIONE ALL'ETÀ ADULTA DEI PAZIENTI E L'ESIGENZA DI UNA NUOVA ORGANIZZAZIONE DEI SERVIZI

Salute mentale, prendiamo per mano i giovani

La revisione sistematica della letteratura scientifica internazionale dei modelli, infrastrutture, politiche e programmi per la salute mentale dei pazienti al raggiungimento della maggiore età pubblicata sull'ultimo numero di European psychiatry evidenzia quanto ancora ci sia da fare per garantire appropriatezza e continuità nei vari percorsi di cura.

Il passaggio all'età adulta rappresenta una fase importante della vita delle persone, ma assume un rilievo ancora maggiore per i pazienti portatori di una patologia cronica, ancor più se complessa come è il caso dei disturbi neuropsichici dell'età evolutiva. I pazienti in carico ai servizi di neuropsichiatria infantile e dell'adolescenza sono il 5% della popolazione italiana di età inferiore ai 18 anni (circa 500.000 bambini e ragazzi) al compimento della maggiore età dovrebbero venire indirizzati ad analoghi servizi sanitari per l'adulto. In realtà, in circa due terzi dei casi non sono previsti servizi per l'adulto che garantiscano adeguate risposte sanitarie: è il caso delle persone con disabilità, che dopo i 18 anni sono considerate esclusivamente di competenza sociale e che quando presentano problemi sanitari complessi trovano risposte puntiformi per specifiche sintomatologie. Spesso, e per disturbi meno gravi come la dislessia e i disturbi di apprendimento, sono costretti a cercare supporto nel privato.

Un terzo dei pazienti invece, quelli con disturbi psichiatrici, vengono indirizzati ai servizi di psichiatria dell'adulto. Il passaggio è, nella maggioranza dei casi, traumatico (sia per il paziente che per la famiglia), anche perché improvviso (la data del compleanno), non previsto né preparato, e che spesso altera il difficile e faticoso controllo raggiunto del disturbo. Spesso il paziente (e la famiglia) non è informato, preparato, accompagnato o adeguatamente accolto nel nuovo servizio; il passaggio non è concordato e condiviso tra gli operatori. I pazienti e le loro famiglie si trovano abbandonati alla ricerca dei "nuovi" operatori e servizi referenti, per territorio e competenze, o rimbalzati dai servizi che dovrebbero accoglierli.

La situazione evidenziata e ribadita nel lavoro sopra citato non è esclusiva della realtà italiana e dell'area neuropsichiatrica: avviene prima del diciottesimo anno per il passaggio dal pediatra di famiglia al Mmg, avviene per il passaggio da uno specialista ad un altro per qualsiasi cronicità e complessa. I ruoli e le responsabilità di sostegno e accompagnamento sono spesso disattesi. In un servizio pubblico di carattere universalistico e in particolare per i percorsi di cura e tutela della salute mentale questa situazione è indice di diritti negati.

Ci sono diversi modelli di intervento applicati in particolar modo nei Paesi del Nord Europa, negli Stati Uniti, in Canada e in Australia, che necessitano, però, ancora di attenta valutazione in termini di costi, esiti, fattibilità, sostenibilità nel tempo, soddisfazione dei pazienti e familiari affinché si possano definire i protocolli più appropriati da applicare anche nei nostri servizi territoriali. Anche in Italia sono in corso alcune esperienze interessanti che necessitano di appropriata valutazione per poi proporne una generalizzazione al territorio nazionale.

La transizione tra servizi sanitari al compimento della maggiore età rimanda ad interventi di organizzazione, formazione e monitoraggio. Affinché questi siano appropriati è necessario disporre di stime attendibili del numero di pazienti e delle caratteristiche dei loro bisogni assistenziali, che ancora mancano. Tuttavia sarà davvero possibile migliorare, in termini di efficacia e mantenimento nel tempo, i percorsi terapeutici e assistenziali volti a rispondere ai bisogni di salute mentale dei bambini, degli adolescenti e delle loro famiglie solo con il pieno coinvolgimento e la condivisione di utenti, famiglie e operatori (sanitari e sociali). Temi ignorati dai decisori istituzionali, ma anche dimenticati da molti operatori locali.

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Metilfenidato e ADHD. Per quanto spesso criticabile sul piano metodologico e carente di dati sugli effetti nel lungo periodo, la letteratura indica la terapia farmacologica (principalmente il metilfenidato) come l'approccio più efficace al bambino con ADHD. Studi retrospettivi, inoltre, indicherebbero che questa terapia è efficace anche nel ridurre le conseguenze a distanza della malattia (incidenti, aumento di mortalità, insuccesso scolastico e sociale, criminalità). Un po' in controtendenza, una metanalisi basata sul metodo della *Cochrane* e pubblicata sul *BMJ* (Storebø OJ, et al. Methylphenidate for at-tention-deficit/hyperactivity disorder in children and adolescents: Cochra-ne systematic review with meta-analy-ses and trial sequential analyses of randomised clinical trials. *BMJ* 2015; 351:h5203) conclude ora che le evi-denze di efficacia del metilfenidato nell'ADHD sono in realtà modeste, di bassa qualità e di fatto limitate (e so-lo per il breve periodo) a due aspetti: il miglioramento del giudizio degli insegnanti sul comportamento del bambino e del giudizio dei genitori sulla qualità della vita del bambino stesso. Tutto questo comunque senza aumentato rischio dei temuti effetti collaterali maggiori (cardiologici soprattutto) e al prezzo invece di una aumentata frequenza di effetti collaterali minori, come disturbi del sonno e calo dell'appetito. Nel complesso si tratta di una metanalisi, svolta con molto rigore da professionisti della metanalisi, che ci invita a essere più diffidenti che convinti (*vedi* anche il commento negli Appunti di terapia sulle Pagine elettroniche di *Medico e Bambino* di questo mese). Lasciando qualche perplessità in chi con questi bambini ha a che fare quotidianamente. E, quotidianamente, ha la percezione che in molti casi il farmaco sia così clamorosamente efficace da poter essere considerato alla stregua di un farmaco "salvavita". Ma attenzione! È vero. Sull'efficacia, la *compliance* e la sicurezza del metilfenidato nel lungo periodo mancano evidenze basate su studi prospettici, su ampia casistica ben selezionata. E di questo dobbiamo tener conto e avere la capacità (e onestà) di discuterne con i genitori. Senza peraltro accondiscendere al pericoloso atteggiamento opposto di diffidenza e stigmatizzazione della terapia farmacologica. Il problema, infatti, non è tanto quello se il metilfenidato serve o no. Per sapere che serve, almeno nel breve periodo, non abbiamo bisogno di severe metanalisi. Il problema è invece quello di una diagnosi corretta e tempestiva (e la nostra legislazione che impone la supervisione dei centri di riferimento ci favorisce nel far bene rispetto a ogni altro Paese del mondo) e di un approccio specialistico che garantisca anche il riconoscimento delle eventuali comorbidità (disturbo d'ansia, tratto calloso anaffettivo, tratto autistico). E di conseguenza che garantisca anche la scelta del farmaco più adeguato (che in prima istanza, nel caso del prevalere del disturbo inattentivo sarà e dovrà essere inevitabilmente il più sperimentato e quindi il metilfenidato). Questo è il meglio che possiamo e dobbiamo fare. A fronte di evidenze incomplete, certo. E da implementare. Ma pur sempre a fronte delle evidenze che abbiamo e delle suggestioni che queste ci danno. E sarà bene agire, sempre, esattamente come se si trattasse di nostro figlio.

Murgia V, Marchetti F. Medico e Bambino Pagine Elettroniche 2016; 19(1)
http://www.medicoebambino.com/?id=AP1601_10.html

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APPUNTI DI TERAPIA

METILFENIDATO: EVIDENZE SUL SUO UTILIZZO NELL'ADHD

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L'articolo di Storebø e coll. di cui si parla in questo numero[1] è una revisione sistematica con metanalisi dei dati pubblicata sul *BMJ* di novembre scorso, che ha l'intento di rispondere al seguente quesito: "nei bambini e negli adolescenti, il metilfenidato è utile o dannoso per il trattamento dell'ADHD (*attention-deficit/hyperactivity disorder*)"? Lo stesso gruppo in novembre ha pubblicato la stessa revisione sul sito della Cochrane[2].

L'interesse per l'argomento è elevatissimo perché l'ADHD è il disturbo psichiatrico più comunemente diagnosticato e trattato nel bambino, con una prevalenza del 3,4%[1]. È un disturbo neurobiologico complesso, a forte componente genetica ed eziologia multifattoriale, con diagnosi esclusivamente clinica. Il disturbo, per il suo carattere persistente, causa una significativa compromissione del funzionamento dell'individuo e ha un impatto significativo sul suo contesto di vita e sulla società[3]. È documentato un rischio aumentato di incidenti e di morte per incidente nei bambini affetti da ADHD[4]. L'ADHD viene sempre più considerato come un disturbo psichiatrico anche dell'età adulta, con una elevata comorbidità con altri disordini psichiatrici[5].

Come ci fanno osservare gli Autori della revisione, nonostante il metilfenidato sia in uso da più di 50 anni, ancora non era stata condotta una revisione sistematica che riguardasse sia i benefici sia i potenziali rischi di questo farmaco. Ciò ha spinto gli Autori dell'articolo a condurre una revisione sistematica di tutti i trial clinici randomizzati (RCT) sull'argomento. I revisori hanno adottato la metodologia della Cochrane Collaboration (Cochrane Handbook) e le linee guida PRISMA.

È stata condotta una ricerca sui database elettronici per sperimentazioni cliniche parallele e crossover randomizzate che comparavano il metilfenidato con un placebo o con nessun intervento nei bambini e adolescenti con diagnosi di ADHD. Sono stati inseriti tutti i lavori rintracciati sino a febbraio 2015. I trial sono stati inclusi a prescindere dalla lingua, dall'anno di pubblicazione e dal fatto che fossero già stati pubblicati (*ndr si rimanda alla lettura dell'articolo originale per la descrizione esaustiva della metodologia adottata*).

Gli ***outcome primari*** erano: sintomi di ADHD (disattenzione, iperattività e impulsività) sia a breve termine sia a lungo termine, ed eventi avversi seri conseguenti all'uso del farmaco (morte, pericolo di vita, ricovero in ospedale o prolungamento della degenza ospedaliera esistente, disabilità persistente o grave, e qualsiasi evento medico importante che potrebbe aver messo a repentaglio la vita del partecipante o richiesto interventi per impedirlo).

Gli ***outcome secondari*** erano gli eventi avversi non gravi (tra cui variazioni della crescita, problemi cardiologici, neurologici, gastrointestinali, e problemi del sonno e dell'appetito), il comportamento generale e la qualità della vita (misurati con strumenti validati).

L'analisi ha incluso 38 studi a gruppi paralleli (5111 partecipanti, con una durata media del trattamento di 49 giorni) e 147 con crossover (7134 partecipanti, 14 giorni). L'età media dei partecipanti (su un totale di 12.245 pazienti) era di 9,7 anni. La maggior parte dei lavori è stata condotta in Paesi ad alto reddito.

Il rischio di bias era consistente, infatti nessuno degli studi a gruppi paralleli e solo 6 dei 147 trial con crossover avevano un basso rischio di bias in tutti i domini. In generale usando GRADE[6] gli Autori hanno valutato che la qualità delle evidenze era di livello molto basso (very low) per tutti gli outcome.

SINTOMI DELL'ADHD

Si è stabilito che un cambiamento di -6,6 punti nella scala di valutazione dei sintomi dell'ADHD (ADHD Rating Scale) potesse rappresentare una differenza minima clinicamente rilevante.

Dati sui sintomi erano presenti in 25 trial con gruppo parallelo e in 74 di quelli con crossover. L'analisi dei risultati di 19 trial con gruppo parallelo suggeriscono un

effetto positivo del metilfenidato sulla valutazione dei sintomi da parte degli insegnanti (differenza media standardizzata -0,77, Intervallo di Confidenza al 95% (IC 95%) da -0,90 a -0,64, 1698 partecipanti), corrispondente a una differenza media di **-9,6 punti** nella scala di valutazione dei sintomi dell'ADHD (IC 95% da -13,75 a -6,38), valore maggiore della differenza minima clinicamente rilevante di -6,6 punti.

Tutti e 19 i trial erano a elevato rischio di bias, principalmente per: presenza di conflitto di interesse, mancanza di cecità dei partecipanti, mancanza di cecità dei valutatori degli effetti dell'intervento, selezione nella pubblicazione dei dati, o bias di selezione. Il risultato del GRADE era "very low quality" per elevato rischio di bias ed eterogeneità degli studi. I risultati degli interventi erano influenzati dalla scala di valutazione utilizzata (test per differenze nei sottogruppi P=0,006).

Negli studi a lungo termine il metilfenidato sembra avere un efficacia minore (differenza media standardizzata -0,47, IC95% da -0,72 a -0,22, 1 trial, 253 partecipanti) se comparata con quella degli studi di breve durata (-0.81, IC 95% -0,94 a-0,68, 18 trial, 1445 partecipanti; test per la differenza tra sottogruppi, P=0,02).

ANALISI SU SOTTOGRUPPI

Né l'età né la comorbidità sembrano influenzare significativamente l'effetto del trattamento. Questo invece sembra venire influenzato in maniera significativa dal sottotipo di ADHD; infatti, è stato osservato un effetto maggiore nel tipo con disattenzione predominante. I dati da cui sono state tratte queste valutazioni, però, sono scarsi.

EVENTI AVVERSI MAGGIORI

È stato possibile inserire nell'analisi solo 9 trial a gruppi paralleli (4,9%) che riportavano eventi avversi maggiori. Dai risultati di questi trial emerge che il metilfenidato non era associato a un aumentato numero totale di eventi avversi maggiori (risk ratio: 0,98, IC 95%: 0,44 -2,22, 1532 partecipanti). Tutti i trial erano a elevato rischio di bias. Il risultato del GRADE era "very low quality". Tuttavia, i dati sugli eventi avversi maggiori non avevano molta forza statistica ed inoltre, non sono disponibili dati sulla incidenza a lungo termine di questo tipo di eventi.

EVENTI AVVERSI MINORI

Gli Autori hanno potuto inserire nell'analisi 26 studi con gruppi paralleli (14%) che riportavano eventi avversi minori. Il metilfenidato aveva un rischio più elevato di causare un numero maggiore di eventi avversi minori (risk ratio 1,29; IC 95%: 1,10 -1,51; 21 trial, 3132 partecipanti).

Tra gli eventi avversi registrati si ritrovano problemi a carico dei sistemi neurologico, digestivo, urinario, circolatorio, respiratorio, riproduttivo, muscoloscheletrico e immunologico, oltre che differenze in altezza, peso, BMI, e segni vitali. I segni più comuni erano: **riduzione dell'appetito** (risk ratio: 3,66; IC 95%: 2,56-5,23; 16 trial, 2962 partecipanti) e **problemi del sonno** (risk ratio: 1,60, IC 95%: 1,15-2,23, 13 trials, 2416 partecipanti). Tutti i trial erano a elevato rischio di bias principalmente per effetto di mancanza di cecità dei partecipanti, mancanza di cecità dei valutatori, presenza di conflitto di interesse, dati di outcome incompleti, selezione nella pubblicazione degli outcome. Il risultato del GRADE era "very low quality".

Anche nei 67 trial con crossover, che riportavano eventi avversi minori alla fine del secondo periodo, il metilfenidato aveva un rischio più elevato di causare un numero maggiore di eventi avversi (risk ratio: 1,33; IC 95%: 1,11-1,58; 21 trial, 2072 partecipanti).

COMPORTAMENTO GENERALE

Gli insegnanti hanno valutato che il comportamento generale del bambino migliorava con il metilfenidato (differenza media standardizzata -0,87, IC 95% da -04 a -0,71, 5 trial, 668 partecipanti). Anche dagli studi con crossover emergerebbe un effetto favorevole del trattamento (differenza media standardizzata -0,69, IC 95% da -0,78 a-0,60, 16 trial, 2014 partecipanti).

QUALITÀ DELLA VITA

Solo 3 studi con gruppo parallelo hanno indagato la qualità della vita. È stato riscontrato un piccolo effetto benefico sulla qualità della vita (differenza media standardizzata 0,61, IC 95% da 0,42 a 0,80, 3 trial, 514 partecipanti), che corrisponde a una variazione del *Child Health Questionnaire* (CHQ) di 8 punti, maggiore della differenza minima clinicamente rilevante di 7,0 punti.

Anche questi 3 studi avevano un rischio di bias di vario tipo e un GRADE "very low quality".

DISCUSSIONE

In questa metanalisi e analisi sequenziale dei RCT è stato osservato che il metilfenidato riduce i sintomi dell'ADHD in bambini e adolescenti. È stato osservato anche un possibile piccolo effetto benefico sulla qualità della vita e il comportamento generale. L'effetto del metilfenidato sia sulla scala di valutazione dell'ADHD sia sul Child Health Questionnaire dovrebbero essere considerati clinicamente rilevanti se ci si basa sulle differenze minime prestabilite nel protocollo. L'uso del metilfenidato è associato, in generale, a un rischio relativamente elevato di eventi avversi minori che riguarderebbe più di ¼ dei bambini trattati. Nonostante siano stati descritti eventi avversi maggiori durante l'assunzione del metilfe-

nidato (morte cardiaca improvvisa e altri problemi cardiaci), la metanalisi non ha dimostrato che il farmaco sia associato a questi eventi nel trattamento di breve durata. La forza dei dati sugli eventi avversi maggiori è però scarsa e mancano informazioni che hanno previsto un follow up di lungo termine. I dati ottenuti devono essere valutati nel contesto di un basso livello di qualità degli studi inseriti. Solo 6 dei 185 trial sembravano essere a ridotto rischio di bias. Un altro problema potrebbe essere il rischio di riconoscimento del trattamento attivo con metilfenidato, e quindi l'assenza di cecità, a causa dei numerosi e facilmente riconoscibili effetti collaterali del farmaco.

PUNTI DI FORZA E LIMITI DELLO STUDIO

A detta degli Autori questa revisione sistematica ha numerosi punti di forza e qualche punto di debolezza. I punti di forza sono: aver sviluppato un protocollo secondo le istruzioni del *Cochrane Handbook for Systematic Reviews of Interventions*, aver pubblicato il protocollo prima di iniziare il lavoro di revisione, aver ricercato i dati in modo estensivo e accurato, aver utilizzato in generale un metodologia rigorosa.

Possono essere considerati limiti dello studio: non avere consultato i siti del FDA e del EMA alla ricerca di trial non pubblicati; la durata media degli studi breve (meno di 2 mesi), pochi trial avevano una durata di più di 6 mesi. Comparando gli studi a breve termine con quelli a lungo termine (più di 6 mesi) l'effetto del farmaco a giudizio degli insegnanti sui sintomi dell'ADHD (ADHD Rating Scale) decresceva con il tempo di durata dello studio. Questo non succedeva quando i sintomi venivano valutati da valutatori indipendenti e dai genitori.

CONCLUSIONI DEGLI AUTORI

Il metilfenidato somministrato a bambini e adolescenti affetti da ADHD potrebbe migliorare i sintomi del ADHD, il comportamento generale e la qualità della vita. Il farmaco nel trattamento a breve termine non sembra causare una aumentato rischio di eventi avversi maggiori, mentre il trattamento è associato a un rischio relativamente aumentato di eventi avversi minori. Questi risultati dovrebbero essere interpretati alla luce di parecchie limitazioni metodologiche degli studi e quindi di una conseguente qualità delle evidenze molto bassa per tutti gli outcome.

Sono necessari più trial clinici randomizzati controllati senza rischi di bias e con un placebo attivo (da condurre prima negli adulti) perché si possano trarre conclusioni definitive sul trattamento con il metilfenidato nei bambini e adolescenti affetti da ADHD.

COMMENTO

Dalla lettura di questo importante lavoro di revisione di Storebø e coll. emerge chiaramente che gli Autori non hanno potuto trarre conclusioni definitive sull'efficacia del metilfenidato, a causa della scarsa qualità dei pur numerosi studi analizzati (N=185).

Fazel, in un editoriale apparso nello stesso numero del BMJ[7], sostiene che "i risultati della revisione sono potenzialmente importanti e allo stesso tempo confondenti per i clinici e i milioni di famiglie interessate dal problema" e suggerisce di leggere i risultati di questa revisione nel contesto della letteratura complessiva sull'ADHD e alla luce di 4 aree da enfatizzare:

1) La ricerca su questo problema, uno dei più comuni disturbi del neurosviluppo, è in condizioni critiche, anche per la mancanza di fondi. Le cose sono complicate dalla mancata integrazione della ricerca con i servizi di erogazione delle cure.
2) È necessario prendere in considerazione numerosi disegni di ricerca, comprendendo anche ricerche osservazionali e qualitative che riportino il punto di vista dei pazienti e di chi li cura. Le revisioni Cochrane purtroppo includono solo i RCT.
3) La percentuale di pazienti che hanno manifestato eventi avversi è inferiore a quella che ci si aspetterebbe clinicamente. Per i dati sugli eventi avversi maggiori potrebbero essere utili studi osservazionali e database di prescrizione.
4) Nonostante le conclusioni degli Autori, c'è un consenso di clinici e linee guida sugli effetti benefici del metilfenidato sui sintomi di ADHD a breve termine.

In condizioni come l'ADHD, dice Fazel, decidere l'uso clinico appropriato di un farmaco non è un compito facile. I clinici dovrebbero definire interventi "tagliati su misura del bambino-adolescente con ADHD" che considerino la comprensione dei modelli neurocognitivi del problema, i potenziali effetti sui neurotrasmettitori del metilfenidato e i risultati di evidenze osservazionali di elevata qualità.

La domanda centrale è la seguente: i clinici possono permettersi di attendere i risultati di altri studi di buona qualità per decidere, secondo coscienza, se iniziare un trattamento farmacologico in un bambino con diagnosi "altamente probabile o certa" di ADHD?

Nel prendere la decisione è di non poca importanza considerare che questa condizione:

- causa una significativa compromissione del funzionamento dell'individuo e ha un impatto significativo sul suo contesto di vita e sulla società (aumentato rischio di disturbo della condotta e oppositivo-provocatorio, di insuccesso sociale, incidenti, criminalità e uso di sostanze).

- tende a protrarsi nell'età adulta con sintomi che variano a seconda dell'età considerata e il non trattamento nella infanzia potrebbe avere riflessi negativi su tutta la vita.
- i bambini con ADHD hanno un rischio di incidenti e una mortalità per incidente aumentati rispetto agli altri bambini. Il trattamento farmacologico (98% dei casi con metilfenidato) ha ridotto sino al 43% il rischio di lesioni e sino al 45% le visite al Pronto soccorso nei bambini affetti da ADHD a 12 anni[8].

Alla luce di queste considerazioni e pur nella consapevolezza che le evidenze sono di bassa qualità, i clinici, in presenza di una diagnosi di ADHD "altamente probabile o certa", potrebbero avere minore incertezza nell'iniziare il trattamento farmacologico e cognitivo-comportamentale, a patto di monitorarne attentamente l'efficacia e la sicurezza a breve e lungo termine con registri e database condivisi. Il Registro nazionale italiano e della Regione Lombardia sull'ADHD[9] sono stati a riguardo sicuramente utili, ma tra luci ed ombre. L'epidemiologia indica con chiarezza che i Centri di riferimento della Regione Lombardia (come praticamente in ogni Regione d'Italia) non riescono a intercettare in maniera adeguata i pazienti con tale disturbo. Lascia in particolare stupiti soprattutto il bassissimo numero di pazienti inseriti in terapia farmacologica. I dati del Registro lombardo riportano che tra i pazienti con sottotipo combinato solo il 20% riceve una terapia farmacologica, l'80% un intervento psicologico, il 20%, in apparenza, nessun intervento. Il parere di alcuni esperti italiani di ADHD è che "tali strumenti (quelli dei Registri, ndr), ideati per migliorare appropriatezza e corretta gestione di un disturbo frequente e invalidante, sembrano aver contribuito in maniera significativa a una sorta di mascheramento diagnostico (in alcuni stimolato forse dalla conseguente possibilità di poter così non prescrivere un farmaco ritenuto forse utile ma difficile da gestire) e alla conseguente negazione di un importante bisogno di salute, per il quale da anni sono disponibili strumenti terapeutici altamente efficaci e sicuri"[10].

La metanalisi pubblicata sul BMJ, anche questa tra luci ed ombre, ci dice chiaramente che la strada anche farmacologica nel bambino con ADHD deve essere pensata e intrapresa nei casi meritevoli di trattamento anche farmacologico, insieme necessariamente ad altri interventi di tipo cognitivo-comportamentale, senza più alibi e reticenze che sono più di tipo ideologico che di vero bisogno assistenziale.

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