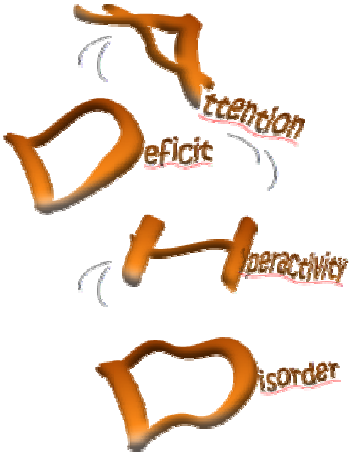
NEWSLETTER



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ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD OTTOBRE 2014

American Journal of Managed Care. 2014;20.

IMPACT OF ATYPICAL ANTIPSYCHOTIC USE AMONG ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sikirica V, Pliszka SR, Betts KA, et al.

Objectives To compare treatment patterns, resource utilization, and costs to US third-party payers of stimulant-treated adolescent attentiondeficit/ hyperactivity disorder (ADHD) patients who switched to or augmented with atypical antipsychotics (AAPs; not FDA-indicated for ADHD) with those who switched to or augmented with nonantipsychotic medications

Study Design Retrospective cohort study conducted using a US commercial medical/pharmacy claims database.

Methods Adolescent patients with an ADHD diagnosis and (greater-than or equal to)1 stimulant medication claim between January 2005 and December 2009 were identified. Patients were classified into the AAP or non-antipsychotic cohorts based on subsequent claims for AAPs or nonantipsychotic medications, respectively. Patients with psychiatric diagnoses for which AAPs are often prescribed were excluded. Patients were matched 1:1 from the AAP to the non-antipsychotic cohort using propensity score matching. Treatment patterns, resource utilization, and costs in the 12 months after AAP or non-antipsychotic initiation were compared using Cox models, Poisson regression, and Wilcoxon signedrank tests, respectively

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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.

Results After propensity score matching, a total of 849 adolescents were included in each of the matched cohorts. Patients in the AAP cohort had a significantly higher rate of medication augmentation (27.7% vs 15.5%; hazard ratio = 2.56; 95% confidence interval [CI], 1.90-3.46; P <.001) than patients in the non-antipsychotic cohort. The AAP cohort also had significantly higher incidences of inpatient admissions (0.13 vs 0.05; incidence rate ratio [IRR] = 2.45; 95% CI, 1.73-3.48; P <.001), emergency department visits (0.39 vs 0.31; IRR = 1.27; 95% CI, 1.08-1.49; P = .004), and outpatient visits (14.82 vs 13.19; IRR = 1.12; 95% CI, 1.10-1.15; P <.001), and incurred significantly higher mean annual medical ($3622 vs $3311; P = .002), drug ($4314 vs $2884; P <.001), and total healthcare ($7936 vs $6195; P <.001) costs.
Conclusions Stimulant-treated adolescents with ADHD who switched to or augmented with AAPs had significantly greater drug augmentation, healthcare resource utilization, and costs compared with the non-antipsychotic cohort. Atypical antipsychotics (AAPs) are one of the most common and costly classes of prescription drugs, with annual expenditures exceeding $13 billion, representing nearly 5% of all drug expenditures in the US.1,2 AAPs are approved by the FDA for the treatment of schizophrenia, behavioral symptoms in autism, and mixed or manic bipolar disorder, and the benefits and risks of AAPs are well documented for these indications.3 However, AAP use for off-label indications has rapidly increased, and now accounts for the majority of AAP utilization.4,5 A recent study found that AAP use in children grew by 62% from 2002 to 2007.6 Due to the potential side effects of AAP use and limited clinical evidence regarding the efficacy and safety of such off-label uses, the utilization of atypical antipsychotics for off-label indications is controversial.5,7,9 Among studies of off-label AAP use, heightened attention has been paid to attention-deficit/hyperactivity disorder (ADHD), as almost a third of offlabel AAP use is related to this condition.7-9. ADHD can pose a significant barrier to personal development and cause substantial psychological difficulties for patients and their families if left untreated.10 There are many pharmacologic treatment options for ADHD, including stimulants and non-stimulants, which have well-established efficacy and safety profiles.11 Conversely, the risks and benefits of AAP use in current clinical practice for ADHD are largely unknown.12 The few clinical studies that investigated AAP use in ADHD patients are confounded by patient comorbidities for which AAPs may be appropriate, and are therefore difficult to interpret.13-16 However, the pediatric population appears to be at higher risk than adults for AAPinduced adverse events including weight gain, elevation in prolactin levels, extrapyramidal symptoms, sedation, and cardiac events.1,8,19 Additionally, there is limited evidence regarding the real-world economic outcomes of AAP use for ADHD, and recent literature has called for further investigation of the health outcomes in pediatric populations.6 A companion study examined this effect in children aged 6 to 12 years with ADHD, finding that patients who utilized AAPs had higher rates of drug switching and augmentation, greater medical resource utilization, and higher total healthcare costs compared with patients who used nonantipsychotic therapies.20 However, no peer-reviewed publications have investigated the economic costs of AAP use specifically in adolescents with ADHD. There is evidence that both the rates of ADHD diagnosis and AAP prescription for ADHD can vary by age category, which indicates the need for specific attention to the adolescent subpopulation.5,7,9,21. Therefore, the purpose of this study was to compare, from a US third-party payer perspective, treatment patterns, resource utilization, and healthcare costs of stimulanttreated adolescents with ADHD who switched to or augmented their stimulant treatment with AAPs, versus those who did the same with non-antipsychotic medications.

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Ann Neurol. 2014;76:S226-S227.

GLUTAMATE AND GABA IN CHILDREN WITH ADHD AND COMPLEX MOTOR STEREOTYPIES: A 7T 1H MRS STUDY.

Singer HS, Mahone EM, Horska A, et al.

Objective: Motor stereotypies are repetitive, rhythmic, fixed, purposeful but purposeless movements that stop with distraction. Previously thought to be secondary to autism, intellectual disability, or sensory deprivation, complex motor stereotypies (CMS) can also occur in otherwise typically developing children. Existing data suggests that nullprimarynull CMS is a motor control abnormality localized within cortico-striatal-thalamo-cortical pathways. This study evaluated the hypothesis of cortical hyper-excitability (elevated glutamatergic or reduced GABAergic neurotransmission) using single-voxel magnetic resonance spectroscopy to measure brain glutamate (Glu) and GABA concentrations.

Methods: Medication free participants included 24 typically developing children (mean 7.561.4 years, 14 girls) and 19 with primary CMS (mean 6.761.3 years, 3 girls). MRI/MRS, preceded by 10-20 minutes of mock scanner training, was performed at 7T. Single voxel 1H MRS (TR/ TE/TM53000/14/26 ms, SW53000 Hz, 2048 datapoints, NS596) data were acquired in 5-9 ml voxels in the left anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), premotor cortex (PMC) andstriatum (STR). Concentration ratios to creatine (Cr) were calculated and linear mixed-effect model analysis was used to examine group differences in metabolite concentrations, controlling for age and sex.
Results: The MRI/MRS protocol (45-60 min) was welltolerated. GABA/Cr was significantly lower in CMS (ageadjusted mean: 0.1960.06) than controls (0.2460.07, p=0.004). The ACC (p=0.009) and STR (p<0.015) showed significant reductions in GABA/Cr. No group differences in Glu/Cr were observed. Figure 1.
Discussion: High-field MRS studies can assist in understanding the pathophysiology of movement disorders and guide the development of pharmacotherapy. Our study suggests that GABA metabolism may be impaired in children with primary complex motor stereotypies. Conclusions: High-field MRS studies can assist in understanding the pathophysiology of movement disorders and guide the development of pharmacotherapy. Our study suggests that GABA metabolism may be impaired in children with primary complex motor stereotypies.

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Ann Neurol. 2014;76:S189.

PHYSICAL COMORBIDITY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AMONG US ADOLESCENTS.

Lateef TL, Sheppard B, He J, et al.

Objective: To examine the pattern and extent to which other physical and developmental conditions are comorbid with ADHDin youth in a representative sample of the US population
Methods: The National Comorbidty Survey-Adolescent Supplement is a face-to-face surveys of adolescents aged 13- 18 years in the continental US. Sufficient information to assess the DSM-IV criteria for ADHD and all its subtypes was available in the diagnostic module. A caretaker/parental self-administered report was used to assess a broad range of other physical and developmental conditions, such as autism spectrum disorders and learning disability. The sample for these analyses was 6483 adolescents with systematic caretaker/ parent reports
Results: Adolescents with ADHD reported higher rates of other developmental disorders, including autism spectrum disorders (OR, 5.39; 95% CI, 2.40-12.08) and learning disability (OR 6.46; 95% CI, 4.72-8.83). Also, we report in a nationally representative sample that enuresis (OR, 1.95; 95% CI, 1.36-2.82), gastrointestinal problems (OR 2.06, 95% CI, 1.33-3.19), asthma (OR, 1.49; 95% CI, 1.04- 2.14) and seasonal allergies (OR, 1.39; 95% CI, 1.01-1.91) were more common in adolescents with ADHD compared to their unaffected counterparts.
Conclusions: Adolescent ADHDis associated not only with other developmental disorders such as learning disability and autism spectrum disorders that affect cognitive processes but may also be a manifestation of broader multisystem conditions that involve inflammatory/immune processes. Our findings suggest that comorbid medical conditions should be evaluated comprehensively in determining treatment options in youth with ADHD. Such comorbidity also could be an important source of the clinical and etiologic heterogeneity in ADHD.

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Ann Pharmacother. 2014;48:1350-55.

PRIAPISM ASSOCIATED WITH THE USE OF STIMULANT MEDICATIONS AND ATOMOXETINE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN.

Eiland LS, Bell EA, Erramouspe J.

Objective: To review the association of priapism with stimulant medications and atomoxetine commonly used in the treatment of attention-deficit/hyperactivity disorder (ADHD).

Data Sources: A comprehensive literature search was conducted through PubMed (1966-May 15, 2014) using the search terms priapism, methylphenidate, amphetamine, atomoxetine, attention-deficit disorder with hyperactivity, and pediatrics. Google Scholar, Scopus, and the Food and Drug Administration (FDA) Web site were also searched. References from identified literature were also reviewed.
Study Selection and Data Extraction: All identified literature focused on ADHD treatment. Literature regarding priapism caused by methylphenidate, amphetamines, and atomoxetine were included.
Data Synthesis: Stimulant medications and atomoxetine have been linked to the occurrence of priapism in children. Specifically, methylphenidate has been implicated in a recent FDA safety announcement warning as a result of 15 case reports (mean age = 12.5 years), and thus, the drug label and medication guides have been updated to reflect this concern. Prolonged erections and priapism occurred with immediate- and long-acting products, dose increases, and drug withdrawal periods. Priapism has also occurred in 4 patients taking amphetamines and one 11-year-old patient taking atomoxetine for ADHD.
Conclusions: Priapism has been associated with stimulants, amphetamines, and atomoxetine use for ADHD in children. Providers and health care practitioners should educate male patients prescribed these ADHD medications as well as caregivers regarding the signs, symptoms, and complications with priapism. Discontinuation and evaluation of the medication is warranted if this adverse drug reaction occurs. Depending on the priapism subtype, other products may be initiated or medications not associated with priapism may be utilized.

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Biol Psychol. 2014;103:125-34.

ALTERED NEUROPHYSIOLOGICAL RESPONSES TO EMOTIONAL FACES DISCRIMINATE CHILDREN WITH ASD, ADHD AND ASD + ADHD.

Tye C, Battaglia M, Bertoletti E, et al.

There are high rates of overlap between autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). Emotional impairment in the two disorders, however, has not been directly compared using event-related potentials (ERPs) that are able to measure distinct temporal stages in emotional processing. The N170 and N400 ERP components were measured during presentation of emotional face stimuli to boys with ASD (n=19), ADHD (n=18), comorbid ASD+ ADHD (n=29) and typically developing controls (n=26). Subjects with ASD (ASD/ASD+ADHD) displayed reduced N170 amplitude across all stimuli, particularly for fearful versus neutral facial expressions. Conversely, subjects with ADHD (ADHD/ASD+ADHD) demonstrated reduced modulation of N400 amplitude by fearful expressions in parietal scalp regions and happy facial expressions in central scalp regions. These findings indicate a dissociation between disorders on the basis of distinct stages of emotion processing; while children with ASD show alterations at the structural encoding stage, children with ADHD display abnormality at the contextual processing stage. The comorbid ASD. +. ADHD group presents as an additive condition with the unique deficits of both disorders. This supports the use of objective neural measurement of emotional processing to delineate pathophysiological mechanisms in complex overlapping disorders.

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BioMed Research International. 2014.

EMOTION RECOGNITION PATTERN IN ADOLESCENT BOYS WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER.

Aspan N, Bozsik C, Gadoros J, et al.

Background. Social and emotional deficits were recently considered as inherent features of individuals with attention-deficit hyperactivity disorder (ADHD), but only sporadic literature data exist on emotion recognition in adolescents with ADHD. The aim of the present study was to establish emotion recognition profile in adolescent boys with ADHD in comparison with control adolescents.
Methods. Forty-four adolescent boys (13-16 years) participated in the study after informed consent; 22 boys had a clinical diagnosis of ADHD, while data were also assessed from 22 adolescent control boys matched for age and Raven IQ. Parent- and self-reported behavioral characteristics were assessed by the

means of the Strengths and Difficulties Questionnaire. The recognition of six basic emotions was evaluated by the "Facial Expressions of Emotion-Stimuli and Tests."
Results. Compared to controls, adolescents with ADHD were more sensitive in the recognition of disgust and, worse in the recognition of fear and showed a tendency for impaired recognition of sadness. Hyperactivity measures showed an inverse correlation with fear recognition.
Conclusion. Our data suggest that adolescent boys with ADHD have alterations in the recognition of specific emotions.

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Child Psychiatry Hum Dev. 2014 Oct;45:533-43.
SLEEP–WAKE PATTERNS REPORTED BY PARENTS IN HYPERACTIVE CHILDREN DIAGNOSED ACCORDING TO ICD-10, AS COMPARED TO PAIRED CONTROLS.
Gomes AA, Parchão C, Almeida A, et al.
This study aimed primarily to compare the parent-reported sleep of children with ICD-10 hyperkinetic disorder (HKD) versus community children. Thirty children aged 5–13 years (83.3 % boys) diagnosed with HKD by their child and adolescent psychiatrists took part in this study, plus 30 community children, matched for sex, age, and school year. Compared to the controls, the HKD children showed significantly later bedtimes, stronger bedtime resistance, longer sleep latency, shorter sleep; more frequent behaviors and symptoms concerning falling asleep into parents bed, needing something special to initiate sleep, nightmares, sleep talking, sleep bruxism, fear from darkness, bedwetting, and, most notably, loud snoring (26.7 %); they also tended to show higher daytime somnolence. Attention deficit/hyperactivity disorder (ADHD)/HKD children may thus have more sleep-related problems than typically developing children. Alternatively, our results may reflect misdiagnoses; thus, special attention should be directed to comorbidity and differential diagnosis issues between sleep disturbances and ADHD/HKD.

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Compr Psychiatry. 2014;55:1601-08.
THE ASSOCIATION OF INTERNET ADDICTION SYMPTOMS WITH ANXIETY, DEPRESSION AND SELF-ESTEEM AMONG ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Yen C-F, Chou W-J, Liu T-L, et al.
Conclusions Prevention and intervention programs for Internet addiction in adolescents with ADHD should take anxiety, depression, and self-esteem into consideration
Method A total of 287 adolescents aged between 11 and 18 years who had been diagnosed with ADHD participated in this study. Their severity of Internet addiction symptoms was assessed using the Chen Internet Addiction Scale. Anxiety and depression symptoms and self-esteem were assessed using the Taiwanese version of the Multidimensional Anxiety Scale for Children (MASC-T), the Center for Epidemiological Studies Depression Scale (CES-D), and the Rosenberg Self-Esteem Scale (RSES), respectively. The association between the severity of Internet addiction symptoms and anxiety and depression symptoms and self-esteem were examined using multiple regression analyses
Background The aims of this study were to examine the associations of the severity of Internet addiction symptoms with various dimensions of anxiety (physical anxiety symptoms, harm avoidance, social anxiety, and separation/panic) and depression symptoms (depressed affect, somatic symptoms, interpersonal problems, and positive affect) and self-esteem among adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) in Taiwan
Results The results indicated that higher physical symptoms and lower harm avoidance scores on the MASC-T, higher somatic discomfort/retarded activity scores on the CES-D, and lower self-esteem scores on the RSES were significantly associated with more severe Internet addiction symptoms.

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Curr Allergy Asthma Rep. 2014 Nov;14:469.

ROLE OF OBESITY IN OTITIS MEDIA IN CHILDREN.

Ahmed S, Arjmand E, Sidell D.

The ongoing childhood obesity epidemic has garnered significant attention among healthcare providers due to its short- and long-term sequelae. Multiple diseases have been associated with obesity, not limited to hypertension, diabetes, and attention deficit hyperactivity disorder. Over the past decade, the relationships between obesity and otologic conditions have been investigated. In this setting, otitis media has remained the focus of research, representing one of the most common pediatric illnesses. Initial studies suggesting a relationship between the two conditions have been supported with epidemiological studies controlling for socioeconomic factors. The purpose of this article is to review our current understanding of the relationship between otitis media and obesity and to discuss the healthcare implications of this association. In addition, several identifiable factors associated with each condition are discussed, as are potential pathophysiologic mechanisms that may help to elucidate the complex and multifactorial relationship between the two disease entities.

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Dev Cognitive Neurosci. 2014;10:104-16.

DIFFERENTIATING NEURAL REWARD RESPONSIVENESS IN AUTISM VERSUS ADHD.

Kohls G, Thonessen H, Bartley GK, et al.

Although attention deficit hyperactivity disorders (ADHD) and autism spectrum disorders (ASD) share certain neurocognitive characteristics, it has been hypothesized to differentiate the two disorders based on their brain's reward responsiveness to either social or monetary reward. Thus, the present fMRI study investigated neural activation in response to both reward types in age and IQ-matched boys with ADHD versus ASD relative to typically controls (TDC). A significant group by reward type interaction effect emerged in the ventral striatum with greater activation to monetary versus social reward only in TDC, whereas subjects with ADHD responded equally strong to both reward types, and subjects with ASD showed low striatal reactivity across both reward conditions. Moreover, disorder-specific neural abnormalities were revealed, including medial prefrontal hyperactivation in response to social reward in ADHD versus ventral striatal hypoactivation in response to monetary reward in ASD. Shared dysfunction was characterized by fronto-striato-parietal hypoactivation in both clinical groups when money was at stake. Interestingly, lower neural activation within parietal circuitry was associated with higher autistic traits across the entire study sample. In sum, the present findings concur with the assumption that both ASD and ADHD display distinct and shared neural dysfunction in response to reward.

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Environ Int. 2014 Oct;71:29-35.

ACCESS TO URBAN GREEN SPACES AND BEHAVIOURAL PROBLEMS IN CHILDREN: RESULTS FROM THE GINIPLUS AND LISAPLUS STUDIES.

Markevych I, Tiesler CM, Fuertes E, et al.

AIM: We investigated whether objectively measured access to urban green spaces is associated with behavioural problems in 10-year old children living in Munich and its surrounding areas.

METHODS: Behavioural problems were assessed in the GINIplus and LISAplus 10-year follow-up between 2006 and 2009 using the Strengths and Difficulties Questionnaire. Access to green spaces was defined using the distance from a child's residence to the nearest urban green space. Associations between access to urban green spaces and behavioural problems were assessed using proportional odds and logistic regression models in 1932 children with complete exposure, outcome and covariate data.

RESULTS: The distance between a child's residence and the nearest urban green space was positively associated with the odds of hyperactivity/inattention, especially among children with abnormal values compared to children with borderline or normal values (odds ratio (OR)=1.20 (95% confidence interval (CI)=1.01-1.42) per 500 m increase in distance). When stratified by sex, this association was only statistically significant among males. Children living further than 500 m away from urban green spaces had

more overall behavioural problems than those living within 500 m of urban green spaces (proportional OR=1.41 (95% CI=1.06-1.87)). Behavioural problems were not associated with the distance to forests or with residential surrounding greenness.
CONCLUSION: Poor access to urban green spaces was associated with behavioural problems in 10-year old children. Results were most consistent with hyperactivity/inattention problems.

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Epidemiol Psychiatr Sci. 2014 Sep;1-9.
PREVALENCE OF SEVERE ADHD: AN EPIDEMIOLOGICAL STUDY IN THE ITALIAN REGIONS OF TUSCANY AND LATIUM.
Donfrancesco R, Marano A, Calderoni D, et al.
Background. The rate with which attention deficit/hyperactivity disorder (ADHD) is diagnosed varies widely across countries, suggesting that cultural factors influence the clinical interpretation of child behaviour. This study estimated the point prevalence of severe ADHD among elementary and middle-school Italian children.
Method. An epidemiological sample of 2016 children attending 2nd-8th grade in the Italian regions of Tuscany and Latium was selected based on census distribution of the school-age population. Teachers completed the Italian version of the ADHD Rating Scale for Teachers (SDAI). For children with at least six inattention symptoms and/or at least six hyperactivity/impulsivity symptoms rated 'very often' by the teachers, the parents completed the Italian ADHD Rating Scale for Parents (SDAG). Children with documented ADHD symptoms at both school and home received a complete psychiatric interview with the Kiddie Schedule for Affective Disorders and Schizophrenia-present and lifetime version (K-SADS-PL).
Results. Of the 1887 assessed children, 4.45% (95% CI 3.58-5.51) met the ADHD cut-off on teacher ratings, 1.43% (0.96-2.12) had ADHD symptoms endorsed by both teacher and parent, and 1.32% (0.87-1.97) were further confirmed by the psychiatric evaluation. The male:female ratio was 7:1. The inattentive type accounted for about half of the ADHD cases.
Conclusions. When applying stringent criteria for both severity and pervasiveness of symptoms, it is estimated that about 1.3% of the Italian elementary and middle-school children suffer from severe ADHD.

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Eur Neuropsychopharmacol. 2014;24:S717.
THE ROLE OF NEUROPSYCHOLOGICAL ASSESSMENT IN ADHD CHILDREN.
Petrica S, Druga S.
Objective: According to specific guidelines, ADHD diagnosis is usually based on standardized rating scales, parent and teacher reports and observing the child's behavior in various settings (school, family, peer relations). However, giving that ADHD is a neuro-developmental disorder consisting of impaired attention and working memory skills, poor impulse control and different behavioral problems, neuropsychological assessment might be useful for a more comprehensive understanding of the child's difficulties (language processing, learning disorders, sensory problems, social and emotional difficulties etc.). The present paper aims to identify correlations between ADHD severity, social and family functioning, school behavior and performance and neuropsychological deficits in ADHD children.
Method: The study involved evaluation of number of hospital admissions, social and familial environment, peer relations, child's behavioral problems in school, academic achievements and relation with neuropsychological deficits (attention and executive functions, working memory, learning, language, visuospatial and sensorimotor functions) in 97 ADHD patients, aged 6 to 14 years. Individuals with IQ<80 and somatic or neurological comorbidities were excluded from our clinical sample. Patient assessment was carried out based on Child Behaviour Checklist, ADHD-RS - parent version, Vanderbildt Assessment Scale - teacher version and neuropsychological assessment tests - Nepsy.
Results: There were significant statistical correlations ($p<0.05$) between attention/executive functioning and parental bonding/family relationships ($p = 0.04$) and also between sensorimotor functioning and school behavioral problems of the child ($p = 0.0007$). Language processing was statistically significant correlated to parental bonding/family relationships ($p = 0.006$) and also with child's academic achievement ($p =$

0.013). There were no statistically significant correlation between ADHD severity, school performance, child's behavior and working memory and learning skills, visuospatial and language processing, sensorimotor or attention/executive functioning in the studied sample. Neuropsychological impairment depending on the age of the subjects, we found the poorest results in terms of sensorimotor functioning at the age of 11 years (60% of children having results far below the expected level for age) and also at the age of 6 years (when 50% of children had results far below the expected level for age). At the age of 11 years children achieved the poorest results in executive function/attention (60% of children had borderline results considering the expected level for age) and also at the age of 7 years, 43.78% of children achieved results far below the expected level for age.
Conclusions: Familial factors play an important role in occurence of both behavioral and emotional difficulties in children and also in more complex cognitive processes. Understanding and identifying these risk factors should be useful for developing effective intervention strategies in ADHD children. The neuropsychological assessment is useful in providing a better undestanding of child's strengths and difficulties and may help considering preventive interventions in children's neuropsychiatric disorders associated with neuropsychological impairment in order to improve social and academic functioning.

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Eur Neuropsychopharmacol. 2014;24:S352-S353.

GENDER DISTRIBUTION, SUBTYPES AND OTHER ASSOCIATED CONDITIONS OF ADHD IN SCHOOL POPULATION AGED 6-12 YEARS-A CROSS SECTIONAL STUDY.

Sushevska PL.

Background: 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. It is diagnosed twice more often in boys than in girls. 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 be accompanied by other disorders, such as oppositional defiant disorder, conduct disorder, anxiety or depression.
Methods: The study was done on a sample of 400 schoolchildren. Presence of ADHD symptoms was estimated using the Vanderbilt Assessment Scale, with teachers and parents as informants, and a specifically designed questionnaire for collecting sociodemographic data. There were 211 boys and 189 girls. Information about the pupils was collected from the pupils' teachers and parents.
Results: According to the teacher rating scale, a subtype of attention deficit and the opposite-defiant disorder were dominant conditions. From the parent rating scale - predominantly hyperactive/ impulsive type of disorder, as well as the oppositional-defiant disorder. Our results showed that boys more often have ADHD symptoms compared to girls (boys:girls ratio = 2:1). The results of this screening study showed that in 84 (21%) respondents the symptoms of the disorder in the activity and attention were registered. According to the statements of teachers 60 (15%) of the analyzed children, opposed to 46 (11.5%) children, according to statements of parents, had ADHD symptomatology. The difference in the number of respondents with and without ADHD assessed by teachers or parents is statistically insignificant ($p>0.05$). According to the teacher scale, the predominant subtype of attention deficit dominates in 38 (63.3%) respondents, while 17 (28.3%) participants were diagnosed with ODD. The same number and percentage of respondents, 14 (23.3%), have combined inattention/ hyperactivity type of ADHD and anxiety or depression, while in one subject, according to this scale, there was a predominantly hyperactive/impulsive type. According to the parent scale, ADHD was represented with predominantly hyperactive/impulsive type of disorder reported in 19 (41.3%) students. ODD (oppositional defiant disorder) was also registered in 19 (41.3%) respondents. Eleven (23.9%) students were diagnosed with predominant type of attention deficit. Combined inattention/hyperactivity type, according to this scale, was reported in 4 (8.7%) participants, while conduct disorder was registered in one participant.
Conclusion and Discussion: The difference in the number of children with ADHD after the statements of parents and teachers is probably due to uncritical and biased attitude of the parents in assessing their children, or the inability of parents to recognize their children's deviations from normal behaviour. In terms of the predomination of symptoms after the statements of teachers, deficit of attention subtype is prominent. The reason is because the monitoring and development of teaching requires attention, sitting

quietly in the chair, following the instructions of the teacher with children who have difficulties with ADHD. In home environment, parents refer to predominantly of greater freedom of behaviour. In the class, students compare themselves with other peers and respect the rules of behaviour for the given situation. This was the reason of more common presence of the oppositional-defiant disorder at home.

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Eur Neuropsychopharmacol. 2014;24:S442-S443.

THE NEUROCOGNITIVE PROFILE IN ADULT BIPOLAR DISORDER AND ADHD.

Tan D, Yilmaz T, Ersan F, et al.

Purpose: Bipolar disorder (BD) and adult attention deficit hyperactivity disorder (ADHD) may present with overlapping symptoms, making the differential diagnosis a challenging task. Neurocognitive deficits have been proposed as vulnerability markers or endophenotypes for BD. Compared to the high number of studies which investigated neurocognitive deficits in children with ADHD, little is known about the neurocognitive performance of adults with ADHD. The study aims to evaluate neurocognitive profiles of adults with ADHD in comparison to BD and healthy controls.

Methods: Twenty-nine consecutive patients with adult ADHD, 31 euthymic patients with DSM-IV BD type-I or II who were in remission for 6 months, and 56 healthy controls (HC) with no personal or family history of psychiatric illness were included in the study. All participants aged between 18-65 years. Clinical condition of the participants was confirmed through Structured Clinical Interview for the DSM-IV-TR Axis I Disorders (SCID-I) [1]. Information on demographics, clinical characteristics and treatment history of BD patients was registered by using the standardized registration program for bipolar disorders-Turkey (SKIP-TURK) forms [2]. Bipolar patients needed to be scoring 7 or less on both the validated and reliable Turkish versios of the Young Mania Rating Scale (YMRS) and the 21-item Hamilton Depression Rating Scale (HAM-D 21). Continious variables were analysed using ANOVA with post-hoc Bonferroni correction. Chisquare test was used for the assessment of categorical variables.

Results: The mean age of the patients with ADHD, BD, and HC groups was, 27.28(plus or minus) 8.03, 43.0(plus or minus)13.29 and 35.43(plus or minus)11.77 years respectively. (p<0.001). Forty-eight point three percent (n = 14) of the ADHD, 80.6% (n = 25) of the BD, and 41.1% (n = 23) of the HC was composed of females (p = 0.002). The level of education in years was 15.13(plus or minus)2.88 in ADHD, 11.93(plus or minus)3.66 in BD and 13.62(plus or minus)3.46 in HC. The level of education differed significantly only between BD and ADHD (p <0.001). BD performed worse than ADHD and HC on Rey Auditory Verbal Learning Task (RVLT), immediate and delayed figure performance, trail A and B, digit backwards, digit symbol, and Stroop tests. Both BD and ADHD groups performed similar to each other and worse than HC on auditory consonant triagram, verbal fluency, category fluency and Stroop tests. BD did worse than HC on digits forward test. Primarily, education had a strong impact on most of the neurocognitive tests.

Conclusions: Our findings support the concept that both ADHD at adult age and BD share some common cognitive deficits while they differ in some others. The better performance of ADHD patients over BD on RVLT, immediate and delayed figure performance, trail A and B, digit backwards, digit symbol, and semantic facilitation tests may provide empirical support to further differentiate the neuropsychological profile of BD and adult ADHD patients and pave the way for the use of neuropsychological assessment for differential diagnosis, complementary to the clinical interview [3]

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Eur Neuropsychopharmacol. 2014;24:S728-S729.

OPPOSITE EFFECTS OF ACUTE METHYLPHENIDATE ADMINISTRATION IN CHILDREN VERSUS ADULT ADHD PATIENTS DURING EMOTIONAL PROCESSING.

Ferguson B, Schrantee AGM, De Ruiter MB, et al.

Purpose: Children and adults diagnosed with attention-deficit hyperactivity disorder (ADHD) show deficits in their ability to accurately recognize facial expressions of emotions [1,2]. Emotion recognition is particularly associated with activity in the amygdala and connected prefrontal areas are modulated by

dopamine (DA) [3]. In children suffering from ADHD, treatment with stimulants such as methylphenidate (MPH), a drug that targets the DA system, has been shown to normalize increased activity in the amygdala during emotional processing [1]. However, in children the brain is still in development, and the effects of stimulants may therefore differ from adult ADHD patients. To this end, we assessed the effect of MPH on emotional processing in children and adults suffering from ADHD using functional magnetic resonance imaging (fMRI) during an emotion recognition task. We expected to find a reduction in activation following MPH administration in the amygdala. In addition, we expected that these effects are modulated by age.
Methods: fMRI data was collected as part of a randomized clinical trial (Netherlands Trial Register no NTR3103) in which medication-naive children and adults with ADHD (any subtype) were enrolled. Present preliminary analysis was conducted on participant's first visit data, as they performed a facial emotion- (fear and anger) and shape-recognition task in a 3.0T scanner, before and 90 minutes after an oral MPH challenge (0.5 mg/kg with a maximum of 20 mg in children and 40 mg in adults). 12 children (aged 10-12 years, all male) and 16 adults (aged 23-30, all male) were included in the analysis. fMRI data was pre-processed using FSL-FEAT (standard pre-processing) and regressors were modelled per participant according to facial emotion vs. shapes, per participant, per session. First level contrast images were analysed with a FEAT higher level analysis using wholebrain and region-of-interest (ROI on amygdala) statistics with cluster p = 0.05 FDR corrected.
Results: In both children and adults, recognition of fearful and angry faces induced reliable activation in bilateral amygdala and visual processing areas compared to the control task (viewing shapes). MPH administration in children led to a decrease in activation in the right fusiform gyrus. In adult patients, MPH induced a decrease in brain activity in bilateral fusiform gyrus, bilateral amygdala and various cortical regions. Although children and adults differed in the extent the amygdala was activated by MPH, the interaction effect was not significant. However, we did observe significant interaction effects in the left lateral occipital cortex and precentral gyrus: these brain structures were less active in children, but more active in adult ADHD patients following the challenge with MPH.
Conclusions: In line with previous studies, acute MPH administration reduced brain activation to emotional stimuli in children and adults with ADHD in various brain areas. Interestingly, we found that MPH induced small but opposite effects in specific brain regions of children when compared to adults during emotional processing. These findings suggest that the acute effects of DA agents such as MPH are dependent on age. In our ongoing trail we will obtain evidence whether chronic treatment with MPH also affects the developing brain differently than the developed adult brain.

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Eur Neuropsychopharmacol. 2014;24:S117.

EFFECTS OF PSYCHOTROPIC DRUGS IN THE ADHD BRAIN.

Rubia K, Cubillo AI, Chantiluke K, et al.

Our meta-analysis of positron emission tomography studies showed that long-term stimulant medication is associated with abnormally elevated striatal dopamine transporters, which are reduced in medication-naive patients with ADHD [1]. Parallel to this, our meta-regression analyses of whole-brain structural and functional magnetic resonance imaging studies (sMRI/fMRI) showed that stimulant medication is associated with normal basal ganglia volumes and function, which are abnormal in medication-naive patients with ADHD [2]. Our meta-analysis of acute stimulant effects showed that stimulants most consistently increase right inferior frontal cortex (IFC) and basal ganglia activation [3]. A direct placebo-controlled randomised comparison between Methylphenidate and Atomoxetine in medication-naive ADHD children showed that both drugs increase and normalise bilateral IFC activation during timing and inhibition, but Atomoxetine had a drug-specific effect on the activation/normalisation of the noradrenergically innervated dorsolateral prefrontal cortex (DLPFC) during working memory while Methylphenidate had a drug-specific effect on the dopaminergically innervated basal ganglia and supplementary motor area during timing and motor execution. Fluoxetine relative to placebo increased and normalised the reduced activation in ADHD children relative to controls in right DLPFC during working memory and in right IFC during inhibition, suggesting that Fluoxetine has similar frontal upregulation and normalisation effects to the two catecholamines. In conclusion, monoamine agonists appear to have positive effects on key biochemical,

structural and functional striatal and frontal abnormalities in ADHD, suggesting they may be underlying these abnormalities.

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Eur Neuropsychopharmacol. 2014;24:S727.

EFFECTS OF METHYLPHENIDATE ON COGNITION IN ADHD ACROSS THE LIFESPAN: PRELIMINARY RESULTS OF A META-REGRESSION ANALYSIS.

Tamminga H, Reneman L, Huizenga H, et al.

Purpose: Stimulants like methylphenidate (MPH) are the first choice of pharmacological interventions for children and adults with attention-deficit hyperactivity disorder [1]. However, the human brain is in development until the early 20's [2], and different behavioral responses to MPH have been shown for younger compared to older children [3]. This raises the question whether cognitive effects of MPH are related to the developmental stage of individuals with ADHD, and whether MPH effect might be associated with medication history of participants. Thus, the aims of the present meta-analysis were to determine whether the effect of MPH on cognitive functions is age-related, and whether medication naivety is associated with MPH effect.

Methods: Double-blind, placebo controlled trials, reporting data on the effects of MPH on response inhibition, working memory and sustained attention, were included in a meta-regression analysis. Only samples with an ADHD diagnosis were included. In order to ensure comparability of effect sizes across study designs, an estimated correlation between measurements of 0.5 was taken into account when calculating effect sizes of crossover designs. Age and medication naivety were included in the analysis as moderators.

Preliminary results: Forty-five studies (n = 1534) with 61 data points were included in the analyses, resulting in mean effect sizes of 0.41 for response inhibition (95% CI [0.22-0.61]), 0.27 for working memory (95% CI [-0.01-0.55]), and 0.45 for sustained attention (95% CI [0.26-0.63]). Effects of MPH on response inhibition and sustained attention were significant (both $p<0.0001$). The mean effect size for working memory was not significant ($p = 0.021$). Overall, age did not significantly moderate the effect of MPH ($QM = 0.02$, $df = 1$, $p = 0.90$), but an age- response relationship was found for working memory ($QM = 4.42$, $df = 1$, $p = 0.04$). The influence of medication naivety was assessed with single dose trials in which the population was either described as 100% naive (5 studies), or as 0% naive (8 studies). Medication naivety of samples was not a significant moderator of MPH effect ($QM = 0.34$, $df = 1$, $p = 0.56$).

Discussion: The present analysis shows moderate positive effects of MPH on response inhibition and sustained attention. The mean effect size for working memory studies was not significant. Interestingly, an age-response relationship was only found for working memory studies, with adult studies demonstrating larger effects. It is uncertain whether this reflects a heightened sensitivity to MPH of adult working memory, as this analysis only comprised two studies with adults and no studies with adolescents. This stresses the need for additional MPH trials with adolescents and adults. In addition, no relationship between naivety to stimulants and MPH effect was found, indicating that acute effects of MPH might be independent of treatment history.

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Eur Neuropsychopharmacol. 2014;24:S297-S298.

SUBCORTICAL SHAPE AND DIFFUSION TENSOR FINDINGS IN CHILDREN WITH ADHD WITH AND WITHOUT CO-EXISTING TIC DISORDER.

Go H, Choi J, Jeong B, et al.

Introduction: Attention deficit and hyperactivity disorder (ADHD) is a child-onset neurodevelopmental disorder, showing frequent co-existence with tic symptoms. Previous imaging studies have found hypoplastic changes of bilateral striatum in both ADHD and Tourette syndrome (TS) separately. However, relationship between two symptoms still left unveiled whether they have common etiology or not. We aimed to investigate unique features by comparing surface morphology and diffusion metrics between patients who suffered from ADHD with and without coexisting tic disorder.

Method: **Subjects**: We enrolled two groups of ADHD patients by advertisements targeted towards children who visit at child and adolescent psychiatric clinic in Deajeon St. Mary's Hospital. ADHD without co-existing tic disorder (AD, n = 18), and ADHD with Tourette syndrome (TS) or chronic tic disorder (ADT, n = 24). Considering age and gender difference in developmental trajectories of brain structure, only boys aged between 7 and 12 years were included in this study. In addition, eighteen age and gender matched typically developing children (TDC) were recruited by public advertisement. The St. Mary's Hospital IRB approved all procedures. The purpose and meaning of this study were explained to subjects and their parents, who gave their written informed consent.
Assessment protocol: Screening interview were performed by psychologist using Kiddie-Schedule for Affective Disorder Schizophrenia-Present and Lifetime Version (greater-than or equal to) Korean version (KSADS- PL-K) to rule out other co-morbidities. To measure severity of both ADHD and tic symptoms, Korean ADHD rating scale (K-ARS) and Yale global tic severity scale (YGTSS) were used, respectively. Using Siemens 1.5T MRI system, high resolution 3D magnetic resonance T1 images and diffusion weighted images with 12 gradient dimension were acquired from each subject.
Data analysis: Surface morphology and volumetric output of each subcortical structure were obtained by using the FIRST tool from FMRIB software library (FSL) version 5.0. Diffusion data were processed with Tract Based Spatial Statistics (TBSS) in FSL and diffusion metrics were acquired from 20 white matter tracts, using Johns Hopkins University White-Matter Tractography atlas. Statistical testing were performed by permutation test and ANCOVA after controlling for effect of age and intracranial volume.
Results: No demographic difference was found among groups ($P<0.001$). Both shrinkage of surface and volume decrease were prominent in right caudate of AD when compared to ADT ($p = 0.003$ and $p = 0.011$, respectively). In the regression analysis, decreased K-ARS score was correlated with shape deformities of both right ($p = 0.047$) and left ($p = 0.027$) caudate nucleus in AD group, but no significant correlation was found in ADT group. Additionally, both AD and ADT were found to have decreased axial diffusivity in left uncinate fasciculus, compared to TDC ($p = 0.006$ and $p = 0.040$, respectively).
Conclusions: Our resultssuggested that the right caudate shape can be a sensitive neuroimaging marker for coexisting tic disorder in ADHD, and the aberrant anatomical connectivity in left frontotemporal network is a distinguishing one between ADHD and TDC.

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Eur Neuropsychopharmacol. 2014;24:S117-S118.

DO ADHD RISK FACTORS ACT ON BRAIN CONNECTIVITY IN CHILDREN AND ADULTS WITH ADHD?

Franke B.

ADHD is among the most prevalent neurodevelopmental psychiatric disorders. With the frequent persistence into adulthood, the disorder imposes a strong burden on society. The etiology of ADHD is not well understood. Heritability plays a strong role in ADHD, and in most patients multiple genetic risk factors of small individual effect contribute to disease. Neuroimaging suggests subtle alterations in both structure and function of the brain in ADHD. Most of this work has been performed in children, and little is known about neural substrates of adult ADHD. It has been suggested that brain maturation is delayed, but our own studies show that some abnormalities persist into adulthood. Our recent international meta-analysis of subcortical brain structure based on MRI analyses in over 1500 cases and comparable numbers of controls performed as part of the ENIGMA consortium [1] confirms age-independent volume reductions in nucleus accumbens, amygdala, caudate nucleus, and putamen. In the IMpACT-NL study [2], we also find significant microstructural alterations in white matter connectivity in corpus callosum, corona radiata and thalamic radiation. Whether and how genetic ADHD risk factors act on brain measures is largely unexplored. We have shown that the risk variant of the NOS1 gene influences striatal activation during reward anticipation [3]. More recent studies suggest that MAOA modulates the functional connectivity between prefrontal cortex and amygdala, and that DRD5 risk factors might act on white matter connectivity in ADHD. Brain connectivity is likely to play an important role in ADHD and might be targeted by genetic ADHD risk factors.

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Eur Neuropsychopharmacol. 2014;24:S733-S734.

LISDEXAMFETAMINE DIMESYLATE: HYDROLYSIS, PHARMACOKINETICS AND DURATION OF THERAPEUTIC ACTION IN CHILDREN AND ADOLESCENTS WITH ADHD.

Hage A, Dittmann RW, Pennick M, et al.

Purpose of the study: Lisdexamfetamine dimesylate (LDX) is the first prodrug stimulant and the only long-acting amfetamine licensed in Europe for the treatment of attention-deficit/ hyperactivity disorder (ADHD). We now present the results of investigations into the site of LDX hydrolysis in human blood, the pharmacokinetic profile of plasma d-amfetamine following a single dose of LDX, and the duration of the therapeutic action of LDX throughout the day following an early morning dose.
Methods: Whole blood, plasma, and blood cell fractions were prepared from fresh human blood collected from 3 male donors and incubated in vitro with LDX (1 (mu)g/mL free base equivalent) in the absence or presence of enzyme inhibitors. NRP104.103 was a randomized, open-label, crossover study in which plasma d-amfetamine concentrations were determined after single doses of LDX 30 mg, 50 mg or 70 mg in children (aged 6-12 years) with ADHD [1]. SPD489-325 was a 7 week, randomized, double-blind, placebo-controlled trial of LDX (optimized daily dose of 30 mg, 50 mg or 70 mg) in children and adolescents (aged 6-17 years) with ADHD [2]. Osmotic-release oral system methylphenidate (OROS-MPH) was included as a reference treatment (optimized daily dose of 18 mg, 36 mg or 54 mg). At baseline and weeks 4 and 7, ADHD-related symptoms and behaviours were assessed using the Conners' Parent Rating Scale-Revised (CPRS-R) at approximately 10:00 hrs, 14:00 hrs and 18:00 hrs following dosing at 07:00 hrs. Comparisons of each active drug with placebo were pre-specified.
Results: In vitro data demonstrated that LDX was hydrolysed by peptidase activity in human red blood cell cytosol. In study NRP104.103 (N = 18), mean plasma d-amfetamine concentrations peaked 3.41-3.58 h post dose and declined with mean t1/ 2 in the range 8.61-8.90 h [1]. Of 336 patients randomized in SPD489- 325, 317 were included in the full analysis set. Baseline CPRS-R scores were similar across treatment groups. At endpoint (last on-treatment visit with valid data), both LDX and OROS-MPH treatment significantly ($p<0.001$) improved CPRS-R scores compared with placebo at 3 h, 7 h and 11 h post dose, with effect sizes of 1.424, 1.411 and 1.300 for LDX and 1.036, 0.976 and 0.922 for OROS-MPH.
Conclusions: For the first time, it was demonstrated that LDX hydrolysis occurs in red blood cell cytosol. The pharmacokinetic profile of d-amfetamine was consistent with the maintenance of efficacy of LDX throughout the day. This was confirmed by improved ADHD-related symptoms and behaviours in children and adolescents receiving LDX and OROS-MPH compared with placebo at all assessments 3 h to 11 h post dose.

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Eur Neuropsychopharmacol. 2014;24:S724-S725.

CHARACTERISTICS OF READMITTED ADHD CHILDREN WHO HAD NON-ADHERENCE TO MEDICATION BEFORE.

Sabuncuoglu O.

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a chronic neuropsychiatric disorder characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity. While psychosocial and/or psychopharmacological interventions are clearly recommended, non-adherence to treatment is a major problem in ADHD management [1]. However, some children or adolescents may be readmitted in time. Since certain aspects of this sub-group remain relatively unknown, this study was designed to investigate descriptive characteristics of the readmitted children with ADHD.
Methods: A retrospective chart review was undertaken of children and adolescents who had been admitted to child psychiatry between 2010 and 2013, in Istanbul/Turkey. The patient files were explored using relevant search terms in Turkish and English, relating to ADHD and study objectives. All of these children had been given diagnoses using DSM-IV criteria. The ADHD children who had a previous history of admission to any child psychiatry clinic were included in the study. Data of Conners Parent and Teacher Rating Scales, that had been given to assess behavioral disturbances, were used where appropriate. Data obtained from the study group was compared with data of ADHD children in their first admission. Chi-squared tests were used to compare categorical variables and t-tests were used to assess patterns involving continuous variables.

Results: Twenty-four (n = 24) children and adolescents with ADHD met the criteria for readmission. Failure in study and examination performance because of concentration difficulties was found to be a significant complaint in readmitted adolescents (n = 12; P<0.01). However, persistence of behavioral difficulties also constituted a sub-group as well. In this regard, search for alternative treatment options and clinicians was an obvious motivating factor (n = 10; P<0.01). Actual or potential adverse effects of stimulant (methylphenidate) or non-stimulant medications (atomoxetine) was an important predictor of non-adherence to treatment. Besides this, misinformation and disinformation about ADHD medications on the Internet and mass media had played a significant role in non-adherence to approved medications. The readmitted children were more likely to have a history of unproven alternative ADHD interventions (n = 6; P<0.0001). However, parents of readmitted children were more eager to use medication than their previous admission. Readmitted children scored lower on the Conners Parent and Teacher Rating Scales (P<0.01 and P<0.01, respectively).
Conclusion: Dropouts and readmissions of patients constitute an essential aspect of ADHD management. It has been reported that negative perceptions of the burden associated with medication use and subsequent adverse effects lead to poor adherence to treatment in ADHD [1,2]. The impact of those negative effects may be more pronounced in developing countries. In order to increase treatment adherence rates, there's a need to know more about the factors associated with readmission. Once the characteristics of 'come-back' children are well-described, the quality and continuity of care provided to ADHD children may be improved.

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Eur Neuropsychopharmacol. 2014;24:S721-S722.

DIVALPROEX SODIUM AND RISPERIDONE IN THE TREATMENT OF COGNITIVE, BEHAVIORAL AND SOCIAL DYSFUNCTION IN PRESCHOOL CHILDREN WITH PDD AND ADHD.

Martsenkovsky I.

There are currently no approved medications for either core (social and language deficits, and repetitive behaviors) or associated (irritability-aggression, hyperactivity/inattention) symptoms of autism [1]. There is a growing body of controlled evidence for pharmacologic intervention, and a summary of randomized controlled trials of medication in children with ASD is included [2-3]. Unfortunately, antipsychotics, antidepressants and antiepileptic drugs have many adverse effects limiting their long-term use inchild and adolescent psychiatric patients. The purpose of this study was obtaining data on the efficacy and safety of risperidone and divalproex sodium in preschool children with autism during sixteen week double blind controlled researches.
Methods used: Eighty-six children with autism, ages 3-6 years, were recruited at the Department of Child, Adolescent Psychiatry and Medical-Social Rehabilitation of Ukrainian Research Institutes Social Psychiatry and Drug Abuse. The diagnosis was made using DSM-IV criteria and confirmed by the Autism Diagnostic Interview (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS-G). Mean daily dosage of risperidone was 0.05- 0.01 mg/kg. The group with expressed behavioral symptoms or tics had significantly higher mean daily dosage (0.07 mg/kg) compared with other groups (0.047 mg/kg) with expressed language deficits. Mean daily dosage of divalproex sodium was dispensed in the form of sprinkles and titrated up to effect and/or valproate level between 50 and 100 pg/ml. Outcome measures included CGI-improvement (primary outcome measure), Overt Aggression Scale - Modified (OAS-M) and the Aberrant Behavior Checklist (ABC).
Summary of results: Primary target symptoms of risperidone were behavioral symptoms (64.5%) including aggression, impulsivity, hyperactivity, stereotypy nonresponsive to other psychiatric treatments, and chronic and severe tics (32.8%). The efficacy of risperidone was measured by clinical global improvement (CGI) of target symptoms, 67.7% of subjects showed moderate or marked improvements and its therapeutic effect appeared to be maintained during at least 5 months. There was statistically significant improvement in irritability in subjects treated with risperidone vs. divalproex sodium as measured by the CGI-improvement (p = 0.002, d = 1.46). The finding is supported by statistically significant differences noted in the secondary outcome measures: the Irritability subscale of the OAS-M (p = 0.005) and the irritability subscale of the ABC (teacher rating) (p = 0.05). Significant improvements were also noted in aggression as measured by the 'assault against objects' subs core of the OAS-M (p = 0.005). There were

no differential side effects between risperidone and divalproex sodium. A variety of adverse events were reported in this study [n = risperidone (divalproex sodium)]: weight gain [n = 2 (3)] most commonly reported, extrapyramidal symptoms [n = 2 (0)], autonomic symptoms [n = 6 (4)], sedation [n = 5 (8)] and symptoms related to hyperprolactinemia [n = 1 (0)] etc.
Conclusions: Results suggest that risperidone and divalproex sodium may be relatively safe and effective drug in managing a wide variety of preschool childrenpsychopathologies such as, behavioral symptoms including aggression, impulsivity, hyperactivity and stereotypy nonresponsive to other psychiatric treatments. Risperidone was more effective, than divalproex sodium.

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Front Human Neurosci. 2014;8.

THE EFFECT OF ALPHA-LINOLENIC ACID SUPPLEMENTATION ON ADHD SYMPTOMS IN CHILDREN: A RANDOMIZED CONTROLLED DOUBLE-BLIND STUDY.

Dubnov-Raz G, Khoury Z, Wright I, et al.

Background: Attention deficit-hyperactivity disorder (ADHD) is the most common neuro-developmental disorder in childhood. Its pharmacologic treatment mostly includes methylphenidate, yet many parents seek alternative, nullnatural,null therapeutic options, commonly omega-3 fatty acids. Previous studies of supplementation with fish oil or long-chain omega-3 fatty acids to children with ADHD yielded mixed results. The use of alpha-linolenic acid (ALA), a medium-chained, plant-based omega-3 fatty acid (18:3 n-3), has not been sufficiently examined in this population
Methods: Forty untreated children with ADHD, aged 6null16 years, were randomized to receive either 2 g/day of oil containing 1 g ALA or placebo, for 8 weeks. Before and after supplementation, the children underwent a physician assessment of ADHD symptoms and a computerized continuous performance functions test. The childrennulls parents and teachers filled out Connersnull and DSM questionnaires
Results: Seventeen (42.5%) children completed the study, eight in the supplementation group, nine in the placebo group. Main drop-out reasons were capsule size, poor compliance, and a sense of lack of effect. No significant difference was found in any of the measured variables tested before and after supplementation, in both study groups. No between-group difference was found in the changes of the various measures of ADHD symptoms throughout the study period
Conclusion: Supplementation of 2 g/day of oil containing 1 g ALA did not significantly reduce symptoms in children with ADHD. Future studies in this field should consider an alternative method to deliver the oil, a higher dose, and a larger sample size.

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Horm Res Paediatr. 2014;82:133-34.

EFFECTS OF METHYLPHENIDATE ON GROWTH AND APPETITE IN ATTENTION-DEFICIT HYPERACTIVITY PATIENTS.

Gurbuz F, Gurbuz BB, Celik G, et al.

Background: Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric problems of adolescent and childhood. Methylphenidate is a psychostimulant drug in use of attention-deficit hyperactivity treatment as a first choice modality.
Objective and hypotheses: The aim of this study is to evaluate the levels of leptin, ghrelin and nesfatin-1 in relation to slowdown in growth and poor appetite.
Method: Total of 89 male children at the age of 7-14 years in two groups was conducted in this study; 48 ADHD and 41 age-matched control group without any disorder. Leptin, ghrelin and nesfatin-1 levels were measured by ELISA together with anthropometric measurements before and after 3 months of the methylphenidate treatment. Additionally, IGF1 and IGFBP3 levels were evaluated. Results were expressed as mean(plus or minus)S.D., median (min-max), n (number of patients), and percent (%).
Results: Lack of appetite was observed in 34 of 48 patients together with a significant decrease in weight, weight SDS, BMI, and BMI SDS values. Interestingly, the height SDS was in trend of decreasing while statistically insignificant. In addition, serum IGFBP3 levels were remained unchanged while there was a significant decrease in IGF1 levels. Most significant data from the study were increased leptin levels and

decreased ghrelin levels after methylphenidate therapy, but no change in nesfatin-1 levels. Interestingly, there was a positive correlation between leptin and nesfatin-1 values after the treatment.
Conclusion: Methylphenidate therapy in ADHD patients has an effect on lack of appetite via an increase in leptin and decrease in ghrelin levels. Mechanisms underlying the growth and appetite status in ADHD patients in relation to treatment modalities were studied, in first in literature. Future studies could be designed to examine the mechanisms supported by our study.

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Indian J Pediatr. 2014.
ADD-H-COMPREHENSIVE TEACHERNULLS RATING SCALE (ACTERS): A MEASURE FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG CHILDREN WITH INTELLECTUAL DISABILITY IN INDIA.
Tsheringla S, Simon A, Russell PSS, et al.
Objective: There is no validated measure for assessing Attention Deficit Hyperactivity Disorder (ADHD) in India, and therefore, the authors validated the ADD-H Comprehensive Teachernulls Rating Scale (ACTeRS)
Methods: Teachers/parents/clinicians of 110 children with ADHD completed the ACTeRS. The diagnosis of ADHD was confirmed by an independent multi-disciplinary team using ICD-10 diagnosis for diagnostic accuracy and criterion validity. The convergent and divergent validity were assessed by another rater. The data was analyzed for diagnostic accuracy, reliability and validity appropriately
Results: An ACTeRS score of (greater-than or equal to)61 [Sensitivity (Sn) =85.51 %; Specificity (Sp) = 90.24 %; Area under the curve (AUC) = 0.94] is appropriate for the diagnosis of ADHD. The test-re-test reliability [Intra-class correlation coefficient (ICC) = 0.87], internal consistency (Cronbachnulls (alpha) = 0.80; range of 0.89null0.93), section-total correlation, face and content validity for the ACTeRS were good. Convergent validity of attention deficit, hyperactivity and oppositional subscales of ACTeRS with the corresponding subscales of Swanson, Nolan & Pelham Rating ScalenullRevised (SNAP-IV) was moderate (r = 0.60, P = 0.005; r = 0.49, P = 0.02; r = 0.58, P = 0.008 respectively), and negative correlation with the Childhood Autism Rating Scale (r = null0.36; P =0.1) for divergent validity was found. The criterion validity analysis showed a high concordance rate of 82.52 % between ACTeRS and International Classification of Diseases, Edition10 (ICD-10) diagnosis of ADHD. A 4-factor structure was replicated
Conclusions: The ACTeRS has adequate psychometric properties for use in the Indian population for identifying ADHD.

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International Journal of Molecular Sciences. 2014;15:17115-29.
METHYLPHENIDATE AMELIORATES DEPRESSIVE COMORBIDITY IN ADHD CHILDREN WITHOUT ANY MODIFICATION ON DIFFERENCES IN SERUM MELATONIN CONCENTRATION BETWEEN ADHD SUBTYPES.
Cubero-Millan I, Molina-Carballo A, Machado-Casas I, et al.
The vast majority of Attention-deficit/hyperactivity disorder (ADHD) patients have other associated pathologies, with depressive symptoms as one of the most prevalent. Among the mediators that may participate in ADHD, melatonin is thought to regulate circadian rhythms, neurological function and stress response. To determine (1) the serum baseline daily variations and nocturnal excretion of melatonin in ADHD subtypes and (2) the effect of chronic administration of methylphenidate, as well as the effects on symptomatology, 136 children with ADHD (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision: DSM-IV-TR criteria) were divided into subgroups using the "Children's Depression Inventory" (CDI). Blood samples were drawn at 20:00 and 09:00 h, and urine was collected between 21:00 and 09:00 h, at inclusion and after 4.61 (plus or minus) 2.29 months of treatment. Melatonin and its urine metabolite were measured by radioimmunoassay RIA. Factorial analysis was performed using STATA 12.0. Melatonin was higher predominantly in hyperactive-impulsive/conduct disordered children (PHI/CD) of the ADHD subtype, without the influence of comorbid depressive symptoms. Methylphenidate ameliorated this comorbidity without induction of any changes in the serum melatonin profile, but treatment with it was associated with a decrease in 6-s-melatonin excretion in both ADHD subtypes. Conclusions: In untreated

children, partial homeostatic restoration of disrupted neuroendocrine equilibrium most likely led to an increased serum melatonin in PHI/CD children. A differential cerebral melatonin metabolization after methylphenidate may underlie some of the clinical benefit.

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J Atten Disord. 2014 Oct;18:607-16.

ADHD PREDOMINANTLY INATTENTIVE SUBTYPE WITH HIGH SLUGGISH COGNITIVE TEMPO: A NEW CLINICAL ENTITY?

Capdevila-Brophy C, Artigas-Pallares J, Navarro-Pastor JB, et al.

OBJECTIVE: The authors investigate differences in the neuropsychological and behavioral profiles of two groups of children with ADHD, one with predominantly inattentive subtype of ADHD (PI) and high sluggish cognitive tempo (SCT; n = 19) and another formed by the rest of the sample (children with ADHD combined subtype and children with PI and low SCT scores; n = 68).

METHOD: Instruments included Wechsler Intelligence Scale for Children and subtests from Developmental Neuropsychological Assessment, Conners' Continuous Performance Test, Behavior Rating Inventory of Executive Function, and Achenbach's Child Behavior Checklist for ages 6 to 18.

RESULTS: PI with high SCT had fewer problems with sustained attention, and more internalizing problems, anxiety/depression, and withdrawn/depressed behavior, and more executive problems with self-monitoring than the rest of the ADHD sample.

CONCLUSION: This study supports revising subtype's criteria and further studying the hypothesis that ADHD with high SCT constitutes a separate clinical entity.

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J Atten Disord. 2014 Oct;18:598-606.

ADHD symptoms are differentially related to specific aspects of quality of life .

Gjervan B, Torgersen T, Rasmussen K, et al.

OBJECTIVE: The objectives of this study were to investigate the relationships between ADHD symptoms and specific domains of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) mental component.

METHOD: A sample of 149 adults participated in the study. Data were collected from the participant's medical records and from self-report questionnaires. Multiple regression analyses were applied to identify predictors of the SF-36 mental component outcomes.

RESULTS: The sample was highly impaired in terms of low health-related quality of life on all SF-36 mental component scales. The ADHD Self-Report Scale (ASRS) inattentiveness was the strongest predictor of vitality and the only significant predictor of role-emotional outcome. The ASRS hyperactivity/impulsivity was the strongest predictor of social function and the only predictor of mental health outcome.

CONCLUSION: Inattentiveness and hyperactivity/impulsivity were differentially related to specific quality-of-life domains. Inattentiveness was significantly predicting vitality and role-emotional outcomes, and hyperactivity/impulsivity predicted social function and mental health outcomes.

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J Atten Disord. 2014 Oct;18:563-75.

THE PREVALENCE OF ADHD: ITS DIAGNOSIS AND TREATMENT IN FOUR SCHOOL DISTRICTS ACROSS TWO STATES.

Wolraich ML, McKeown RE, Visser SN, et al.

OBJECTIVE: To describe the epidemiology of ADHD in communities using a DSM-IVTR case definition.

METHOD: This community-based study used multiple informants to develop and apply a DSM -IVTR-based case definition of ADHD to screening and diagnostic interview data collected for children 5-13 years of age. Teachers screened 10,427 children (66.4%) in four school districts across two states (SC and OK). ADHD ratings by teachers and parent reports of diagnosis and medication treatment were used to stratify children into high and low risk for ADHD. Parents (n = 855) of high risk and gender frequency-matched low

risk children completed structured diagnostic interviews. The case definition was applied to generate community prevalence estimates, weighted to reflect the complex sampling design.
RESULTS: ADHD prevalence was 8.7% in SC and 10.6% in OK. The prevalence of ADHD medication use was 10.1% (SC) and 7.4% (OK). Of those medicated, 39.5% (SC) and 28.3% (OK) met the case definition. Comparison children taking medication had higher mean symptom counts than other comparison children.
CONCLUSIONS: Our ADHD estimates are at the upper end of those from previous studies. The identification of a large proportion of comparison children taking ADHD medication suggests that our estimates may be conservative; these children were not included as cases in the case definition, although some might be effectively treated.

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J Atten Disord. 2014 Oct;18:585-93.
VIEWING THE VIEWERS: HOW ADULTS WITH ATTENTIONAL DEFICITS WATCH EDUCATIONAL VIDEOS.
Hassner T, Wolf L, Lerner A, et al.
OBJECTIVE: Knowing how adults with ADHD interact with prerecorded video lessons at home may provide a novel means of early screening and long-term monitoring for ADHD.
METHOD: Viewing patterns of 484 students with known ADHD were compared with 484 age, gender, and academically matched controls chosen from 8,699 non-ADHD students. Transcripts generated by their video playback software were analyzed using t tests and regression analysis.
RESULTS: ADHD students displayed significant tendencies (p </= .05) to watch videos with more pauses and more reviews of previously watched parts. Other parameters showed similar tendencies. Regression analysis indicated that attentional deficits remained constant for age and gender but varied for learning experience.
CONCLUSION: There were measurable and significant differences between the video-viewing habits of the ADHD and non-ADHD students. This provides a new perspective on how adults cope with attention deficits and suggests a novel means of early screening for ADHD.

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J Atten Disord. 2014 Oct;18:594-97.
DO FIRSTBORN CHILDREN HAVE AN INCREASED RISK OF ADHD?
Marin AM, Seco FL, Serrano SM, et al.
OBJECTIVE: Although previous reports have found no birth-order influence on ADHD risk, the authors hypothesize that being the firstborn is a risk factor for developing ADHD.
METHOD: They selected all of the currently treated ADHD outpatients (n=748) from our database. Families with adopted sons, nonnuclear families, and families with only one child and with sons (affected or unaffected) younger than 6 or older than 18 years were excluded. A total of 181 families with 213 ADHD sons met the inclusion criteria. We used all siblings without a clinical diagnosis of ADHD and who had no contact with our service as our unaffected controls (n=173).
RESULTS: The bivariate analysis showed that ADHD was associated with birth order and that firstborn children had nearly twice the ADHD risk of children with other birth orders.
CONCLUSION: birth order can be an ADHD risk factor in clinical samples.

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JAMA Psychiatry. 2014;71:1165-73.
ROLE OF THE MEDIAL PREFRONTAL CORTEX IN IMPAIRED DECISION MAKING IN JUVENILE ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Hauser TU, Iannaccone R, Ball J, et al.
IMPORTANCE Attention-deficit/hyperactivity disorder (ADHD) has been associated with deficient decision making and learning. Models of ADHD have suggested that these deficits could be caused by impaired reward prediction errors (RPEs). Reward prediction errors are signals that indicate violations of

expectations and are known to be encoded by the dopaminergic system. However, the precise learning and decision-making deficits and their neurobiological correlates in ADHD are not well known. Copyright 2014 American Medical Association. All rights reserved

OBJECTIVE To determine the impaired decision-making and learning mechanisms in juvenile ADHD using advanced computational models, as well as the related neural RPE processes using multimodal neuroimaging

DESIGN, SETTING, AND PARTICIPANTS Twenty adolescents with ADHD and 20 healthy adolescents serving as controls (aged 12-16 years) were examined using a probabilistic reversal learning task while simultaneous functional magnetic resonance imaging and electroencephalogram were recorded

MAIN OUTCOMES AND MEASURES Learning and decision makingwere investigated by contrasting a hierarchical Bayesian model with an advanced reinforcement learning model and by comparing the model parameters. The neural correlates of RPEs were studied in functional magnetic resonance imaging and electroencephalogram

RESULTS Adolescents with ADHD showed more simplistic learning as reflected by the reinforcement learning model (exceedance probability, Px = .92) and had increased exploratory behavior compared with healthy controls (mean [SD] decision steepness parameter (beta): ADHD, 4.83 [2.97]; controls, 6.04 [2.53]; P=.02). The functional magnetic resonance imaging analysis revealed impaired RPE processing in the medial prefrontal cortex during cue as well as during outcome presentation ($P < .05$, family-wise error correction). The outcome-related impairment in the medial prefrontal cortex could be attributed to deficient processing at 200 to 400 milliseconds after feedback presentation as reflected by reduced feedback-related negativity (ADHD, 0.61 [3.90] (mu)V; controls, -1.68 [2.52] (mu)V; P=.04)

CONCLUSIONS AND RELEVANCE The combination of computational modeling of behavior and multimodal neuroimaging revealed that impaired decision making and learning mechanisms in adolescents with ADHD are driven by impaired RPE processing in the medial prefrontal cortex. This novel, combined approach furthers the understanding of the pathomechanisms in ADHD and may advance treatment strategies.

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J Abnorm Child Psychol. 2014 Oct;42:1129-40.

TREATING PARENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE EFFECTS OF BEHAVIORAL PARENT TRAINING AND ACUTE STIMULANT MEDICATION TREATMENT ON PARENT–CHILD INTERACTIONS.

Babinski DE, Waxmonsky JG, Pelham WE.

This multiple baseline study evaluated the efficacy of behavioral parent training (BPT) for 12 parents (M age = 39.17 years; 91 % mothers) and their children (ages 6–12; 83 % boys) both with Attention-Deficit/Hyperactivity Disorder (ADHD), and also explored the acute effect of stimulant medication for parents before and after BPT. Parents rated their own and their children's symptoms and impairment and were stabilized on optimally dosed medication. Then, parents discontinued medication and were randomly assigned to a 3, 4, or 5 week baseline (BL), during which they provided twice-weekly ratings of their impairment, parenting, and their child's behavior. Following BL, parents and their children completed two laboratory tasks, once on their optimally dosed medication and once on a placebo to assess observable effects of medication on parent–child behavior, and they completed additional assessments of family functioning. Parents then completed eight BPT sessions, during which they were unmedicated. Twice-weekly ratings of parent and child behavior were collected during BPT and additional ratings were collected upon completing BPT. Two more parent–child tasks with and without parent medication were conducted upon BPT completion to assess the observable effects of BPT and BPT plus medication. Ten (83.33 %) parents completed the trial. Improvements in parent and child behavior were observed, and parents reported improved child behavior with BPT. Few benefits of BPT emerged through parent reports of parent functioning, with the exception of inconsistent discipline, and no medication or interaction effects emerged. These results, although preliminary, suggest that some parents with ADHD benefit from BPT. While pharmacological treatment is the most common intervention for adults with ADHD, further examination of psychosocial treatments for adults is needed.

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J Abnorm Child Psychol. 2014 Oct;42:1225-36.

A CROSS-SECTIONAL AND LONGITUDINAL INVESTIGATION OF THE EXTERNAL CORRELATES OF SLUGGISH COGNITIVE TEMPO AND ADHD-INATTENTION SYMPTOMS DIMENSIONS.

Bernad MdM, Servera M, Grases G, et al.

The objective was to determine if the external correlates of sluggish cognitive tempo (SCT) and ADHD-inattention (IN) dimensions were the same in cross-sectional and longitudinal analyses. Teachers and aides rated SCT, ADHD-IN, ADHD-hyperactivity/impulsivity (HI), oppositional defiant disorder (ODD), and depression along with academic impairment in 758 Spanish children (55 % boys) on three occasions (twice at the end of the first grade year [6-week separation] and then again 12-months later at the end of the second grade year). Three of eight SCT symptoms showed substantial loadings on the SCT factor and substantially higher loadings on the SCT factor than the ADHD-IN factor for teachers and aides at each assessment (seems drowsy, thinking is slow, and slow moving). Cross-sectional and longitudinal analyses yielded similar results with SCT and ADHD-IN factors having different and unique external correlates (higher scores on SCT predicted lower scores on ADHD-HI and ODD while higher scores on ADHD-IN predicted higher scores on ADHD-HI and ODD with SCT and ADHD-IN both uniquely predicting academic impairment and depression). Developmental and methodological reasons are discussed for the failure to find an inconsistent alertness SCT factor (daydreams, alertness fluctuates, absent-minded, loses train of though, and confused).

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Journal of Attention Disorders. 2014 Oct;18:576-84.

MILD TRAUMATIC BRAIN INJURY AND ADHD: A SYSTEMATIC REVIEW OF THE LITERATURE AND META-ANALYSIS.

Adeyemo BO, Biederman J, Zafonte R, et al.

Objective: This study investigated the association between mild traumatic brain injury (mTBI) and ADHD, which increases risk of injuries and accidents.

Method: We conducted a systematic review and meta-analysis of studies that examined the relationship between mTBI and ADHD.

Results: Five studies, comprising 3,023 mTBI patients and 9,716 controls, fit our a priori inclusion and exclusion criteria. A meta-analysis found a significant association between ADHD and mTBI, which was significant when limited to studies that reported on ADHD subsequent to mTBI and when the direction of the association was not specified, but not for studies that reported mTBI subsequent to ADHD. Heterogeneity of effect size and publication biases were not evident.

Conclusion: The literature documents a significant association between mTBI and ADHD. Further clarification of the relationship and direction of effect between mTBI and ADHD and treatment implications could have large clinical, scientific, and public health implications.

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J Child Adolesc Psychopharmacol. 2014 Aug;24:360-61.

TACTILE HALLUCINATIONS WITH FLUOXETINE AND METHYLPHENIDATE.

Arora GS, Arora HK, Sidhu J, et al.

Presents a case report of an 8-year-old African American male weighing 28.6 kg, with no past psychiatric history, who was initially brought in by his mother for the treatment of his oppositional behavior and crying spells. On further evaluation, it was determined that he had been hyperactive, impulsive, and inattentive and met criteria for attention-deficit/hyperactivity disorder (ADHD). He was started on methylphenidate 5mg twice daily, and was started on fluoxetine 4mg daily for depression, after having been on methylphenidate for 2 weeks. This regimen was continued for 3 more weeks, after which the methylphenidate dose was increased to 10mg twice daily, after ascertaining that the increased physical aggression was not caused by methylphenidate. While on this dose of methylphenidate for another week, the patient reported tactile hallucinations and they were thought to be secondary to methylphenidate. Methylphenidate was discontinued after *7 weeks of treatment. The tactile hallucinations persisted even 1 week after methylphenidate was discontinued. Fluoxetine was discontinued as well, a week after stopping

methylphenidate. The tactile hallucinations became less frequent, and they resolved completely 2 weeks after discontinuation of fluoxetine. Methylphenidate was resumed 1 month after the disappearance of the tactile hallucinations. Methylphenidate dose was titrated up gradually to 15mg three times a day, with no recurrence of tactile hallucinations. Fluoxetine was not reintroduced, as it would have been unethical to restart it given the debilitating side effect and suffering it caused to the patient. Prescribing physicians should be aware of this side effect, especially when fluoxetine is combined with methylphenidate, as it can affect compliance.

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Journal of Child Psychology and Psychiatry. 2014 Oct;55:1117-24.

INHIBITORY CONTROL AND DELAY AVERSION IN UNAFFECTED PRESCHOOLERS WITH A POSITIVE FAMILY HISTORY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Pauli-Pott U, Roller A, Heinzel-Gutenbrunner M, et al.

Background: From current theories on the etiology of attention deficit hyperactivity disorder (ADHD), it can be inferred that delay aversion (DA) and deficits in inhibitory control (IC) constitute basic deficits or endophenotypes of the disorder that already occur in the preschool period. This implies an occurrence of the characteristics in unaffected preschoolers with a positive family history of ADHD. Thus, it is hypothesized that preschoolers who are not affected by ADHD but who have first-degree relatives who suffer, or have suffered, from ADHD show deficits in IC and heightened DA in comparison to preschoolers from the general population.

Methods: Thirty unaffected preschoolers with a positive family history of ADHD were compared with 30 control children matched with respect to age in months, gender, intelligence, and maternal education level. The groups also did not differ in terms of maternal depressive symptoms and the number of psychosocial family risks. A set of age-appropriate neuropsychological tasks on executive IC (e.g. Puppet Says, Day-Night, relying on Go-NoGo and interference paradigms) and DA (e.g. Snack Delay, Gift Wrap, relying on delay of gratification paradigm) was conducted.

Results: Unaffected preschoolers showed significantly higher DA than control children (t(29) = -2.57, p < .008). The result did not change when subclinical ADHD symptoms and symptoms of oppositional defiant disorder were controlled for (F(1,29) = 5.21, p < .031). Differences in IC did not reach statistical significance.

Conclusion: The results are compatible with the assumption that DA constitutes a familial vulnerability marker that can be validly assessed in the preschool period. As this is the first study to address this issue in preschoolers, more research is needed to confirm and further analyze the significance of DA assessments specifically at this developmental stage.

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J Dev Behav Pediatr. 2014 Sep;35:467-69.

"MORE THAN MEETS THE EYE": WHEN THE NEONATAL COURSE MAY IMPACT SEVERAL YEARS OUT.

Dopwell F, Maypole J, Sinha B, et al.

CASE: Nadia is a 7-year-old girl who you have followed since her discharge from the Neonatal Intensive Care Unit (NICU). Her parents are here today for an urgent visit with behavioral concerns, such as inattention, hyperactivity, and aggression. Nadia is a former 40-weeker born through vacuum-assisted vaginal delivery at 9 pounds 7 ounces. Her delivery was complicated with shoulder dystocia, which resulted in resuscitation. Her Apgar scores were 1, 3, and 4 at 1, 5, and 10 minutes, respectively. After intubation and stabilization on mechanical ventilation, Nadia was transferred to the NICU. Her neonatal course included systemic hypothermia using "cool cap" for hypoxic-ischemic encephalopathy (HIE) for a duration of 72 hours. She was extubated on day of life 3. She had an occupational therapy consultation for poor suck/feeding, and it quickly improved. She was discharged on day of life 14. On discharge, Nadia was referred to early intervention (EI) and the NICU follow-up clinic. Nadia was followed by EI until 12 months of age and in the NICU follow-up clinic until 18 months of age, as there were no concerns meeting her developmental milestones or her neuromotor development. At this urgent visit, Nadia's parents report that

she attended a family child care from 1.5 to 3 years of age, Head Start from 3 to 5 years of age and the local public school from 5 years to present. Since starting child care, Nadia's teachers have reported that she requires a lot of redirection and refocusing, fidgets a lot in class, and can be aggressive toward her peers when unprovoked. Since her parents had not seen these behaviors at home, they thought it was a phase that she would grow out of. However, as they began to work with her to complete school assignments, they noticed that it was very difficult for Nadia to sit still and focus on work. They also struggled in the mornings to get her ready and off to school. The parents bring in Conners scales completed by themselves and her lead teacher, and with these and our clinical observations, we diagnose her with attention-deficit/hyperactivity disorder (ADHD), combined type. We discuss risk factors and ADHD management with her parents. During our discussion, Nadia's father, who has done some reading on ADHD, remembers reading an article about HIE and NICU stay being risk factors for ADHD. He wonders if this affects the choice of management of her ADHD symptoms. How would you address his query?

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J Dev Behav Pediatr. 2014 Sep;35:471.

RELIABLE RATINGS OR READING TEA LEAVES: CAN PARENT, TEACHER, AND CLINICIAN BEHAVIORAL RATINGS OF PRESCHOOLERS PREDICT ADHD AT AGE SIX?

Moore RM.

The aim of the present study was to assess if parent, teacher, and clinician ratings of inattention, hyperactivity, and impulsivity in 3- to 4-year-old children could predict ADHDrelated outcomes (i.e., diagnosis, severity) at 6 years of age. ADHD symptoms of participants (n 5 104; 78% males) were assessed through a multimethod battery of parent- and teacher-completed questionnaires or interviews plus observational measures (e.g., actigraphy to assess overactivity and performance on a computerbased task). At 6 years of age, 56 participants (54%) received an ADHD diagnosis. The subgroup with greatest symptom stability was preschool girls who had elevated scores for inattention, hyperactivity, and impulsivity.

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J Dev Behav Pediatr. 2014 Sep;35:448-57.

LONG-TERM STIMULANT MEDICATION TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: RESULTS FROM A POPULATION-BASED STUDY.

Barbaresi WJ, Katusic SK, Colligan RC, et al.

The purpose of this study was to offer detailed information about stimulant medication treatment provided throughout childhood to 379 children with research-identified attention-deficit hyperactivity disorder (ADHD) in the 1976–1982 Rochester, MN, birth cohort. Subjects were retrospectively followed from birth until a mean of 17.2 years of age. The complete medical record of each subject was reviewed. The history and results of each episode of stimulant treatment were compared by gender, DSMIV subtype of ADHD, and type of stimulant medication. Overall, 77.8% of subjects were treated with stimulants. Boys were 1.8 times more likely than girls to be treated. The median age at initiation (9.8 years), median duration of treatment (33.8 months), and likelihood of developing at least one side effect (22.3%) were not significantly different by gender. Overall, 73.1% of episodes of stimulant treatment were associated with a favorable response. The likelihood of a favorable response was comparable for boys and girls. Treatment was initiated earlier for children with either ADHD combined type or ADHD hyperactive-impulsive type than for children with ADHD predominantly inattentive type and duration of treatment was longer for ADHD combined type. There was no association between DSM-IV subtype and likelihood of a favorable response or of side effects. Dextroamphetamine and methylphenidate were equally likely to be associated with a favorable response, but dextroamphetamine was more likely to be associated with side effects. These results demonstrate that the effectiveness of stimulant medication treatment of ADHD provided throughout childhood is comparable to the efficacy of stimulant treatment demonstrated in clinical trials.

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J Dev Behav Pediatr. 2014 Sep;35:471.

ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN YOUNG CHILDREN: PREDICTORS OF DIAGNOSTIC STABILITY.

Murray KE.

Presents a study investigated the diagnostic stability of a diagnosis of attention-deficit hyperactivity disorder (ADHD) before age 7. In this cohort study, 120 patients diagnosed at a tertiary multidisciplinary clinic between 2003 and 2008 were contacted an average of 7 years later to determine the presence or absence of ADHD. More than 70% of the children contacted continued to meet the diagnostic criteria. Presence of parental psychopathology, high baseline symptom level, and low family socioeconomic status were predictive of diagnosis retention. The study had a 70% retention rate from Time 1 to Time 2. Since the original diagnoses were made in a tertiary care clinic, the findings may not easily generalize to other settings, including primary care. K.E.M.

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J Dev Behav Pediatr. 2014 Sep;35:470.

ACETAMINOPHEN EXPOSURE IN UTERO—ASSOCIATIONS WITH SUBSEQUENT BEHAVIOR PROBLEMS.

Nyp SS.

Presents a study aims to to examine the risk of receiving a diagnosis of attention-deficit hyperactivity disorder (ADHD), hyperkinetic disorder (HKD), or receiving medications to treat ADHD (methylphenidate, atomoxetine, or modafinil) among 7-year-old children who were exposed to acetaminophen in utero. The risk of these outcomes increased with increased duration of acetaminophen exposure during gestation. Acetaminophen has long been considered to be an appropriate treatment for pain, fever, and inflammation among pregnant women. The results of this study, however, raise additional doubts about the safety of this treatment during pregnancy. The authors recommend research to further delineate potential neurodevelopmental risks to the fetus. S.S.N.

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Journal of Mazandaran University of Medical Sciences. 2013;23.

PREVALENCE OF ATTENTION DEFICIT HYPER ACTIVITY DISORDER IN HIGH-SCHOOL STUDENTS OF SARI, IRAN.

Shafaat A, Tirgari-Seraj A, Daneshpoor SMM, et al.

Background and purpose: Attention deficit hyper activity disorder (ADHD) is a serious disorder for childhood and adolescents that disables and retards the patient in social relationship. This research aimed to determine the prevalence of ADHD in High-School Students of Sari, Iran.

Materials and methods: In this cross-sectional description-analytical study, the study population was 14-17 years old students of high-schools in Sari town. The data-collection tool was Conners parent questionnaire completed by the students' parent after sending their home. The collected data were analyzed using SPSS software.

Results: The mean age of the cases was 15.8 (plus or minus) 2.1 years. The prevalence of the ADHD prevalence was 14.2%; the prevalence in boys was more but the difference was not significant.

Conclusion: Considering the prevalence of ADHD in Sari, the screening, treatment and follow-up programs should be planned to improve the situation.

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J Pediatr Endocrinol Metab. 2014;27:773-76.

A RARE CASE OF HYPOGLYCAEMIA DUE TO INSULINOMA IN AN ADOLESCENT WITH ACUTELY ALTERED MENTAL STATUS.

Winston KY, Dawrant J.

Background: Multiple endocrine neoplasia type 1 (MEN1) is an inherited neoplasia syndrome that generally presents with hypercalcaemia due to hyperparathyroidism. Insulin-producing tumours are less common components of the syndrome that emerge later during the course of the disease. We report here a case of an adolescent who presented with symptomatic hypoglycaemia as the first indication of MEN1

Case: A 14-year-old boy, known to use illicit drugs, was brought to the hospital with altered mental status. He was hypoglycaemic and further investigations revealed two pancreatic insulinomas. Despite having no relevant family history, genetic evaluation showed a mutation consistent with MEN1.
Conclusion: Insulinomas in adolescents are generally rare and even less common as a first presentation of MEN1. This diagnosis carries implications for potential future neoplasms, both benign and malignant. While intoxication is a more common case of altered mental status in adolescents, clinicians must maintain a high index of suspicion for organic disease.

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J Am Acad Child Adolesc Psychiatry. 2014;53:1092-101.

RESPONSE/REMISSION WITH GUANFACINE EXTENDED-RELEASE AND PSYCHOSTIMULANTS IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Cutler AJ, Brams M, Bukstein O, et al.

Objective: In this post hoc analysis, we assessed whether guanfacine extended-release (GXR) adjunctive to a psychostimulant resulted in greater response and remission rates than placebo + psychostimulant in children and adolescents with attention-deficit/hyperactivity disorder (ADHD)
Method: In this 9-week, double-blind, placebo-controlled dose-optimization study, participants (N=461) aged 6 to 17 years with suboptimal response to psychostimulants were randomized to GXR on awakening (AM) + psychostimulant, GXR at bedtime (PM) + psychostimulant, or placebo + psychostimulant.
Results At the final on-treatment assessment, more participants in both GXR + psychostimulant groups versus the placebo + psychostimulant group achieved response as assessed by 2 criteria: reduction from baseline in ADHD Rating Scale IV (ADHD-RS-IV) total score (1) (greater-than or equal to)40% (GXR AM + psychostimulant = 69.8%, GXR PM + psychostimulant = 70.3%, versus placebo + psychostimulant = 57.9%; p =.032 and p =.026, respectively), or (2) (greater-than or equal to)50% (63.1%, 64.9%, versus 43.4%; p <.001 for both). Results were similar for symptomatic remission (ADHD-RS-IV total score (less-than or equal to)18; 61.1%, 62.2%, versus 46.1%; p =.010 and p =.005, respectively) and syndromal remission (symptomatic remission plus Clinical Global Impressions of Severity of Illness score (less-than or equal to)2). The most common treatment-emergent adverse events in participants receiving GXR + psychostimulant were headache (21.2%) and somnolence (13.6%)
Conclusion GXR + psychostimulant treatment resulted in a greater percentage of participants meeting stringent criteria for response and remission compared with placebo + psychostimulant. The adverse event profile of adjunctive therapy was consistent with known effects of either treatment alone. Clinical trial registration information - Efficacy and Safety of SPD503 in Combination With Psychostimulants; http://clinicaltrials.gov/; NCT00734578

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J Am Acad Child Adolesc Psychiatry. 2014;53:1123-29.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER POLYGENIC RISK SCORES PREDICT ATTENTION PROBLEMS IN A POPULATION-BASED SAMPLE OF CHILDREN.

Groen-Blokhuis MM, Middeldorp CM, Kan K-J, et al.

Objective: Clinically, attention-deficit/hyperactivity disorder (ADHD) is characterized by hyperactivity, impulsivity, and inattention and is among the most common childhood disorders. These same traits that define ADHD are variable in the general population, and the clinical diagnosis may represent the extreme end of a continuous distribution of inattentive and hyperactive behaviors. This hypothesis can be tested by assessing the predictive value of polygenic risk scores derived from a discovery sample of ADHD patients in a target sample from the general population with continuous scores of inattention and hyperactivity. In addition, the genetic overlap between ADHD and continuous ADHD scores can be tested across rater and age
Conclusion: These results indicate genetic overlap between a diagnosis of ADHD and AP scale scores across raters and age groups and provides evidence for a dimensional model of ADHD. Future GWA

studies on ADHD can likely benefit from the inclusion of population-based cohorts and the analysis of continuous scores
Method: The Psychiatric Genomics Consortium has performed the largest genome-wide analysis (GWA) study of ADHD so far, including 5,621 clinical patients and 13,589 controls. The effects sizes of single nucleotide polymorphisms (SNPs) estimated in this meta-analysis were used to obtain individual polygenic risk scores in an independent population-based cohort of 2,437 children from the Netherlands Twin Register. The variance explained in Attention Problems (AP) scale scores by the polygenic risk scores was estimated by linear mixed modeling.
Results The ADHD polygenic risk scores significantly predicted both parent and teacher ratings of AP in preschool- and school-aged children.

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J Can Acad Child Adolesc Psychiatry. 2014;23:157-66.
COMBINATION AND SWITCHING OF STIMULANTS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN QUEBEC.
Ben AL, Sikirica V, Cloutier M, et al.
Objective: To assess the one-year period prevalence of stimulant combination therapy and switching in children/ adolescents with attention deficit/hyperactivity disorder (ADHD) in Quebec, Canada
Method: Patients aged 6-17 years, with at least two ADHD diagnosis codes documented in different visits and at least 30 daysnull supply of a stimulant during their most recent one-year observation period were selected from the Regie de lnullassurance maladie du Quebec database (03/2007null02/2012). Combination therapy was defined as at least 30 consecutive days of concomitant use of multiple stimulants with different active moieties, or use of a stimulant and another psychotropic medication. Therapy switching was defined as a prescription claim for a new psychotropic medication less than 30 days before or after the end of supply of a stimulant. The one-year period prevalence of therapy combination and switching was calculated
Results: The one-year period prevalence of combination therapy and switching among 9,431 children and adolescents with ADHD treated with stimulants was 19.8% and 18.7%, respectively. The most frequent combination categories were atypical antipsychotics (AAP: 10.8%), atomoxetine (ATX: 5.5%) and clonidine (5.3%). The most frequent switched-to categories were other stimulants (7.9%), AAP (5.5%) and ATX (4.7%)
Conclusions: Approximately one in five children/adolescents with ADHD on a stimulant experienced combination therapy or therapy switching; however, the majority of the medications used in combination or switching were not label-indicated for the treatment of ADHD in Canada. These results highlight the need for further research to evaluate the risk-benefit of stimulant combination and switching in children and adolescents with ADHD.

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Klin Psikofarmakol Bul. 2014;24:248-52.
ASSESSMENT OF CARDIOVASCULAR RISKS DUE TO METHYLPHENIDATE IN SIX MONTHS OF TREATMENT IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.
Ari ME, Cetin II, Ekici F, et al.
Objectives: Cardiovascular adverse effects can be seen rarely in patients receiving methylphenidate for attention deficit and hyperactivity disorder (ADHD). In this study, we planned to investigate the effects of methylphenidate on the cardiovascular system in ADHD patients
Methods: One hundred and forty-one patients, who were diagnosed with ADHD and started on methylphenidate treatment between May 2011 and May 2012, were investigated. A cardiologic evaluation was performed on all of the patients before the methylphenidate treatment was begun. Subsequently, the patients were invited for regular visits at three months intervals for assessment of cardiovascular and electrocardiographic (ECG) changes during this treatment. The data of all these patients at the beginning of treatment and within the first 6 months were evaluated. Thirty-five patients (24.8%) suffered from various

cardiovascular symptoms in the first 6 months. Demographic characteristics, heart rate, systolic and diastolic blood pressures, QTc duration on ECG, rhythm Holter and 24-hour blood pressure monitoring results of these patients were evaluated
Results: Thirty-five patients (10 girls and 25 boys) had cardiovascular symptoms in the first 6 months. The mean age of patients was 9.2(plus or minus)2.8 years. Although QTc duration significantly increased after methylphenidate treatment ($p<0.05$), this increase was within normal ranges. Similarly, systolic and diastolic blood pressures of patients increased significantly. This increase was between the 90-95th percentiles in only 5 patients. Twenty-four-hour blood pressure monitoring results were normal, and the methylphenidate treatment of these patients was not stopped. The mean heart rate of patients was also increased, but this increase was not statistically significant. The symptoms with respect to the cardiovascular system were palpitations in 16 patients (45.8%), chest pain in 11 patients (31.5%), palpitations with chest pain in 5 patients (14.2%) and dyspnea in 3 patients (8.5%). All patientsnull ECG and rhythm Holter results were within normal limits. Two patients discontinued treatment because of their parentnulls unwillingness for the drug to be continued
Conclusions: In ADHD patients, the elongation of QTc duration and increase in the systolic and diastolic blood pressures were statistically significant during 6 months of methylphenidate treatment. However, all these changes remained within normal limits. All patients receiving this drug should be monitored carefully for cardiovascular side effects.

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NeuroImage Clin. 2014;6:192-201.
ACUTE NEUROPHARMACOLOGICAL EFFECTS OF ATOMOXETINE ON INHIBITORY CONTROL IN ADHD CHILDREN: A FNIRS STUDY.
Nagashima M, Monden Y, Dan I, et al.
The object of the current study is to explore the neural substrate for effects of atomoxetine (ATX) on inhibitory control in school-aged children with attention deficit hyperactivity disorder (ADHD) using functional near-infrared spectroscopy (fNIRS). We monitored the oxy-hemoglobin signal changes of sixteen ADHD children (6-14 years old) performing a go/no-go task before and 1.5 h after ATX or placebo administration, in a randomized, double-blind, placebo-controlled, crossover design. Sixteen age-and gender-matched normal controls without ATX administration were also monitored. In the control subjects, the go/no-go task recruited the right inferior and middle prefrontal gyri (IFG/MFG), and this activation was absent in pre-medicated ADHD children. The reduction of right IFG/MFG activation was acutely normalized after ATX administration but not placebo administration in ADHD children. These results are reminiscent of the neuropharmacological effects of methylphenidate to up-regulate reduced right IFG/MFG function in ADHD children during inhibitory tasks. As with methylphenidate, activation in the IFG/MFG could serve as an objective neuro-functional biomarker to indicate the effects of ATX on inhibitory control in ADHD children. This promising technique will enhance early clinical diagnosis and treatment of ADHD in children, especially in those with a hyperactivity/impulsivity phenotype.

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Neuropsychiatr Dis Treat. 2014;10:1533-42.
CLINICAL UTILITY OF THE CHINESE STRENGTHS AND WEAKNESSES OF ADHD-SYMPTOMS AND NORMAL-BEHAVIORS QUESTIONNAIRE (SWAN) WHEN COMPARED WITH DISC-IV.
Chan GFC, Lai KYC, Luk ESL, et al.
Background: Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing child and adolescent psychiatric disorder. Early identification and prompt treatment are essential. Rating scales are commonly used by clinicians and researchers to assess ADHD children.
Objective: In the current study, we aimed to examine the clinical utility of the Chinese version of the Strengths and Weaknesses of ADHD Symptoms and Normal Behaviors (SWAN) questionnaire. We validated its subscale scores against the Diagnostic Interview Schedule for Children Version IV (DISC-IV)

and looked into its ability to identify ADHD in a psychiatric clinic setting. We also tested age and gender effects on SWAN scores. Specific subscale cutoff scores of SWAN were subsequently determined.
Method: A total of 290 children aged 6-12 years old studying in local mainstream primary schools were recruited from a clinic setting and interviewed with the parent version of DISC-IV. Their parents and teachers completed the corresponding version of SWAN.
Results: Both parent and teacher versions of SWAN were found to have good concurrent validity with DISC-IV. It could identify ADHD well in a clinic sample. Gender-specific cutoff scores were determined. Sensitivities and specificities were found to be satisfactory. SWAN was also found to perform equally well in identifying ADHD in those with and without comorbid Autistic Spectrum Disorder.
Conclusion: SWAN was proven to be a useful tool to aid the assessment of ADHD in a clinic sample.

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Neuropsychiatr Dis Treat. 2014;10:1645-54.

SELF-REPORTED EFFICACY OF NEUROFEEDBACK TREATMENT IN A CLINICAL RANDOMIZED CONTROLLED STUDY OF ADHD CHILDREN AND ADOLESCENTS.

Duric NS, Assmus J, Elgen IB.

Background: Many non-pharmacological treatments for children and adolescents with attention-defcit/hyperactivity disorder (ADHD) have been attempted, but reports indicate that most are ineffective. Although neurofeedback (NF) is a treatment approach for children with ADHD that remains promising, a variety of appropriate measures have been used in reporting and evaluating its effect
Objective: To report the self-evaluations of NF treatment by children and adolescents with ADHD
Methods: Randomized controlled trial in 91 children and adolescents with ADHD, aged less than 18 years (mean, 11.2 years) participated in a 30-session program of intensive NF treatment. Participants were randomized and allocated by sequentially numbered sealed envelopes into three groups: methylphenidate (MPH) as an active control group, and two trial groups NF with MPH, and NF alone. ADHD core symptoms and school performance were given on a scale of 1 to 10 using a self-reporting questionnaire, and the changes in these scores after treatment were used as the self-reported evaluation. Basic statistical methods (descriptive, analyses of variance, exact x2 test, and paired t -test) were used to investigate the baseline data. Changes in ADHD core symptoms and treatment effects were investigated using a general linear model for repeated measures
Results: Eighty participants completed the treatment study and 73 (91%) responded suffciently on the self-reporting questionnaires. The treatment groups were comparable in age, sex, and cognition as well as in the baseline levels of core ADHD symptoms. All treatments resulted in signifcant improvements regarding attention and hyperactivity ($P<0.001$), and did not differ from each other in effectiveness. However, a signifcant treatment effect in school performance was observed ($P=0.042$), in which only the NF group showed a signifcant improvement
Conclusion: The self-reported improvements in ADHD core symptoms and school performance shortly after treatment indicate NF treatment being promising in comparison with medication, suggesting NF as an alternative treatment for children and adolescents who do not respond to MPH, or who suffer side effects. Further long-term follow-up is needed.

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Neuropsychiatr Dis Treat. 2014;10:1543-69.

ADHERENCE, PERSISTENCE, AND MEDICATION DISCONTINUATION IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER - A SYSTEMATIC LITERATURE REVIEW.

Gajria K, Lu M, Sikirica V, et al.

Untreated attention-deficit/hyperactivity disorder (ADHD) can lead to substantial adverse social, economic, and emotional outcomes for patients. The effectiveness of current pharmacologic treatments is often reduced, due to low treatment adherence and medication discontinuation. This current systematic literature review analyzes the current state of knowledge surrounding ADHD medication discontinuation, focusing on: 1) the extent of patient persistence; 2) adherence; and 3) the underlying reasons for patients' treatment

discontinuation and how discontinuation rates and reasons vary across patient subgroups. We selected 91 original studies (67 with persistence/discontinuation results, 26 with adherence results, and 41 with reasons for discontinuation, switching, or nonadherence) and 36 expert opinion reviews on ADHD medication discontinuation, published from 1990 to 2013. Treatment persistence on stimulants, measured by treatment duration during the 12-month follow-up periods, averaged 136 days for children and adolescents and 230 days for adults. Owing to substantial study heterogeneity, comparisons across age or medication type subgroups were generally inconclusive; however, long-acting formulations and amphetamines were associated with longer treatment duration than short-acting formulations and methylphenidates. The medication possession ratio, used to measure adherence, was <0.7 for all age groups and medication classes during a 12-month period. Adverse effects were the most commonly cited reason for discontinuation in all studies. Original research studies reported the lack of symptom control as a common discontinuation reason, followed by dosing inconvenience, social stigma associated with ADHD medication, and the patient's attitude. In summary, although there was a lack of consistency in the measurement of adherence and persistence, these findings indicate that drug adherence and persistence are generally poor among patients with ADHD. Clinicians may be able to help improve adherence and persistence to ADHD treatment by educating caregivers and patients on treatment goals, administering long-acting medications, and following-up with patients to verify if medication is still effective and well-tolerated.

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Neuropsychiatr Dis Treat. 2014;10:1799-805.

SLEEP AND COGNITIVE PROBLEMS IN PATIENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Lee HK, Jeong J-H, Kim N-Y, et al.

Objectives: Attention-deficit hyperactivity disorder (ADHD) is characterized by inattentive and impulsive behavior. Many ADHD patients reportedly have cognitive dysfunction and sleep problems, including longer sleep latency, lower sleep efficiency, and shorter total sleep time. The purpose of this study was to examine neurocognitive functions and nocturnal sleep parameters in patients with ADHD, using a cognitive function test and actigraphy

Methods: Subjects included 37 male patients with ADHD and 32 controls (7-12 years of age). For each participant, we determined intelligence quotient (IQ) and administered the Matching Familiar Figures Test (MFFT) and 72-hour actigraphy. The relationships between sleep parameters and cognitive functions were assessed

Results: ADHD patients significantly differed from controls in several cognitive functions and sleep variables. In the MFFT, response error rate (P<0.001) and error counts (P=0.003) were significantly increased in ADHD patients compared with control children. MFFT response latency was significantly shorter in ADHD patients than in controls (P<0.001). In addition, sleep latency (P=0.01), wake after sleep onset (WASO) (P<0.001), and fragmentation index (P<0.001) were evaluated by actigraphy and found to be significantly increased in patients with ADHD compared with controls. However, no significant differences in total sleep time or sleep efficiency were observed. WASO and response error rates were positively correlated in patients with ADHD (rho =0.52, P=0.012). Furthermore, fragmentation index sleep variables were significantly positively correlated with response error (rho =0.44, P=0.008) and response latency rates (rho =0.4, P=0.018) in the MFFT. Reaction error rate was significantly associated with the fragmentation index (beta =0.94, P=0.024)

Conclusion: Patients with ADHD had more sleep problems, including significantly increased sleep latency, WASO, and fragmentation index, and poorer cognitive function, compared with controls. Some of these sleep problems, including WASO and the fragmentation index, were positively correlated with impulsivity, illustrated by the cognitive function tests in patients with ADHD. However, further studies with large sample sizes and the addition of polysomnography and determination of ADHD subtypes should be performed to confirm our results regarding sleep and cognitive problems in patients with ADHD.

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Neurosci Lett. 2014;582:49-53.

REFINING THE PICTURE OF REDUCED ALERTING RESPONSES IN ADHD - A SINGLE-TRIAL ANALYSIS OF EVENT-RELATED POTENTIALS.

Heinrich H, Busch K, Studer P, et al.

In attention-deficit/hyperactivity disorder (ADHD), a reduced phasic alerting response (event-related potential component P3 to cue stimuli) has been reported for different subtypes and task types in a series of studies. In order to get a refined picture of this attentional deficit, which is based on the analysis of averaged event-related potentials, we studied the distribution of single-trial cue-P3 amplitudes and the relation between the cue-P3 and the neural state (EEG spectral analysis) when expecting the stimulus. Brain electrical activity was recorded in children of different ADHD subtypes (combined type, predominantly inattentive) and typically developing children while conducting the attention network test. In children with ADHD of the combined type, smaller cue-P3 amplitudes in the averaged signal were due to a larger portion of single trials with reduced cue-P3 amplitudes whereas maximum amplitudes did not differ from typically developing children. In this ADHD subtype, larger activity in the upper theta/lower alpha range (5.5-10.5. Hz) was strongly associated with the range (difference between 0.9 quantile and 0.1 quantile) of the cue-P3 amplitude in single trials (correlation coefficient r = 0.77) indicating a suboptimal neural state before stimulus presentation. In children with ADHD of the predominantly inattentive subtype, single-trial P3 amplitudes were comparable at lower quantiles but maximum amplitudes were reduced. This result pattern indicates an intact triggering of the cue-P3 but a reduced capacity of resource allocation for the predominantly inattentive subtype. Though findings are limited by a relative small sample size, the cue-P3 may be considered as a neurophysiological marker of alerting deficits in ADHD reflecting different underlying mechanisms in ADHD subtypes.

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Noropsikiyatr Ars. 2014;51:195-204.

A COMPARISON BETWEEN SCHOOL AND HOME RATING SCALES AND RELIABILITY-VALIDITY OF THE SCALES-THE SCALES FOR DIAGNOSING ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER.

Aksu ME, Turan F.

Introduction: The purpose of the present research is to compare the Turkish translations of school and home versions of the Scales for Diagnosing Attention-Deficit/Hyperactivity Disorder (SCALES) developed by Ryser and McConnell with respect to age and gender and to examine the correlation between the two scales

Method: The research was conducted with 102 teachers and parents of 891 children aged between 5.0 and 14.11 years. 656 scale forms of parents returned to us were included in the study. The teachers filled in teacher information form, child information form, SCALES-School Rating Scale and the Turkish version of Connersnull Teacher Rating Scale. The parents filled in family information form, child information form and SCALESHome Rating Scale and the Turkish version of the Connersnull Home Rating Scale

Results: When SCALES-Home Rating Scale and SCALES-School Rating Scale scores of each age group were compared using t-test, it was observed that the difference in all sub-scale scores in the 5-9 age group was significant and it was also observed that in the 10-13 and 13+ age groups, the difference was significant only in the hyperactivity field. The correlation between SCALES-School Rating Scale and SCALES-Home Rating Scale was investigated. The correlation between sub-scales measuring the same abilities was found to be between 0.1 and 0.26

Conclusion: We assume that the Turkish version of the SCALES is a valid and reliable instrument for diagnosing ADHD. Since SCALES-Home Rating Scale scores were higher than SCALES-School Rating Scale scores and the correlation between the two scales was low, we assume that the objectivity of parentsnull ratings was limited.. Future validity studies on diagnosed children are needed.

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Orvosi Hetilap. 2014;155:1598-601.

ATTENTION DEFICIT HYPERACTIVITY DISORDER ANALYZED WITH ARRAY COMPARATIVE GENOME HYBRIDIZATION METHOD. CASE REPORT.

Duga B, Czako M, Komlosi K, et al.

One of the most common psychiatric disorders during childhood is attention deficit hyperactivity disorder, which affects 5-6% of children worldwide. Symptoms include attention deficit, hyperactivity, forgetfulness and weak impulse control. The exact mechanism behind the development of the disease is unknown. However, current data suggest that a strong genetic background is responsible, which explains the frequent occurrence within a family. Literature data show that copy number variations are very common in patients with attention deficit hyperactivity disorder. The authors present a patient with attention deficit hyperactivity disorder who proved to have two approximately 400 kb heterozygous microduplications at 6p25.2 and 15q13.3 chromosomal regions detected by comparative genomic hybridization methods. Both duplications affect genes (6p25.2: SLC22A23; 15q13.3: CHRNA7) which may play a role in the development of attention deficit hyperactivity disorder. This case serves as an example of the wide spectrum of indication of the array comparative genome hybridization method. Orv. Hetil., 2014, 155(40), 1598-1601.

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Pharmacoepidemiol Drug Saf. 2014;23:92-93.

DIFFERENCES IN ADHD MEDICATION USAGE PATTERNS IN CHILDREN AND ADOLESCENTS FROM DIFFERENT ETHNIC BACKGROUNDS IN THE NETHERLANDS.

Van Den Ban EF, Souverein PC, van EH, et al.

Background: ADHD medication use in children and adolescents has increased over the past decades in many countries. Differences in incidence and prevalence of ADHD medication use between ethnic groups have been reported. Whether there are also differences in usage patterns is, however, largely unknown.
Objectives: To determine whether there are differences in usage patterns of ADHD medication among native Dutch, Moroccan, Turkish and Surinam children and adolescents in The Netherlands between 1999-2010.
Methods: A cohort of patients under 19 years of age diagnosed with ADHD was evaluated for ADHD medication use. Incident use and discontinuation of ADHD medication was measured for ethnicity (native Dutch, Moroccan, Turkish and Surinam) and adjusted for age, gender and socio-economic status. Coxregression analyses were usd to calculate Hazard Ratios for the risk of early discontinuation.
Results: A total of 817 children with a diagnosis of ADHD was identified. A higher proportion of ADHD diagnosed Moroccan (32%) and Turkish (42%) patients never used ADHD medication compared to Dutch natives (21%). One fifth of native Dutch and Turkish patients already used ADHD medication before the ADHD diagnosis date. Almost all patients that used medication initiated on immediate release methylphenidate (80%). Discontinuation of ADHD medication within 5 years was highest in Moroccan (HR 2.4 [95% CI 1.8-3.1]) and Turkish (HR 1.6 [95% CI 1.1-2.6]) patients. A sensitivity analysis with a postal code matched comparison between Dutch natives and nonnatives showed similar results, suggesting this effect is not explained by socio-economic status.
Conclusions: Differences are found in ADHD medication prescribing and use between ethnical groups. Native Dutch and Turkish patients start more frequently with ADHD medication before the ADHD diagnose date, which can be an indication of differences in either referral patterns and/or access to care. A higher percentage of Moroccan and Turkish patients never start using ADHD medication at all and if they start using medication, discontinuation rate is higher compared to Dutch natives and Surinams.

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Pharmacoepidemiol Drug Saf. 2014;23:58-59.

PRESCRIPTIONS, NONMEDICAL USE AND EMERGENCY DEPARTMENT VISITS OF ADHD STIMULANTS.

Chen L-Y, Crum R, Strain EC, et al.

Background: There are growing concerns about the nonmedical use of attention deficit hyperactivity disorder (ADHD) stimulants. However, little is known regarding the temporal trend in prescription, nonmedical use and emergency department (ED) visits involving these medications and their associations.
Objectives: To investigate the relationship between trends in prescriptions, nonmedical use of, and ED visits for Adderall (dextroamphetamine-amphetamine) and methylphenidate among adults and adolescents.
Methods: Data are from three representative national surveys between years 2006-2011: National Disease and Therapeutic Index (NDTI, office-based practices' survey), National Survey on Drug Use and Health (NSDUH, population survey of substance use), and Drug Abuse Warning Network (DAWN, survey of ED visits). Association of quarterly treatment visits, nonmedical use, and ED visits were examined by ordinary least square (OLS) regression. Source for misused stimulants (NSDUH) and reasons for ED visits (DAWN) were examined by cross tabulation.
Results: In adolescents, visits in which Adderall or methylphenidate were prescribed decreased over the years; whereas, nonmedical use of Adderall remained stable and nonmedical use of methylphenidate declined 0.16% per year. No apparent trend of ED visits involving either drug was noted in adolescents. In adults, prescription visits for Adderall remained stable while nonmedical use and ED visits both increased by approximately 0.10% over the period and were strongly associated. Prescriptions, nonmedical use, and ED visits involving methylphenidate did not change in adults. For both drugs, the major source across age groups was a friend or relative. In two-thirds of the cases, the friend or relative had obtained the medication through prescriptions from a doctor.
Conclusions: Although prescriptions for Adderall among adults did not change in 2006-2011, both its nonmedical use and related ED visits increased significantly. Physician's prescriptions were the major source of the nonmedically used drug. Prevention strategies should target drug diversion routes as well as education on the adverse consequences of ADHD stimulants.

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Pharmacoepidemiol Drug Saf. 2014;23:151-52.

STIMULANT EFFECTIVENESS ON DRIVING CITATIONS AND CRASHES OF CHILDREN WITH ADHD.

Winterstein AG, Gerhard T, Kubilis P, et al.

Background: Observational and driving simulator studies suggest that ADHD causes higher risk-taking behavior, decreased attention and greater risk for car accidents, but little is known about the effectiveness of respective pharmacological treatment. Objectives: To evaluate the effectiveness of central nervous stimulants on driving outcomes in adolescents and young adults with ADHD.
Methods: We established the study cohort by linkage of Florida Medicaid fee-for-service billing data and Division of Motor Vehicle (DMV) records to obtain information on driver licensure, citations and crashes. Eligible subjects entered the cohort after their 15th birthday, an in- or outpatient diagnosis for ADHD, and issuance of a driver's license (DL). Follow-up ended at end of eligibility, >12 months without ADHD diagnosis, DL expiration/ suspension, age 21 or the study endpoint. Two endpoints were ascertained from DMV records: crashes, and citations for active driving violations. We defined exposure based on days' supply plus 25% including methylphenidate, mixed amphetamine salts and atomoxetine. We used logistic regression to estimate propensity scores (PS) based on socio-demographic characteristics, substance abuse (DUI or ICD9 code), DL learner's permit status, 2000 population size in county of residence, and countywide total annual daily vehicular miles traveled per total miles of paved road. Cox proportional hazards regression was used to estimate stimulant effects while adjusting for PS, valid DL status >1 year, and timedependent exposure to antidepressants, antipsychotics, anticonvulsants, anxiolytics and alpha-agonists.
Results: 2161 subjects had a total of 71 crashes and 338 citations. Hazard ratios for stimulants were HR= 1.01 (95% CI 0.61-1.70) for crashes and 0.86 (0.68-1.09) for citations. Antidepressants showed a significant association among all included psychotropics with HR= 0.29 (0.11-0.81) for crashes and 0.68 (0.50-0.95) for citations.

Conclusions: Stimulants showed no effect on citations and crashes. The effect of antidepressants might be due to parental driving restrictions.

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PLoS ONE. 2014;9.

ASSOCIATIONS BETWEEN ACETAMINOPHEN USE DURING PREGNANCY AND ADHD SYMPTOMS MEASURED AT AGES 7 AND 11 YEARS.

Thompson JMD, Waldie KE, Wall CR, et al.

Methods: Participants were members of the Auckland Birthweight Collaborative Study, a longitudinal study of 871 infants of European descent sampled disproportionately for small for gestational age. Drug use during pregnancy (acetaminophen, aspirin, antacids, and antibiotics) were analysed in relation to behavioural difficulties and ADHD symptoms measured by parent report at age 7 and both parent- and child-report at 11 years of age. The analyses included multiple covariates including birthweight, socioeconomic status and antenatal maternal perceived stress

Results: Acetaminophen was used by 49.8% of the study mothers during pregnancy. We found significantly higher total difficulty scores (Strengths and Difficulty Questionnaire parent report at age 7 and child report at age 11) if acetaminophen was used during pregnancy, but there were no significant differences associated with any of the other drugs. Children of mothers who used acetaminophen during pregnancy were also at increased risk of ADHD at 7 and 11 years of age (Conners' Parent Rating Scale-Revised)

Conclusions: These findings strengthen the contention that acetaminophen exposure in pregnancy increases the risk of ADHD-like behaviours. Our study also supports earlier claims that findings are specific to acetaminophen

Objective: Our aim was to replicate and extend the recently found association between acetaminophen use during pregnancy and ADHD symptoms in school-age children.

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PNAS Proceedings of the National Academy of Sciences of the United States of America. 2014 Sep;111:14259-64.

LAG IN MATURATION OF THE BRAIN'S INTRINSIC FUNCTIONAL ARCHITECTURE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sripada CS, Kessler D, Angstadt M.

Attention-deficit/hyperactivity disorder (ADHD) is among the most common psychiatric disorders of childhood, and there is great interest in understanding its neurobiological basis. A prominent neurodevelopmental hypothesis proposes that ADHD involves a lag in brain maturation. Previous work has found support for this hypothesis, but examinations have been limited to structural features of the brain (e.g., gray matter volume or cortical thickness). More recently, a growing body of work demonstrates that the brain is functionally organized into a number of large-scale networks, and the connections within and between these networks exhibit characteristic patterns of maturation. In this study, we investigated whether individuals with ADHD (age 7.2–21.8 y) exhibit a lag in maturation of the brain's developing functional architecture. Using connectomic methods applied to a large, multisite dataset of resting state scans, we quantified the effect of maturation and the effect of ADHD at more than 400,000 connections throughout the cortex. We found significant and specific maturational lag in connections within default mode network (DMN) and in DMN interconnections with two task positive networks (TPNs): frontoparietal network and ventral attention network. In particular, lag was observed within the midline core of the DMN, as well as in DMN connections with right lateralized prefrontal regions (in frontoparietal network) and anterior insula (in ventral attention network). Current models of the pathophysiology of attention dysfunction in ADHD emphasize altered DMN–TPN interactions. Our finding of maturational lag specifically in connections within and between these networks suggests a developmental etiology for the deficits proposed in these models.

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Psychiatry Res. 2014;219:707-09.

THE DEVELOPMENTAL COURSE OF CHILDHOOD INATTENTION SYMPTOMS UNIQUELY PREDICTS EDUCATIONAL ATTAINMENT: A 16-YEAR LONGITUDINAL STUDY.

Pingault J-B, Cote SM, Vitaro F, et al.

In this 16-year longitudinal study, a new trajectory estimation approach was used to verify whether the developmental course of childhood inattention significantly predicted functional impairment. A rising childhood inattention trajectory significantly predicted graduation failure (OR: 1.76 [1.32-2.34]) independently of averaged inattention levels. Rising inattention is, in itself, important for prognosis.

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Psychol Med. 2014 Sep;44:2661-71.

NEURAL CORRELATES OF INHIBITORY CONTROL AND VISUAL PROCESSING IN YOUTHS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A COUNTING STROOP FUNCTIONAL MRI STUDY.

Fan LY, Gau SSF, Chou TL.

Background: Despite evidence of inhibitory control and visual processing impairment in attention deficit hyperactivity disorder (ADHD), knowledge about its corresponding alterations in the brain is still evolving. The current study used counting Stroop functional MRI and the Cambridge Neuropsychological Test Automated Battery (CANTAB) to investigate if brain activation of inhibitory control and visual processing would differ in youths with ADHD relative to neurotypical youths.

Method: We assessed 25 youths with ADHD [mean age 10.9 (S.D. = 2.2) years] and 23 age-, gender- and IQ-matched neurotypical youths [mean age 11.2 (S.D. = 2.9) years]. The participants were assessed by using the Wechsler Intelligence Scale for Children, third edition, and two tests from the CANTAB: rapid visual information processing (RVP) and pattern recognition memory (PRM) outside the scanner.

Results: Youths with ADHD showed more activation than neurotypical youths in the right inferior frontal gyrus [Brodmann area (BA) 45] and anterior cingulate cortex, which were correlated with poorer performance on the RVP test in the CANTAB. In contrast, youths with ADHD showed less activation than neurotypical youths in the left superior parietal lobule (BA 5/7), which was correlated with the percentage of correct responses on the PRM test in the CANTAB.

Conclusions: Our findings suggest that youths with ADHD might need more inhibitory control to suppress interference between number and meaning and may involve less visual processing to process the numbers in the counting Stroop task than neurotypical youths.

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Res Dev Disabil. 2014;35:3543-53.

CYBERBULLYING AMONG MALE ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: PREVALENCE, CORRELATES, AND ASSOCIATION WITH POOR MENTAL HEALTH STATUS.

Yen C-F, Chou W-J, Liu T-L, et al.

The aims of this study were to examine the prevalence rates and multilevel correlates of cyberbullying victims and perpetrators among male adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) in Taiwan. The relationships between cyberbullying involvement and depression, anxiety, and suicidality were also examined. The experiences of cyberbullying victimization and perpetration in 251 male adolescents with ADHD were assessed. Logistic regression analysis was used to examine the correlates of cyberbullying victims and perpetrators. The relationships between cyberbullying involvement and depression, anxiety, and suicidality were examined using multiple regression analysis. A total of 48 (19.1%) and 36 (14.3%) participants reported that they were cyberbullying victims or perpetrators, respectively. Those who had increased age and a higher parental occupational socioeconomic status, and reported more severe traditional passive bullying victimization were more likely to be cyberbullying victims. Those who had increased age and combined-type ADHD, and reported lower BAS reward responsiveness, more severe Internet addiction and more severe traditional passive bullying perpetration were more likely to be cyberbullying perpetrators. Cyberbullying victims reported more severe depression and suicidality than those who were not cyberbullying victims. A high proportion of male adolescents with ADHD are involved in

cyberbullying. Clinicians, educational professionals, and parents of adolescents should monitor the possibility of cyberbullying involvement among male adolescents with ADHD who exhibit the cyberbullying correlates identified in this study.

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Social Work in Health Care. 2014 Aug;53:601-16.

DYNAMICS OF ADHD IN FAMILIAL CONTEXTS: PERSPECTIVES FROM CHILDREN AND PARENTS AND IMPLICATIONS FOR PRACTITIONERS.

Wong HM, Goh ECL.

This article provides in-depth insights on the bidirectional dynamics between parents and their children with attention deficit hyperactivity disorder (ADHD). Five family units (8 parents, 5 children, N = 13) participated in this study. Parents and their child with ADHD were interviewed individually in their homes. Stressful moments of parent–child dynamics revolved around managing their child's behavior and doing homework. Findings highlight the child's agency and power of influence, and the possible recovery of negative dynamics. It is recommended that practitioners adopt the strengths perspective in working with these families and incorporate child's agency and bidirectional dynamics in interventions.

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Zh Nevrologii Psihiatrii im S S Korsakova. 2012;112:44-48.

ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH COMORBID ANXIETY DISORDERS: PHARMACOTHERAPY OPTIONS.

Zavadenko NN, Solomasova AA.

Comorbid anxiety disorders are observed in many patients with attention deficit hyperactivity disorder (ADHD): 25-33% compared to 6-10% in pediatric population. Therapeutic effects of Adaptol have been studied, indicated for children and adolescents with ADHD as monotherapy, in dosages of 25-35 mg/kg for 1-3 months. The positive influence of Adaptol on the core symptoms of ADHD was confirmed: reduction of hyperactivity and impulsivity was registered after 1st month, while clinical manifestations of the attention deficit were decreased on the 2nd-3rd months of the treatment. Anxiolytic activity became apparent from the 1st month and continued to increase on the 2nd-3rd months of the treatment. Simultaneously significant reduction of the oppositional-defiant disorder manifestations were observed.

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Prevalence of severe ADHD: an epidemiological study in the Italian regions of Tuscany and Latium

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Background. The rate with which attention deficit/hyperactivity disorder (ADHD) is diagnosed varies widely across countries, suggesting that cultural factors influence the clinical interpretation of child behaviour. This study estimated the point prevalence of severe ADHD among elementary and middle-school Italian children.

Method. An epidemiological sample of 2016 children attending 2nd–8th grade in the Italian regions of Tuscany and Latium was selected based on census distribution of the school-age population. Teachers completed the Italian version of the ADHD Rating Scale for Teachers (SDAI). For children with at least six inattention symptoms and/or at least six hyperactivity/impulsivity symptoms rated 'very often' by the teachers, the parents completed the Italian ADHD Rating Scale for Parents (SDAG). Children with documented ADHD symptoms at both school and home received a complete psychiatric interview with the Kiddie Schedule for Affective Disorders and Schizophrenia-present and lifetime version (K-SADS-PL).

Results. Of the 1887 assessed children, 4.45% (95% CI 3.58–5.51) met the ADHD cut-off on teacher ratings, 1.43% (0.96–2.12) had ADHD symptoms endorsed by both teacher and parent, and 1.32% (0.87–1.97) were further confirmed by the psychiatric evaluation. The male:female ratio was 7:1. The inattentive type accounted for about half of the ADHD cases.

Conclusions. When applying stringent criteria for both severity and pervasiveness of symptoms, it is estimated that about 1.3% of the Italian elementary and middle-school children suffer from severe ADHD.

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Key words: Attention deficit/hyperactivity disorder, children, Italy, prevalence.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a disorder characterised by developmentally inappropriate and functionally impairing levels of inattention and/or hyperactivity and impulsivity. ADHD becomes typically evident in the first decade of life, and tends to persist through adolescence and adulthood (Swanson *et al.* 1998). Despite extensive research, there is continuous debate on both the validity and prevalence of ADHD (Singh, 2008). The use of medications to treat ADHD has been rapidly increasing worldwide, a phenomenon that has raised concern about the appropriateness and safety of this practice (Dalsgaard *et al.* 2013; Thomas *et al.* 2014). Although neurobiological correlates of ADHD, such as delayed maturation of the brain prefrontal cortex, have been documented (Shaw *et al.* 2012), there is currently no biological marker that can be used for diagnostic purposes. Thus, ADHD remains a clinical diagnosis that is largely based on the observation of the child's behaviour by parents and teachers.

The prevalence of ADHD is estimated to be about 5% worldwide, but with a large variability that is mainly attributed to differences in diagnostic and ascertainment methods (Polanczyk *et al.* 2007, 2014). In the USA, rates of 8.7 and 15.5% have been reported (Froehlich *et al.* 2007; Rowland *et al.* 2013). Such unexpectedly and increasingly high rates raise concern about the specificity of the assessment methods. Even if the validity of the ADHD construct has been proven regardless of cultural characteristics (Rohde *et al.* 2005;

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Buitelaar *et al.* 2006), the actual application of the diagnosis to community care is strongly influenced by cultural factors (Skounti *et al.* 2007).

In fact, the presence of the core symptoms of inattention, hyperactivity and/or impulsivity does not *per se* result in a diagnosis of ADHD, unless these behaviours are deemed by parents and teachers to cause functional impairment. Thus, even if the distribution of objectively measured behaviours relevant to ADHD in the population is consistent across countries and cultures, the critical factor is whether their presence is considered sufficiently extreme and impairing by parents and educators to be considered abnormal.

Over the past 30 years, the more restrictive nosological construct of *hyperkinetic disorder* of the International Classification of Diseases (ICD) has been largely replaced by the broader criteria of the Diagnostic and Statistical Manual of Mental Disorder (DSM) (Taylor & Sonuga-Barke, 2008). Hyperkinetic disorder can be considered a subset of ADHD, probably accounting for about one-fourth of children clinically treated for ADHD of hyperactive or combined type (Santosh *et al.* 2005). While the DSM is dominant in the USA, European psychiatry is still influenced, to varying degrees, by the more conservative criteria, thus leading to substantial differences in the rate with which ADHD is diagnosed and managed in clinical practice. The rate of diagnosis is also influenced by differences in the educational systems, as ADHD is considered reason for receiving special education in some countries but not in others (Al-Yagon *et al.* 2013).

Not surprisingly, differences in diagnostic threshold carry important clinical implications for treatment. There are striking differences worldwide in the use of medications for the treatment of ADHD. In the USA, it was estimated that 3.5% of the population under age 19 received stimulant medications in 2008 (Zuvekas & Vitiello, 2012), and a more recent study has reported that 6.1% of children aged 4–17 years were taking medication for ADHD in 2011 (Visser *et al.* 2014). In striking contrast, the paediatric use of stimulant medications is <1% in Italy or France (Frauger *et al.* 2011). Multiple factors probably contribute to these discrepancies, including, among the others, differences in nosology, healthcare and education systems, drug regulatory policy and general attitude of the public towards the use of medications in children (Vitiello, 2008). Among these factors, the interpretation of the child behaviour by parents and teachers as abnormal, and hence in need of treatment, plays a critical role (Moffitt & Melchior, 2007).

Italy is one of the economically developed countries with the lowest use of medications for ADHD. Only a few studies have attempted to evaluate the rate of ADHD in Italian children. A pilot epidemiological study estimated that 3.9% of 4th grade students were 'likely cases' of ADHD based only on teacher ratings (Gallucci *et al.* 1993). In a sample of first graders in Italy, teachers endorsed symptom criteria for ADHD in 7.1% of the children (3.5% with inattentive subtype and 3.6% with hyperactive or combined subtype) (Mugnaini *et al.* 2006). Parent ratings, however, were not obtained, and, as underscored by the authors of this study, the real prevalence of the disorder is likely to be lower. It is remarkable that an epidemiological study of Italian adolescents (age 10–14 years) found that the overall prevalence of mental disorders (8.2%) was similar to that reported in other European countries, but the prevalence of externalising disorders, which also includes ADHD, was only 1.2% (Frigerio *et al.* 2009). More recently, in a sample of elementary and middle school population in Syracuse, Italy, the prevalence of ADHD was estimated to be 3%, with most of the cases meeting criteria for the combined or hyperactive type, and about a quarter for the inattentive type (Bianchini *et al.* 2013).

There is evidence that the population rate of ADHD varies widely based on the diagnostic criteria and the ascertainment methods used (Skounti *et al.* 2007; Rowland *et al.* 2013). In particular, the cut-off chosen for symptom endorsement is a key factor. It is conventionally accepted that a manifestation of inattention or hyperactivity that occurs 'often' in the eyes of the teacher or the parent qualifies for a symptom of ADHD and therefore counts towards the diagnosis. However, the increasing rate of ADHD reported in epidemiological studies over recent years suggests that the current criteria may be too broad. In particular, concern has been raised that many of the children diagnosed with ADHD in the community have only mild or moderate symptoms, and that some of those diagnosed may not meet the full diagnostic criteria for the disorder (Thomas *et al.* 2014).

The clinical interpretation of mild symptoms is more likely to be influenced by contextual and cultural factors than that of severe hyperactivity, impulsivity or inattention, which can be more clearly recognised as abnormal. A focus on severe ADHD can help targeting treatment intervention to those most in need while minimising inappropriate exposure to medications. Based on current clinical guidelines, pharmacotherapy is especially indicated for severe ADHD (National Institute for Health and Clinical Excellence, 2013).

The purpose of this study was to assess the prevalence of severe ADHD using an epidemiological sample of Italian school children by adopting extremely stringent criteria for symptom endorsement. The aim was to estimate the proportion of children with unquestionably abnormal levels of inattentive and/or

hyperactive and impulsive behaviour, for which treatment would be clearly indicated.

Methods

Sample selection and characteristics

An epidemiological sample of 2016 children was derived from 17 elementary and middle public schools in the Italian regions of Tuscany and Latium. The schools were selected according to the Italian population census, which indicated that 67.02% of children under age 15 lived in municipalities with <50 000 inhabitants, 18.50% in municipalities between 50 000 and 250 000 inhabitants, and 14.46% in municipalities with over 250 000 inhabitants, and that 45.01% of Italian students attended schools with <250 students (Istituto Nazionale di Statistica, 1995; Italian Ministry of Public Education, 2000). Within these schools, a representative sample for grades 2–8 was randomly obtained, reflecting an equal distribution of children attending these grades in the Italian population (Italian Ministry of Public Education, 2000).

The study was approved by the relevant school districts. Written informed consent was requested from the parents to assess their child in school. Of the 2016 parents contacted, 1893 (93.9%) gave permission. Teachers completed rating scales for 1887 children (Fig. 1 and Table 1). All the data were collected in the school year 2002–2003.

Procedures and assessments

At the first step, the teachers of the 1893 children for whom parental permission was granted were asked to complete the Italian version of the ADHD Rating Scale for Teachers (*Scala per i Disturbi di Attenzione/Iperattività per Insegnanti* or SDAI) (Cornoldi *et al.*

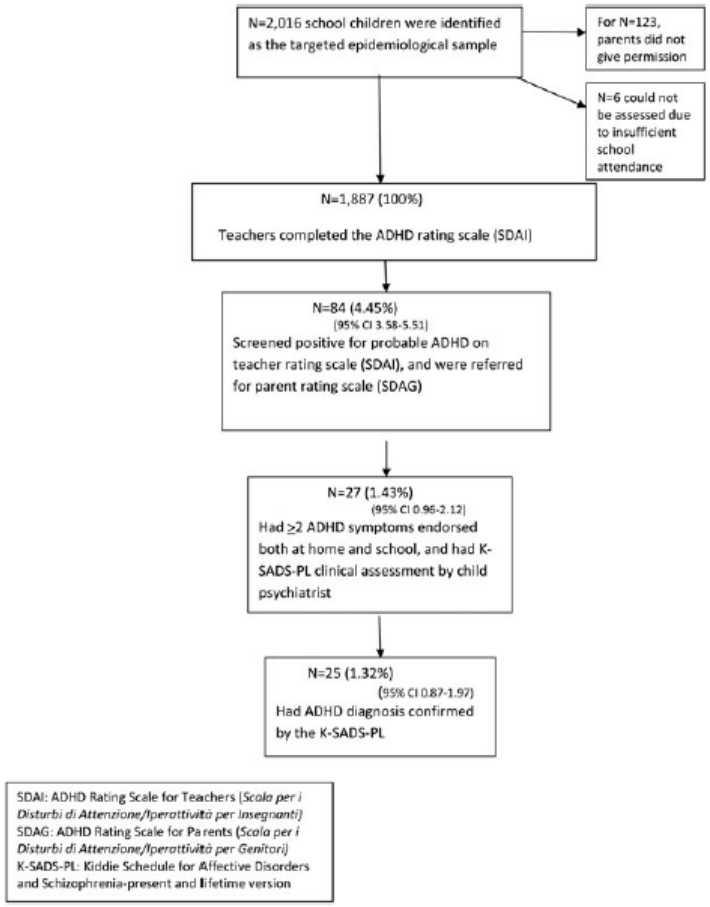

Fig. 1. Study's steps and subject flow.

Table 1. *Sample characteristics*

	N	%
Total	1887	100
Males	924	48.97
Females	963	51.03
From municipalities with:		
<50 000 people	1,188	62.96
50 000–250 000 people	415	21.99
>250 000 people	284	15.05
School grade:[a]		
2	256	13.57
3	243	12.88
4	252	13.35
5	271	14.36
6	325	17.22
7	303	16.06
8	237	12.56

[a]The proportion of males within the grades ranged from 46.81 to 54.38%.

1996; DuPaul *et al.* 1997). The SDAI Scale asks the teacher to rate on a 4-point scale the frequency/intensity of the each of the nine symptoms of inattention and the nine symptoms for hyperactivity/impulsivity reported of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (*DSM-IV*; American Psychiatric Association, 1994). Each symptom can be scored as 'never or rarely', 'sometimes', 'often' or 'very often'. The SDAI has demonstrated excellent inter-rater reliability and test–retest reliability (Marzocchi & Cornoldi, 2000).

At the second step, the parents of the children with at least six inattentive symptoms and/or at least six hyperactivity/impulsivity type scored as present 'very often' were asked to complete the parent version of the ADHD rating scale (*Scala per i Disturbi di Attenzione/Iperattività per Insegnanti* or SDAG) (Cornoldi *et al.* 1996), which is structured in the same way as the SDAI.

Last, children with at least six inattentive symptoms and/or at least six hyperactivity/impulsivity type scored as present 'very often' by the teacher and at least two of these symptoms scored to be present 'very often' also by the parent were further assessed with a comprehensive in person psychiatric evaluation. Each child and parent were separately administered the Italian version of the Kiddie Schedule for Affective Disorders and Schizophrenia-present and lifetime version (K-SADS-PL, Kaufman *et al.* 1997). The K-SADS-PL is a semi-structured psychiatric interview to assess the presence of the most common psychiatric disorders. The K-SADS-PL was administered by an experienced child psychiatrist trained in the use of this diagnostic instrument (RD). Children's intelligence level was measured by Wechsler Intelligence Scale for Children-Revised (WISC-R), and an IQ<70 was an exclusion criterion from a diagnosis of ADHD. Other exclusion criteria were: a diagnosis of bipolar disorder, major depression, dysthymic disorder, schizophrenia, developmental pervasive disorder or generalised anxiety disorder. Functional impairment was assessed using Children's Global Assessment Scale (CGAS), on a scale from 0 (severe impairment) to 100 (superior functioning), with a score below 70 indicating clinically the significant dysfunction (Shaffer *et al.* 1983). The Strengths and Difficulties Questionnaire (SDQ) was completed by the teachers and parents (Goodman *et al.* 2000).

To evaluate the sensitivity of the ascertainment process for ADHD, a sample of 102 children (mean age 8.9 years) and their parents, randomly selected from the children with a negative teacher ADHD rating scale (SDAI) score, were interviewed with the K-SADS PL 1.0. Of them, none met the criteria for ADHD. Inter-rater reliability of the K-SADS-PL interviewers was assessed on a sample of 87 children. The agreement between the interviewers was 89.66%., and the Cohen's kappa coefficient for the diagnosis of ADHD was 0.81.

Data analysis

Descriptive statistics was applied to the data. The number and percentage of children exceeding the set cut-off scores on the SDAI, both SDAI and SDAG and further meeting criteria for ADHD on the K-SADS-PL were computed. Within the subgroup of children with ADHD on the K-SADS-PL, the prevalence of ADHD subtypes and abnormal scores on the parent and teacher SDQ and clinician C-GAS scores were examined.

A conservative approach to missing data was adopted. Of the parents who were requested to complete the SDAG, 5.56% were failed to return the forms, and 8.82% of the parent SDQ forms were similarly missing. In the absence of parent information, a diagnosis of ADHD could not be formulated, and these children were accounted as non-ADHD cases.

Results

Figure 1 and Table 2 summarise the study steps, subject flow and main findings. Of the 2016 children included in the epidemiologically selected sample, 123 children could not be assessed because their parents did not give permission, and other six children could not be assessed because they had been absent

Table 2. *Rate of ADHD by assessment step (N = 1887)*

	ADHD	Male/ Female	Inattentive type of ADHD	Hyperactive type of ADHD	Combined type of ADHD	2nd–5th school grade (*N* = 1022)	6nd–8th school grade (*N* = 865)
	N (%) (95% CI)	*N* (ratio)	*N* (%) (95% CI)	*N* (%) (95% CI)	*N* (%) (95% CI)	*N* (%) (95% CI)	*N* (%) (95% CI)
Teacher ADHD Rating Scale (SDAI)	84 (4.45) (3.58–5.51)	73/11 (7:1)	51 (2.70) (2.04–3.56)	18 (0.95) (0.58–1.53)	15 (0.79) (0.46–1.33)	65 (6.36) (4.98–8.08)	19 (2.20) (1.37–3.48)
Teacher & Parent Rating Scales (SDAI + SDAG)	27 (1.43) (0.96–2.12)	23/4 (7:1)	19 (1.01) (0.65–1.57)	4 (0.21) (0.07–0.58)	4 (0.21) (0.07–0.58)	21 (2.05) (1.31–3.17)	6 (0.69) (0.28–1.58)
Confirmed by Psychiatric Interview (SDAI + SDAG + K-SADS)	25 (1.32) (0.87–1.97)	22/3 (7:1)	12 (0.64) (0.35–1.15)	3 (0.16) (0.04–0.51)	10 (0.53) (0.27–1.01)	20 (1.96) (1.23–3.07)	5 (0.58) (0.21–1.43)

from school for extended periods of time. A total of 1887 children (93.6% of the selected sample) were assessed on the ADHD Rating Scale for Teachers (SDAI).

The distribution of the SDAI total score in the sample followed a positively, right skewed distribution (Fig. 2). In total 78% of the children had at least one ADHD-relevant behaviour rated by the teacher to be present 'sometimes'; 39% had at least one behaviour rated 'often'; and 6% had at least one behaviour rated 'very often'.

Of the 1887 children assessed, 4.45% (95% CI 3.58–5.51) met the number and severity of symptoms for ADHD in the school setting (based on teacher rating); 1.43% (95% CI 0.96–2.12) had also severe symptoms at home (based on both teacher and parent ratings), thus meeting the diagnostic criterion of pervasiveness across more than one setting; and 1.32% (95% CI 0.87–1.97) had their diagnosis of ADHD confirmed by a comprehensive psychiatric evaluation by a child psychiatrist.

Among the children who screened positive on both the teacher and parent ADHD ratings, the psychiatric evaluation did not confirm the diagnosis in three cases: in two cases the symptoms could be better explained by another, non-ADHD, condition, and in one case the full criteria for ADHD were not met because there was no clear-cut evidence of dysfunction.

The prevalence of severe ADHD was 1.96% (95% CI 1.23–3.07) among elementary school children, and 0.58% (95% CI 0.21–1.43) among middle school children. The male/female ratio was 7:1. The demographic and clinical characteristics of the children with severe ADHD are summarised in Table 3. They had C-GAS scores ranging between 40 and 60, which are indicative of clinically significant impairment in global functioning. All had SDQ-teacher abnormal scores, and 19 had SDQ-parent abnormal scores, further documenting functional impairment. ADHD-inattentive type was documented in 12 (48%) of the cases, and ADHD hyperactive or combined type in the other 13 (52%). Sixteen (52%) met the DSM-IV criteria for oppositional defiant disorder and four of these also for conduct disorder.

Discussion

By examining an epidemiological sample of elementary and middle school children in two regions of Italy, and requiring extremely stringent criteria for the endorsement of ADHD-relevant symptoms by both teachers and parents, with final confirmation after a clinical assessment with a child psychiatrist,

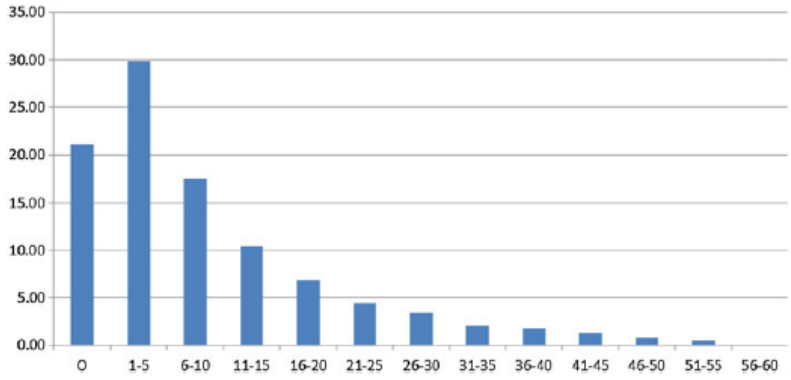

Fig. 2. Frequency distribution of total scores of ADHD rating scale for teachers (SDAI) ($N = 1887$).

Table 3. *Characteristics of the identified ADHD sample*[a]

Total *N*	25 (100%)
Age (year, mean ± S.D.)	9.58 ± 1.84
Male (*N*)	23 (92%)
IQ (mean ± S.D.)	96.85 ± 15.53
ADHD-inattentive (*N*)	12 (48%)
ADHD-hyperactive	3 (12%)
ADHD-combined	10 (40%)
With ODD[b]	16[c] (64%)

[a]ADHD, diagnosed by psychiatric interview based on K-SADS-PL.
[b]ODD, oppositional defiant disorder.
[c]Of these, 14 were male. Four (all male) also met criteria for conduct disorder.

we estimated that about 1.3% of children suffer from severe ADHD. These children are functionally impaired as documented by CGAS scores in the 40–60 range. This is a conservative estimate because of the requirement that each ADHD symptom be present 'very often' based on both teacher and parent report. Not surprisingly, the rate is much lower than reported in other studies that used the DSM-III-R or DSM-IV criteria with the usual cut-off of 'often' for presence of ADHD symptoms. By sacrificing diagnostic sensitivity, we have aimed at maximising specificity and therefore avoiding false-positive diagnoses. Focus on severe ADHD can help in planning for more targeted treatment interventions.

Our data confirm that ADHD symptoms are continuously distributed in the population (Fig. 2), so that any cut-off for disorder identification can be considered arbitrary. By selecting 'very often' to endorse the presence of each symptom, the likelihood of false positive was minimised. In fact, a score of 'often' for at least one item of the ADHD Rating Scale for Teachers (SDAI) was found for 39% of the surveyed children, whereas a score of 'very often' for a least one item was found only in 6% of them. By requiring that severe ADHD symptoms may also be present in non-school setting as documented by the ADHD Rating Scale for Parents (SDAG), we ensured the pervasiveness of the condition. Two-thirds of the children meeting the strict criteria by teacher rating did not qualify for pervasiveness of severe ADHD symptoms based on parent rating (Fig. 1).

The 1.3% rate of severe ADHD in this study is similar to the prevalence of hyperkinetic disorder, a nosological construct commonly used before the advent of the DSM criteria of ADHD (Taylor *et al.* 2004). A diagnosis of hyperkinetic disorder requires the concurrent presence of all three in the core domains of ADHD (i.e., hyperactivity, impulsivity and inattention) and the exclusion of any comorbid condition. The 7:1 male/female ratio for severe ADHD in this study is remarkable. That ADHD is substantially higher in boys and has been consistently documented across studies and countries, but usually with a rate of about 3:1. The data indicate that the male/female ratio increases with the severity of the condition. It should be noted that about half of the children

identified with severe ADHD had predominantly inattentive symptoms (Table 3). These data do not obviously rule out that prominent, although not extremely severe, hyperactivity and impulsivity were concomitantly present in these children, but point to the relevance of inattention as a severe cause of impairment in a subset of children. These results also confirm the developmental nature of ADHD, with attenuation of the symptoms as children grow into adolescence.

The study sample was epidemiologically derived and based on the distribution of the school-age population in the targeted geographical area of Tuscany and Latium. Although limited to two regions, the data are likely informative at the Italian national level given the common cultural characteristics and the same educational and health care system across the entire country. Several limitations of the study should be acknowledged. First, the data were collected in 2002–2003 and only recently analysed. Despite the 10-year hiatus, however, it seems unlikely that the rate could have changed during this period as a recent systematic review and meta-regression analyses of data across the past 3 decades have found no evidence of a historical increase in the population prevalence of ADHD when consistent and validated assessment methods are used (Polanczyk *et al.* 2014). Second, because of funding limitations for this study, a more detailed examination of the sample or inquiry into the use of different symptom cut-offs could not be done.

It should also be noted that there is currently no universally agreed upon definition of *severe ADHD* (Thomas *et al.* 2014). Neither the American nor the Australian diagnostic guidelines operationalise the criteria for severity, and the UK National Institute for Health and Clinical Excellence (NICE) guidelines equalise severe ADHD to hyperkinetic disorder (National Institute for Health and Clinical Excellence, 2013).

More than 20 years ago, it was observed that the diagnosis of ADHD 'is seldom, if ever, made by clinicians in Italy' and that 'psychostimulants generally considered to be an important, if not the primary treatment for ADHD, are not available in the Italian pharmacopoeia' (Gallucci *et al.* 1993). In fact, no pharmacological treatment of ADHD was available in Italy until 2007, when methylphenidate and atomoxetine were introduced but subjected to strict prescribing regulations through enrolment into a national registry (Arcieri *et al.* 2012). In the first 3 years (2007–2010), only 1758 were enrolled in the registry vis-à-vis a population of about 7 million children and adolescents aged 6–18 years (Arcieri *et al.* 2012).

The data from this study indicate that, even if extremely conservative criteria are applied, about 1.3% of school-age children suffer from severe symptoms of ADHD that are pervasive, frequently accompanied by comorbid behavioural disturbance, and associated with clinically significant functional impairment. The impairment is global and not limited to school setting. Given the level of dysfunction, treatment is clearly indicated. While there is no cure for ADHD, symptoms can be successfully managed, and a number of evidence-based treatment modalities are available, including psychosocial and pharmacological interventions.

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Conflict of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human research.

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