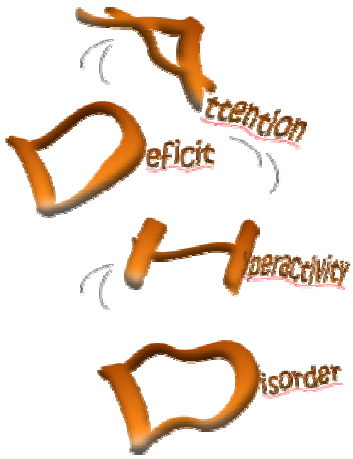
NEWSLETTER



INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD AGOSTO 2014

Act Nerv Super. 2014;56:37-44.

AUDITORY ERPS IN CHILDREN WITH DEVELOPMENTAL COORDINATION DISORDER.

Holeckova I, Cepicka L, Mautner P, et al.

The present study aims to investigate and compare the auditory attention performance of children with developmental coordination disorder (DCD) and normally developing children (NDC) using cognitive evoked potentials (ERPs) in passive conditions. ERPs data showed that children with DCD have less ability to detect small physical differences between acoustic stimuli (no MMN response in DCD children) and have a reduced attentional engagement and stimulus evaluation of salient stimuli (a reduction of P3 amplitude in DCD children). The results of our study suggest that children with DCD do not only suffer from a visuospatial attention deficit as previous studies reported but also have auditory attention deficit.

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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.

Addictive Behaviors. 2014 Aug;39:1278-85.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SUBTYPES AND SUBSTANCE USE AND USE DISORDERS IN NESARC.

De Alwis D, Lynskey MT, Reiersen AM, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is associated with substance use and substance use disorders (SUD). However, relatively little is known about the relationship between DSM-IV ADHD subtypes and substance use or DSM-IV abuse/dependence in epidemiological samples.

Methods: Data were obtained from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC, N=33,588). Respondents reported on ADHD symptoms (DSM-IV) for the period of time when they were 17 years or younger. Lifetime use and DSM-IV abuse/dependence of alcohol, nicotine, cannabis, cocaine, sedatives, stimulants and heroin/opiates were compared across those with ADHD symptoms but no diagnosis (ADHDsx; N = 17,009), the Combined (ADHD-C; N=361), Predominantly Inattentive (ADHD-I; N=325), and the Predominantly Hyperactive-Impulsive (ADHD-HI; N=279) ADHD subtypes. Taking amore dimensional approach, inattentive and hyperactive-impulsive symptom counts and their associations with substance use and misuse were also examined.

Results: After adjustments for conduct disorder,major depressive disorder, any anxiety disorder and other sociodemographic covariates, substance use and SUD were associated with ADHDsx, ADHD-C, ADHD-I and ADHD-HI. Overall, substance use and SUD were more weakly associated with the ADHDsx group compared to the three ADHD diagnostic groups. Statistically significant differences were not evident across the three diagnostic groups. Hyperactive–impulsive symptoms were more consistently associated with substance use and SUD compared to inattentive symptoms.

Conclusions: ADHD subtypes are consistently associated with substance use and SUD. The relatively stronger association of hyperactive/impulsive symptoms with substance use and abuse/dependence is consistent with the extant literature noting impulsivity as a precursor of substance use and SUD.

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ADHD Atten Deficit Hyperact Disord. 2014.

RELATIONSHIP BETWEEN SYMPTOM IMPAIRMENT AND TREATMENT OUTCOME IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A PHYSICIAN PERSPECTIVE.

Setyawan J, Fridman M, Hodgkins P, et al.

We evaluated the association between those symptoms/behaviours of attention-deficit/hyperactivity disorder (ADHD) that were present at diagnosis and outcomes of treatment in children and adolescents in six European countries. Physicians abstracted clinical records from patients (6-17 years) diagnosed with ADHD between 2004 and 2007 and treated for (greater-than or equal to) 2 years. Physicians scored the severity of impairment for core ADHD symptoms and additional (non-core) ADHD symptoms/behaviours at diagnosis and estimated treatment adherence (defined as an estimated >80 % adherence on weekdays and >50 % adherence on weekends). Treatment modalities included pharmacological treatment, behavioural therapy, or both. Pharmacological treatment was further subclassified by medication class. The outcome, optimal treatment success (OTS), was defined as complete symptom control with high satisfaction with treatment. Multivariate logistic regression modelling examined the relationship between OTS and symptom impairment. Of 730 patients, 200 (27 %) achieved OTS. These patients were more likely to demonstrate lower impairment in non-core ADHD symptoms/behaviours and have fewer pre-existing comorbidities. They were also more likely to be adherent and engaged with treatment, with an explicit treatment goal to improve inattention/school performance. Neither core symptoms' severity nor treatment types were associated with OTS. OTS rates were low, with patients having less impairment of non-core ADHD symptoms/behaviours and fewer comorbidities more likely to achieve OTS. Potentially modifiable factors affecting OTS were as follows: treatment adherence, treatment engagement, and a treatment goal to improve inattention/school performance. These data suggest that there may be opportunities to optimize current treatment use, and develop new treatment strategies to improve core and non-core ADHD symptoms/behaviours.

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Am J Med Genet Part A. 2014;164:2180-86.

AUTISM SPECTRUM DISORDERS AND HYPERACTIVE/IMPULSIVE BEHAVIORS IN JAPANESE PATIENTS WITH PRADER-WILLI SYNDROME: A COMPARISON BETWEEN MATERNAL UNIPARENTAL DISOMY AND DELETION CASES.

Ogata H, Ihara H, Murakami N, et al.

This study aims to compare maternal uniparental disomy 15 (mUPD) and a paternal deletion of 15q11-13 (DEL) of Prader-Willi syndrome (PWS) in regard to autism spectrum disorders (ASD). Forty-five Japanese individuals with PWS were recruited from a single recruitment center. The participants consisted of 22 children (aged from 6 to 12) and 23 adolescents (aged from 13 to 19). Six children and seven adolescents were confirmed as having mUPD. Sixteen children and 16 adolescents were confirmed as having DEL. Under blindness to the participants' genotypes, a single psychologist carried out behavioral and psychological assessments, including the Wechsler Intelligence Scales, Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS), and ADHD-Rating Scale-IV (ADHD-RS-IV). Two comparisons were made: one between mUPD and DEL children and another between mUPD and DEL adolescents. In children, no significant differences were found between mUPD and DEL participants in terms of autistic (PARS childhood, P=0.657) and impulsive behaviors (ADHD-RS-IV hyperactive/impulsive, P=0.275). In adolescents, mUPD patients showed significantly more autistic symptomatology (PARS adolescent, P=0.027) and significantly more impulsive behavior (ADHD-RS-IV hyperactive/impulsive, P=0.01) than DEL patients. Our findings about Japanese PWS patients were consistent with previous researches from western countries not focused on Asian patients, indicating that mUPD cases would be more prone to ASD than DEL cases, regardless of ethnoregional differences. In addition, our data suggested that the behavioral difference between mUPD and DEL cases in terms of autistic and impulsive symptoms tend to be unrecognizable in their childhood.

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Am J Med Genet Part B Neuropsychiatr Genet. 2014;165:502-09.

GLUTAMATERGIC COPY NUMBER VARIANTS AND THEIR ROLE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Akutagava-Martins GC, Salatino-Oliveira A, Genro JP, et al.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder with a strong genetic component. The glutamate metabotropic receptor genes (GRMs) have been considered potential candidates for ADHD susceptibility. The aim of the present study was to investigate if copy number variants (CNVs) in GRM1, GRM5, and GRM8 genes are overrepresented in ADHD subjects. A total of 1038 individuals with ADHD and 1057 subjects without this disorder were investigated. No significant difference in the total number of CNVs was found comparing the entire ADHD sample and the population sample without ADHD (P=0.326, OR=1.112, 95% CI=0.762-1.624). The presence of CNVs was associated with lower intelligence quotient (IQ) scores in ADHD samples (P=0.026, OR=1.824, 95% CI=1.066-3.121) but not in the sample of individuals without ADHD. CNVs in GRM5 were associated with presence of anxiety disorders in ADHD cases (P=0.002, OR=3.915, 95% CI=1.631-9.402), but not in individuals without ADHD. Taken together, our results suggest a role for glutamate in ADHD as CNVs in the glutamatergic genes investigated herein were associated with cognitive and clinical characteristics of ADHD individuals.

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Applied Psychophysiology and Biofeedback. 2014 Jun;39:99-107.

A PILOT FEASIBILITY STUDY OF NEUROFEEDBACK FOR CHILDREN WITH AUTISM.

Steiner NJ, Frenette E, Hynes C, et al.

Neurofeedback (NFB) is an emerging treatment for children with autism spectrum disorder (ASD). This pilot study examined the feasibility of NFB for children with ASD. Ten children ages 7–12 with high functioning ASD and attention difficulties received a NFB attention training intervention. A standardized checklist captured feasibility, including focus during exercises and academic tasks, as well as off-task behaviors. Active behaviors and vocalizations were the most frequent off-task behaviors. Positive reinforcement and breaks including calm breathing exercises were the most common supports. Low motivation was associated with higher feasibility challenges, yet parental involvement and accommodations were helpful.

This pilot study shows that it is feasible to conduct NFB sessions with children with high functioning autism and attention difficulties.

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Arch Pediatr. 2014.

A SURVEY ON ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Quiviger S, Caci H.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder described in international classifications and thought to affect about 5% of school-aged children and 3% of adults in the general population. In France, most clinicians are not formally trained in assessing and treating ADHD, leading to underdiagnosis of the disorder. ADHD impacts all the aspects of these children's daily life (school performance, family and social life) and later their adult life. We invited all the private-practice pediatricians in the east of the Provence-Alpes-COte d'Azur region (southeast France) to participate in a survey: 57 out of 81accepted. The results show that their knowledge on ADHD could be improved, and that their a priori conception of the etiology of the disorder (neurodevelopmental syndrome versus societal syndrome) guides their clinical approach. We recommend pediatricians be trained to improve screening, diagnosis, and ADHD treatment monitoring in children. This recommendation might also apply to general practitioners for children and parents/adults.

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Arch Dis Child. 2014;99:A145-A146.

INTERNET ADDICTION DISORDER/PROBLEMATIC INTERNET USE AND ADHD.

Finlay F, Furnell C.

Aims Many children and young people use the internet for playing games and to help with homework, but for some their use of the internet is excessive. Families have asked whether a connection between ADHD and Internet Addiction is known. We aim to answer this question.

Methods Searches of PUBMED and EMBASE were carried out using keywords nullADHDnull, nullInternet addictionnull and nullpathological Internet usenull. All studies identified as relevant were reviewed independently by the two researchers.

Results Internet Addiction or Problematic Internet Use (PIU) is excessive computer use that interferes with daily life. It has been discussed extensively as a diagnosis but is not currently included in DSM-V. The reward mechanism is thought to be a behavioral addiction similar to gambling. Excessive and addictive internet use and computer game playing is increasingly a problem with the studies reviewed reporting a prevalence of 2 to 20% in young people. In ADHD, Internet Addiction is one of a range of co-morbidities, along with depression, anxiety, personality disorder, eating disorders, sleep disorders and tic disorders. Whether web based activities appeal to the short attention of ADHD suffers or whether excessive Internet use may cause inattention, remains to be elucidated. In Internet Addiction, co-morbid conditions including depression, hostility, substance abuse disorder and social anxiety disorder are identified with ADHD being a common and consistent association. Those with Internet addiction were found to have less control over time and more impulsivity.

Conclusion For the majority the internet is a useful and stimulating way to discover and explore the world however for some children and young people their use becomes pathological. Children and young people today often have access to a range of electronic devices meaning internet use can quickly become problematic. The studies reviewed demonstrate a clear association between ADHD and problematic internet use. Families who present to clinic and identify internet use as a primary problem, along with those with an ADHD diagnosis should have this newly emerging condition considered along with screening for the associated co-morbidities.

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Arch Dis Child. 2014;99:A66.

SIGNIFICANCE OF SOCIAL FACTORS IN DETERMINING OUTCOMES IN ADHD.

Gupta AK, Srivastava OP.

Aims To ascertain whether social risk factors have a significant association with complex ADHD and assess the relative role played by biological risk factors and coexisting neurodevelopmental disorders. This will enable a better understanding of factors that complicate management of ADHD and thus facilitate optimal management.

Methods 102 patients with a diagnosis of ADHD were identified using a computerised coding system. Each case was assessed individually using computer system entries and case notes. A specially designed proforma was used to identify the following risk factors: social risk factors (e.g. parenting issues, child protection concerns) biological risk factors (e.g low birthweight, antenatal use of drugs/alcohol) coexisting neurodevelopmental conditions (e.g. autistic spectrum disorder, Tourette's syndrome) Patient outcomes were separated into two groups: Easy to manage (ETM) - no additional measures needed (only school support, parental support, medication) Difficult to manage (dtm) - additional emotional/behavioural problems necessitating input from external agencies.

Results Social risk factors were present in the majority of cases (70%), and were more prevalent in the DTM group (82%), than in the ETM group (53%). (Table Presented) There was a significant difference between the outcomes seen in the SR group (66%) and the NSR group (32%). The x2 value for this difference was 8.752 ($p < 0.05$). The difference between the percentages of patients with DTM versus ETM outcome was not significant in the BR group (55% & 45% respectively) or the NDD group (57% & 43% respectively), but was significant in the SR group (66% & 34%).

Conclusion The SR group was significantly more difficult to manage compared to the BR group and NDD group. There was a marked difference in outcome seen in the SR group, compared with the NSR group. The majority of DTM cases involve social risk factors, some of which are potentially modifiable. Although the presence of biological risk factors and coexisting disorders cannot be altered, early identification and amelioration of adverse social risk factors can potentially modify their effect and hence improve outcome.

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Arch Dis Child. 2014;99:A62.

THE VOICE OF CHILDREN WITH ADHD AND THEIR WISHES.

Puvanendran K, Nagaraj M.

Aim It is recommended that all health organisations must demonstrate how they have listened to the voice of children and young people, and how this will improve their health outcomes. Children with ADHD attending the follow up clinic participated.

Method A touch pad was used to collect questionnaire based information over a three month period. 36 completed data were analysed to evaluate their satisfaction and wishes.

Results Demography: 76% Male. 24% Female. 50% were in the age group 6-10, 47% 11-15 and 3% 16-18.

Conclusion 76% of children are male. Approximately equal number of primary and secondary school age. 36% of children are unhappy about having ADHD. 31% are unhappy at school. It is good to note 95% are happy at home. 45% are happy with medication and 12% unhappy. 91% reported that the paediatrician listened to them. 31% have a good understanding of ADHD. Varying wishes as above; mostly related to improving social skills and self-esteem. This has also been highlighted by parents. The needs of parents and children need to be addressed.

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Arch Dis Child. 2014;99:A64-A65.

PARENT SATISFACTION SURVEY OF ADHD SERVICE.

Abbas E, Valli S.

Introduction ADHD is a complex and diverse condition associated with many co morbidities. NICE and European guidelines emphasise using person-centred approaches. Measuring treatment satisfaction in

ADHD is a valuable part of treatment individualisation but limited data is available on the relationship between treatment efficacy and satisfaction.
Aim 1. To assess parent satisfaction with our current ADHD services. 2. To assess the treatment outcome of ADHD patients.
Methods A postal questionnaire asking about our services in line with NICE guidelines, were sent alongside the Strength and Difficulties questionnaire (SADQ) and Connor's Questionnaire (CQ) to 100 parents of children with ADHD. Electronic patient records and case files were also accessed to compare these questionnaires.
Results The response rate was 47%, 87% of these were male and 13% female. 57% of children were diagnosed before the age of 10 years with 40% having co morbidities. 49% of children had special educational statements and 66% were recipients of disability living allowance. 91% of parents were satisfied with the information we provided about ADHD. 72% found information about behavioural management helpful, 65% attended behavioural therapy sessions with 41% finding the sessions helpful. Only 32% of parents attended the psychosocial training course. Only 25% were seen by child and adolescent psychiatrists due to co morbidities. 93% were given information in various forms about medications and its side effects. 90% were on medication, with 75% using first line of medication. 50% of children experienced some form of side effects, however the majority was temporary. Overall, 75% of parents reported improvement in their child's behaviour but specifically more so at school than home (68% compared to 53% respectively). The SADQ showed improvement pre- and post-treatment (21% v 24%) whereas CQ scoring showed no improvement (28% v 17% respectively).
Conclusion ADHD requires individualised, multi-modal management. Now every newly diagnosed child with ADHD, and their parents, is offered Behavioural therapy and psychosocial training. Most parents were satisfied with our advice and management options, but further studies with larger numbers including teachers' opinions should be considered to fully assess satisfaction and outcome measures such as behavioural change after treatment.

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Asian J Psychiatry. 2014.

DISTINGUISHING BETWEEN AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER BY USING BEHAVIORAL CHECKLISTS, COGNITIVE ASSESSMENTS, AND NEUROPSYCHOLOGICAL TEST BATTERY.

Matsuura N, Ishitobi M, Arai S, et al.

Children with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) share many common symptoms, including attention deficit, behavioral problems, and difficulties with social skills. The aim of this study was to distinguish between ASD and ADHD by identifying the characteristic features of both the disorders, by using multidimensional assessments, including screening behavioral checklists, cognitive assessments, and comprehensive neurological battery. After screening for comorbid disorders, we carefully selected age-, sex-, IQ-, and socio-economic status-matched children with typical development (TD). In the Wechsler Intelligence Scale for children, a lower score was observed for the ASD group than for the TD group in Picture concept, which is a subscale of perceptual reasoning. A lower score was shown by the ADHD group than by the TD group in the spatial working memory test in the Cambridge Neuropsychological Test Automated Battery (CANTAB(registered trademark)). Although ASD and ADHD have many similar symptoms, they can be differentiated by focusing on the behavioral and cognitive characteristics of executive function.

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Aust New Zealand J Psychiatry. 2014;48:19.

HOW IMPORTANT AND RELEVANT IS OCCUPATIONAL DYSFUNCTION IN COMPLEX ADHD PRESENTATIONS?

Langford K, Ho S, Chen W.

Background: Children's occupations are broadly grouped into their student, leisure and self-care roles. Successful functioning within these roles relies on the integration of numerous skills and abilities (performance components). Occupational dysfunctions are often overlooked in routine ADHD

assessments. The Complex ADHD Service (CADHS) is a statewide Tier 4 clinic for children with severe impairments related to complex ADHD. This study examines the prevalence of performance component deficits and associated occupational dysfunction amongst CAHDS referrals.
Method: Consecutive cases assessed by CAHDS were audited. The prevalence of subtypes were recorded and computed.
Findings: The audit yielded 64 consecutive cases of Complex ADHD children assessed in CAHDS. The average age was 11, ranging from 3.5 to 16.5; 84% were boys. 100% of CADHS referrals were found to have 2 or more occupational related deficits, while 73% had 6 or more deficits (defined as scoring below 17th centile). In the break-down of subtypes, the most prevalent problem (91%) was sensory integration difficulties, 70% were sensory seekers, 80% had handwriting difficulties, 67% had planning and organizational deficits, 60% had auditory processing problems, 55% had gross motor difficulties, 51% had balance deficits, 71% had visual perceptual skill variability and 45% had an ocular motor irregularity. Parents, referrers and schools of assessed children rated these findings highly relevant and important in the assessment outcome.
Conclusion: Children with complex ADHD are very likely to have significant impairments in their occupational performance. Accurate identification and feedback of these findings to parents, educational personnel and referrers forms a major contribution in the service provided by CADHS.

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Aust New Zealand J Psychiatry. 2014;48:20.

MAPPING THE JOURNEY FROM SUSPICION TO TREATMENT: WESTERN AUSTRALIAN PILOT FROM AUSTRALIAN PAEDIATRIC ADHD STUDY.

Jongeling BR, Kaiser S, Smith G, et al.
Introduction: Despite the high prevalence of ADHD, there are no Australian data investigating the ADHD families' journeys and the critical steps which lead to accessing services and treatments.
Aim: To map the families' and patient's journeys from initial suspicion to information/service seeking processes before finally receiving diagnosis and treatments. The empirical findings may also reveal potential barriers to accessing service.
Methods: Service users' experiences were captured by standardised instruments in the WA subsample (of a larger prospective longitudinal study, Australian Paediatric ADHD Study) recruited by paediatricians from metropolitan and regional WA. Baseline and follow-up surveys were completed online or on paper by parents, children and paediatricians.
Results: 107 children (74% male) have been recruited to the study, age ranging 4 - 15; and 76% of parents first noted anomalies (i.e. behaviour/emotions/learning) before the child's 5th birthday (median 4 years of age). The median age of 'someone suggesting ADHD' was 6, and 'receiving a formal diagnosis' was 8, revealing a 2 year gap from concern to 'suggested diagnosis', and a 4 year gap to 'actual diagnosis'. Prior to diagnosis, parents sought information on ADHD from a range of sources -internet (71%), psychologist (43%), child's school (37%), allied health practitioner (37%), books (35%), friends (33%); and strikingly, 92% of parents reported seeking help from other 'stepping-stone' professionals. Once in paediatric clinics, 70% cases required two or more consultations prior to the ADHD diagnosis. Other assessments included parent questionnaire (93%) teacher questionnaire (90%), cognitive Assessments (71%). Treatments received included medications (80%) and Behavioural intervention (88%).
Conclusion: Parents report a long journey to ADHD diagnosis. 'Someone suggesting ADHD' and 'accessing information from multiple sources and from a professional' appears to form two pivotal steps. This study reveals potential barriers in accessing service.

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Aust New Zealand J Psychiatry. 2014;48:109.

A GUIDE TO NATIONAL ADHD GUIDELINES: BEST PRACTICE FOR THE ADHD CLINICIAN.

Paterson R.

Background: The RANZCP has guidelines for the management of child attention deficit hyperactivity disorder (ADHD) and adult ADHD (published in 2009 and 2012, respectively), but they both have shortcomings. The child ADHD guideline is past its review by date and the adult ADHD guideline simply refers the reader to the Canadian and British guidelines. The NHMRC ADHD guidelines were ready for release in 2009, but were never finally approved and, instead, the NHMRC released a much briefer and more general document, The Clinical Practice Points, relating to children and adolescents only. Where does this leave a clinician needing guidance on ADHD?

Objectives: I will briefly summarise how this situation came about and guide the clinician to a best practice 'distillate' of the various guidelines.

Methods: Review of the two NHMRC guidelines, as well as the Canadian and British guidelines.

Findings Best practice conclusions drawn.

Conclusions: NHMRC Draft Guidelines (2009) should be released ASAP, ideally after a modest update of the latest research and DSM 5 criteria.

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Aust New Zealand J Psychiatry. 2014;48:19-20.

ADHD AND EMOTIONAL LIABILITY (EL): GENETIC ARCHITECTURE, PHENOTYPIC CORREALTIONS AND NEW PERSPECTIVES.

Chen W.

Objectives: To evaluate empirical evidence for genetic substrates underlying the observed association between ADHD and Emotional Lability (EL) and phenotypic correlations of EL.

Methods: (1) Structural Equation Modeling (SEM) of Manchester twin data (age range 5-18 years) to decompose genetic architecture of Inattention (IA), Hyperactivity (HA), Impulsivity (IMP) and EL (DuPaul rating scale and Conners 10-item scale, completed by parents). (2) Latent class analysis of IMAGE ADHD probands and their siblings in relation to EL and ASD symptoms.

Findings: (1)There were moderate to strong phenotypic correlations between HI, IA and EL. Multivariate twin modeling revealed that a common pathway model best accounted for the covariance between these dimensions, represented by a highly heritable latent factor. Post-hoc analyses identified unique genetic associations of EL with IA (after controlling for HI) and with HI (after controlling for IA); confirmed that all additive genetic influences on HI, IA and EL were shared and identified a significantly stronger association of EL with the latent ADHD factor in older individuals. (2)ADHD LCA with IA, HA and IMP symptoms all shows significant association of EL, especially those with elevated HA-IMP symptoms. The 'Moderate Combined Subtype' ADHD latent class showed similar levels of impairments and EL expression as that of the other severe ADHD classes. Pure IA subtype of ADHD, by comparison, embodies the lowest elevated risk of EL. However, in the presence of ASD symptoms, the risk of EL is marked increased in the pure IA subtype.

Conclusions: (1) ADHD and EL share common genetic etiological factors. The finding that a single, heritable, latent factor accounted for covariation among these phenotypes indicates that their co-occurrence is primarily the result of overlapping genetic effects. EL may be regarded as the third dimension in the 'IA-IMP-EL spectrum' phenotype and should be a target for assessment and treatment in clinical practice. (2) All subtypes of ADHD with IA, HA and IMP symptoms were significantly associated with elevated degree of EL. The 'Moderate Combined Subtype' ADHD latent class showed similar levels of impairments to other severe subtypes, but these children will remain diagnostically 'homeless' in DSM5. In the presence of ASD symptoms, the risk of EL is markedly elevated in pure IA cases, suggestive of a specific 'IA-ASD-EL spectrum' subtype, indicating that ASD must be evaluated in individual with EL and pure IA subtype of ADHD within clinical settings.

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Aust New Zealand J Psychiatry. 2014;48:20-21.

SOCIAL AND COMMUNICATION DIFFICULTIES IN CHILDREN WITH ADHD AND NON-ADHD CONTROLS: A COMMUNITY-BASED STUDY.

Jongeling B, Green J, Rinehart N, et al.

Objectives: To examine in a community-based sample the prevalence and type of ASD symptoms in children with and without ADHD, differences in ASD symptoms by ADHD subtype and gender and to examine the correlates of autism spectrum disorder symptoms and child functioning, and autism spectrum disorder symptoms and parent/ family functioning.

Methods: Participants were parents of Grade 1 children (age 6 -8 years) participating in Cohort 2 of the Children's Attention Project. Children were assessed as positive for ADHD if they scored above the 75th centile (boys) and 80th percentile (girls) using the parent and teacher Conners' 3 ADHD index; met diagnosis using the NIMH Diagnostic Interview Schedule for Children (DISC) IV. Children who screened negative were matched on gender and school. ASD symptoms were screened using the Social Communication Questionnaire (SCQ).

Results: Social and communication questionnaire results were significantly higher in children with ADHD. Both boys and girls with ADHD had higher SCQ total scores and SCQ subscale scores than those without ADHD. There were no significant differences in SCQ total score and SCQ subscale scores by ADHD subtype.

Conclusion: Autism spectrum disorder symptoms are more common in children with ADHD. In contrast to previous research, ASD symptoms did not differ by ADHD subtype or gender. Child and parent functioning correlates will be discussed.

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Aust New Zealand J Psychiatry. 2014;48:21.

OVEL SUBTYPES WITH THE ASD-ADHD SPECTRUM DISORDERS.

Rommelse N.

Objective: Autism spectrum disorders (ASD) and attention- deficit/hyperactivity disorder (ADHD) frequently cooccur. The current study examined the empirical evidence for distinct novel subtypes within ASD -ADHD spectrum disorders, their phenotypic distinctions and concurrent validity with comorbid symptoms and neurocognitive profiles.

Method: Latent class analysis was performed on Social Communication Questionnaire (SCQ) and Conners' Parent Rating Scale (CPRS-R:L) data for 644 children and adolescents (5 through 17 years of age) originating from both a school and clinical sample. Classes were compared for comorbid symptoms and cognitive profiles of motor speed and variability, executive functioning, attention, emotion recognition, and detail-focused processing style.

Results: Latent class analysis revealed five classes: two without behavioral problems, one with only ADHD behavior, and two novel ADHD-ASD subtypes (one predominantly 'ADHD(+ASD)', and one predominantly 'ASD(+ADHD)'. There was some specificity of deficits across classes with ADHD(+ASD) subtype being most strongly associated with Emotional Lability, Working Memory deficits and most functionally impaired, while ASD(+ADHD) class formed an intermediately impaired group (with superior visual spatial abilities), yet impaired emotion recognition, and ADHD-only class less impaired.

Conclusions: Our findings, if replicated, can be highly relevant to clinical practice, in particular, delineating the concurrent impairment patterns of these novel subtypes, so that children presenting to clinics can be subclassified and treated with greater precision. For research, the overlapping cognitive deficits may be used to further unravel the shared etiological underpinnings of ASD and ADHD, and the nonoverlapping deficits may indicate why some children develop ADHD despite their enhanced risk for ASD.

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Aust New Zealand J Psychiatry. 2014;48:115.

FUNCTIONAL IMPAIRMENT IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: RESULTS FROM SHORT-AND LONG-TERM STUDIES OF LISDEXAMFETAMINE DIMESYLATE.

Doddamani L, Hodgkins P, Adeyi B, et al.

Background: The prodrug stimulant lisdexamfetamine dimesylate (LDX) is an effective, long-acting treatment for the symptoms of ADHD. Management of ADHD should address day-to-day functioning, as well as symptoms.

Objective: Evaluate functional outcomes from two international, double-blind, randomised trials (SPD489-325 and SPD489-326) in patients with ADHD, aged 6-17 years.

Methods: In SPD489-325, patients received placebo or optimized doses of LDX or the reference treatment, osmotic-release oral system methylphenidate (OROSMPH) for (less-than or equal to) 7 weeks. Statistical comparison of LDX versus OROS-MPH was not pre-specified. In SPD489-326, a (greater-than or equal to) 26-week open-label LDX treatment period preceded a 6-week, placebo-controlled, randomized-withdrawal period. The change in Weiss Functional Impairment Ratings Scale-Parent Report (WFIRS-P) scores was a secondary efficacy outcome.

Findings: In SPD489-325 (N = 317), nominally significant placebo-adjusted effects of LDX were observed in the WFIRS-P Family, Learning and School, Social Activities and Risky Activities domains and in the total (effect size (ES) 0.924; $p < 0.001$); OROS-MPH effects were significant in all domains and in the total (ES 0.772; $p < 0.001$). In SPD489- 326, WFIRS-P scores were improved or stable in the open-label period (N = 262). In the randomised-withdrawal period (N = 153), scores worsened in the placebo group, but not the LDX group; with LDX significantly more effective at the endpoint, in the Family, Learning and School, and Risky Activities domains (all $p < 0.001$) and in the total (ES 0.908; $p < 0.001$).

Conclusions: Short-term treatment with LDX or OROSMPH led to improved functional impairment scores in children and adolescents with ADHD. The benefits of LDX were maintained during continued long-term treatment, as demonstrated by the worsening of scores following withdrawal to placebo.

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Aust New Zealand J Psychiatry. 2014;48:18.

NOVEL TOPICS IN ADHD AND IN THE SPECTRUM PHENOTYPES OF ADHD-AUTISM AND OF ADHD-EMOTIONAL LIABILITY PRESENTATIONS.

Chen W, Silva D, Jongeling B, et al.

ADHD is a common and important yet complex neurodevelopmental disorder. This symposium focuses on some recent developments in ADHD research and its link with autism spectrum disorders. Data from the Telethon Institute (WA) provides novel insights on early causal pathways and developmental trajectories of ADHD. Infection, head injury, burns, poisons, epilepsy, and ear and tonsillar diseases are key post-natal risk factors associated with ADHD, which significantly lowers educational attainments and worsens with the increasing age. ADHD children are more likely to have a justice record. Emotional Liability (EL) is commonly associated with ADHD. The second study presents the findings from a twin analysis using the Manchester Twin data, which demonstrates substantial genetic overlap as a shared common latent factor accounting for EL-intellectual impairment (IA) impulsivity (IMP) symptomatic triads. EL may be regarded as the third dimension in the 'IA-IMP-EL spectrum' phenotype. This presentation also examines the interplay between ADHD and ASD symptoms in the expression of Emotional Lability (EL) problems. EL was strongly associated with all subtypes of ADHD, especially those with elevated HA-IMP symptoms, but there appears an 'Inattention-ASD-EL subtype', which is highly relevant to clinical assessment and management. Occupational dysfunctions are often over-looked in ADHD assessments. The third presentation provides novel data from Complex ADHD Service (CAHDS) WA, which revealed their prevalence and importance. 100% of CADHS referrals had 2 or more occupational related deficits. The commonest problem was sensory integration difficulties. Parents, referrers and schools of assessed children rated these findings as clinically relevant. The fourth study maps the long journey taken by ADHD families from initial suspicion to receiving diagnosis and treatments in WA. 'Someone suggesting ADHD' and 'accessing information from multiple sources and from a professional' appears to form two pivotal steps. The empirical findings also reveal potential barriers to accessing services. In the second part of this presentation, Autism spectrum disorder symptoms are found to be more common in children with ADHD. In contrast to previous research,

autism spectrum disorder (ASD) symptoms did not differ by ADHD subtype or gender. Child and parent functioning correlates will be discussed.The last presentation examines the empirical evidence for distinct novel subtypes within ASD -ADHD spectrum disorders, their phenotypic distinctions and concurrent validity with comorbid symptoms and neurocognitive profiles. The ADHD(+ASD) subtype was found to be most strongly associated with Emotional Lability, Working Memory deficits and most functionally impaired. It also demonstrates ASD symptoms as the rarer phenotypic expression of that risk liability, using a sophisticated family study design and familial cross-disorder analysis amongst high risk ASD and ADHD families. Furthermore, the the role of parental ASD+ADHD symptoms on parenting styles, parental stress and depressive symptoms as well as the impacts on the wellbeing of the offspring and spouse. The results highlight the increased burden of raising a child with ASD and/or ADHD; as well as its reciprocal relationship with parental ASD, ADHD and depressive symptoms.

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Aust New Zealand J Psychiatry. 2014;48:22.

IMPACTS OF PARENTAL ADHD+ASD SYMPTOMS ON FAMILY FUNCTIONING AND EFFECTS UPON OFFSPRINGS' AND SPOUSES' WELLBEING.

Rommelse N.

Objectives: An understudied and sensitive topic nowadays is that even subthreshold symptoms of Autism Spectrum Disorder (ASD) and Attention-Deficit/ Hyperactivity Disorder (ADHD) in parents may relate to their parenting styles and create increased parenting stress. The aim of this study was to explore the role of parental ASD+ADHD symptoms on parenting styles, parenting stress and depressive symptoms as well as the impact thereof on the wellbeing of the offspring and spouse.

Methods: 96 families were recruited with one child (2-20 years) with a clinical ASD (+ADHD) diagnosis, and one unaffected sibling close in age. Parental ASD, ADHD and depressive symptoms were assessed using selfreports. Parenting styles, parenting stress and family functioning were assessed with self-, spouse and/or child report.

Findings: Fathers and mothers used a more permissive and less authoritative but authoritarian parenting style for affected and unaffected children. Increased parenting stress was mainly present regarding affected offspring. Spouse correlations were found for ASD, depression, and parenting stress. Paternal ASD and maternal ADHD symptoms were related to increased parenting stress; and parental ADHD symptoms with depressive symptoms and parenting stress.

Conclusions: The results highlight the increased burden of raising a child with ASD and/or ADHD and the reciprocal relationship this has with parents' ASD, ADHD, and depressive symptoms, and levels of stress.

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Aust New Zealand J Psychiatry. 2014;48:18-19.

UNDERSTANDING THE LIFE COURSE OF ATTENTION DEFICIT DISORDER: POPULATION LINKAGE STUDY WESTERN AUSTRALIA.

Silva D.

Objectives: To provide an overview of the data linkage opportunities in Western Australia (WA) relating to Attention Deficit Disorder (ADHD) and to investigate the early risk factors, early markers, causal pathways and health, education and justice outcomes for children prescribed stimulant medication (SM) for ADHD.

Methods: Using de-identified population linked data from the stimulant notification register, midwives notification, hospital morbidity, justice records and education data, 16,883 children and adolescents aged 4-25 years diagnosed with ADHD and prescribed stimulant medication were identified and compared with 32,728 non-ADHD children.

Findings: Mothers of children who were subsequently diagnosed with ADHD and treated with SM were significantly more likely to be single, younger and smoked during pregnancy. Post natal pathways were examined using hospital morbidity data where children under 4 years subsequently diagnosed with ADHD were significantly more likely to be admitted to hospital with an infection, head injury, burns, poisons,

epilepsy, and ear and tonsillar disease, compared with their non-ADHD counterparts. Children with ADHD were 3 times more likely to have a justice record compared with their non-ADHD counterparts, and at a younger age. ADHD children had significantly lower education scores for both numeracy and literacy, and these scores became progressively worse with the increasing age of the child.
Conclusions: This large population study using linked data on ADHD children can provide information on early causal pathways and outcomes which will assist policy makers and clinical practitioners better understand this common mental health condition at multiple levels.

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Behav Genet. 2014.
CONTRAST EFFECTS AND SEX INFLUENCE MATERNAL AND SELF-REPORT DIMENSIONAL MEASURES OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Ebejer JL, Medland SE, van der Werf J, et al.
The heritability of attention-deficit/hyperactivity disorder (ADHD) is higher for children than adults. This may be due to increasing importance of environment in symptom variation, measurement inaccuracy when two raters report behavior of a twin-pair, a contrast effect resulting from parental comparison of siblings and/or dimensionality of measures. We examine rater contrast and sex effects in ADHD subtypes using a dimensional scale and compare the aetiology of self, versus maternal-report. Data were collected using the Strengths and Weaknesses of ADHD and Normal Behaviour Scale (SWAN): maternal-report for 3,223 twins and siblings (mean age 21.2, SD = 6.3) and self-report for 1,617 twins and siblings (mean age 25.5, SD = 3.2). Contrast effects and magnitude of genetic and environmental contributions to variance of ADHD phenotypes (inattention, hyperactivity-impulsivity, combined behaviours) were examined using structural equation modeling. Contrast effects were evident for maternal-report hyperactivity-impulsivity (b = -0.04) and self-report inattention (-0.09) and combined ADHD (-0.08). Dominant genetic effects were shared by raters for inattention, hyperactivity-impulsivity and combined ADHD. Broad-sense heritability was equal across sex for maternal-report inattention, hyperactivity-impulsivity and combined ADHD (0.72, 0.83, 0.80). Heritability for corresponding subtypes in self-reported data were best represented by sex (0.46, 0.30, 0.39 for males; 0.69, 0.41, 0.65 for females). Heritability difference between maternal and self-report ADHD was due to greater variance of male specific environment in self-report data. Self-reported ADHD differed across sex by magnitude of specific environment and genetic effects.

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Behav Change. 2013;30:262-72.
PARENT-ENDORSED REASONS FOR NOT COMPLETING HOMEWORK IN GROUP-BASED BEHAVIOURAL PARENT TRAINING FOR HIGH-RISK FAMILIES OF YOUTH WITH ADHD.
Chacko A, Anderson L, Wymbs BT, et al.
Background: This study examined reasons parents endorsed/provided for not completing homework tasks during their participation in a group-based behavioural parent training (BPT) intervention.
Method: Eighty single mothers anonymously completed a questionnaire at the end of each of eight BPT sessions to ascertain reasons for not completing assigned homework.
Results: Data suggests that there are varied reasons for poor HW completion that are related to various aspects of the homework process, but most notably the implementation phase of homework.
Conclusions: Therapists should utilise various strategies to support homework completion, with special attention focused on methods for 'in-vivo' support for parents.

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Biol Psychiatry. 2014;76:422-29.

DIFFERENTIAL OSCILLATORY ELECTROENCEPHALOGRAM BETWEEN ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER SUBTYPES AND TYPICALLY DEVELOPING ADOLESCENTS.

Mazaheri A, Fassbender C, Coffey-Corina S, et al.

Background A neurobiological-based classification of attention-deficit/ hyperactivity disorder (ADHD) subtypes has thus far remained elusive.

The aim of this study was to use oscillatory changes in the electroencephalogram (EEG) related to informative cue processing, motor preparation, and top-down control to investigate neurophysiological differences between typically developing (TD) adolescents, and those diagnosed with predominantly inattentive (IA) or combined (CB) (associated with symptoms of inattention as well as impulsivity/ hyperactivity) subtypes of ADHD.

Methods The EEG was recorded from 57 rigorously screened adolescents (12 to17 years of age; 23 TD, 17 IA, and 17 CB), while they performed a cued flanker task. We examined the oscillatory changes in theta (3-5 Hz), alpha (8-12 Hz), and beta (22-25 Hz) EEG bands after cues that informed participants with which hand they would subsequently be required to respond.

Results Relative to TD adolescents, the IA group showed significantly less postcue alpha suppression, suggesting diminished processing of the cue in the visual cortex, whereas the CB group showed significantly less beta suppression at the electrode contralateral to the cued response hand, suggesting poor motor planning. Finally, both ADHD subtypes showed weak functional connectivity between frontal theta and posterior alpha, suggesting common top-down control impairment.

Conclusions We found both distinct and common task-related neurophysiological impairments in ADHD subtypes. Our results suggest that task-induced changes in EEG oscillations provide an objective measure, which in conjunction with other sources of information might help distinguish between ADHD subtypes and therefore aid in diagnoses and evaluation of treatment.

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Child Adolesc Ment Health. 2014.

ADAPTING A SPECIALIZED ADHD PARENTING PROGRAMME FOR USE WITH 'HARD TO REACH' AND 'DIFFICULT TO TREAT' PRESCHOOL CHILDREN.

Mcewan F, Thompson M, Laver-Bradbury C, et al.

Background: Effective implementation of parent training programmes for preschool Attention-Deficit/Hyperactivity Disorder type is constrained by barriers limiting take-up and effective engagement by 'hard to reach' and 'difficult to treat' families.

Method: We describe an evidence-driven adaptation and piloting of an existing empirically supported preschool ADHD parenting programme to address these problems.

Results: The New Forest Parenting programme was changed substantially in terms of length; content and delivery on the basis of information gathered from the literature, from parents and practitioners, further modifications were made after the pilot study.

Conclusions: The adapted-NFPP is currently being assessed for efficacy in a large multicentre randomized controlled trial.

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Child Adolesc Psychiatr Clin North Am. 2014.

BEHAVIOR MANAGEMENT FOR PRESCHOOL-AGED CHILDREN.

Williford AP, Shelton TL.

This article summarizes behavior management strategies for preschool children who are at high risk for attention-deficit/hyperactivity disorder that have found to be effective in improving child behavior. Both parent and teacher training programs are reviewed, as these have been backed by substantial research evidence. In addition, multimodal treatments that include some combination of parent training, teacher

training, and social skills training are also reviewed. Interventions emphasize the need for a strong adult-child relationship combined with proactive behavior management strategies to improve child behavior.

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Child Adolesc Psychiatr Clin North Am. 2014.
RESTRICTION AND ELIMINATION DIETS IN ADHD TREATMENT.
Nigg JT, Holton K.
Food elimination diets are defined and the history of their investigation in relation to attention-deficit/hyperactivity disorder (ADHD) is reviewed. After noting that a consensus has emerged that an elimination diet produces a small but reliable aggregate effect, the present review provides updated quantitative estimates of effect size and clinical response rates to elimination diets. It then highlights key issues that require research attention, in particular characterization of dietary responders. Finally, because some children may benefit, clinical guidelines at the present state of knowledge are summarized. It is concluded that updated trials of elimination diets are sorely needed for ADHD.

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Child Adolesc Psychiatr Clin North Am. 2014.
NUTRITIONAL SUPPLEMENTS FOR THE TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Bloch MH, Mulqueen J.
Polyunsaturated fatty acid supplementation appears to have modest benefit for improving ADHD symptoms. Melatonin appears to be effective in treating chronic insomnia in children with ADHD but appears to have minimal effects in reducing core ADHD symptoms. Many other natural supplements are widely used in the United States despite minimal evidence of efficacy and possible side effects. This review synthesizes and evaluates the scientific evidence regarding the potential efficacy and side effects of natural supplements and herbal remedies for ADHD. We provide clinicians with recommendations regarding their potential use and role in overall ADHD treatment.

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Child Adolesc Psychiatr Clin North Am. 2014.
SOCIAL SKILLS TRAINING.
Mikami AY, Jia M, Na JJ.
Children with attention-deficit/hyperactivity disorder (ADHD) have prominent social impairment, which is commonly manifested in unskilled behaviors in social situations and difficulties in being accepted and befriended by peers. This social impairment often remains after administration of medication and behavioral contingency management treatments that address the core symptoms of ADHD. This article reviews traditional social skills training (SST) approaches to remediating social impairment, and presents the evidence for their efficacy and significant limitations to their efficacy. The article introduces potential reasons why the efficacy of traditional SST may be limited, and concludes with some promising alternative SST approaches.

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Child Adolesc Psychiatr Clin North Am. 2014.
FAMILY THERAPY FOR ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Robin AL.
Adolescents with attention deficit hyperactivity disorder (ADHD) and their parents experience a great deal of conflict and coercion because the executive function deficits of ADHD interact with the parents' characteristics, family stress, and parenting practices. This article provides a step-by-step description of the defiant teen approach to family therapy, which is designed to help adolescents with ADHD and their

parents reduce conflict and coercion. The article also summarizes 2 studies supporting the effectiveness of the defiant teen approach.

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Child Adolesc Psychiatr Clin North Am. 2014.

COGNITIVE BEHAVIORAL THERAPY FOR ADOLESCENTS WITH ADHD.

Antshel KM, Olszewski AK.

Attention deficit/hyperactivity disorder (ADHD) often persists into adolescence and has the same functional impairments as were present during childhood. Medications lessen ADHD symptoms yet do not reliably affect functioning. Thus, there exists a great need for psychosocial treatments in adolescents with ADHD. Nonetheless, relative to the vast literature that has been reported on children with ADHD, much less data have been reported about psychosocial interventions for adolescents with ADHD. Cognitive behavioral therapy interventions that are being used with adolescents rely more on traditional behavioral principles than cognitive therapy tenets.

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Child Adolesc Psychiatr Clin North Am. 2014.

NEUROPSYCHOLOGICALLY INFORMED STRATEGIC PSYCHOTHERAPY IN TEENAGERS AND ADULTS WITH ADHD.

Seidman LJ.

Stimulants are the primary treatment for ADHD. Psychotherapy may augment pharmacologic treatment. In this article, we discuss strategies psychotherapists may use in working with teenagers and adults, including individuals who reject medications or take them suboptimally. Individuals with ADHD often have other psychiatric issues, including affective or cognitive comorbidities. Having ADHD does not protect people from the difficulties of life, and psychotherapy can help to disentangle "ADHD" from other issues. A psychotherapist knowledgeable about ADHD assessment can improve diagnostic precision. Psychotherapy can integrate forms of treatment in which the central goal is increasing mastery and competence of the individual.

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Child Adolesc Psychiatr Clin North Am. 2014.

MIDDLE SCHOOL-BASED AND HIGH SCHOOL-BASED INTERVENTIONS FOR ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Evans SW, Langberg JM, Egan T, et al.

The development and evaluation of psychosocial treatments for adolescents with attention-deficit/hyperactivity disorder has lagged behind the treatment development work conducted with children with the disorder. Two middle school-based and high school-based treatment programs have the most empirical work indicating beneficial effects. Treatment development research addressing many of the basic questions related to mediators, moderators, and sequencing of treatments is needed. Implications for future treatment development research are reviewed, including the potential benefits of combining treatments of a variety of modalities to address the large gaps in the literature.

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Child Adolesc Psychiatr Clin North Am. 2014.

TOWARDS AN EVIDENCE-BASED TAXONOMY OF NONPHARMACOLOGIC TREATMENTS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Faraone SV, Antshel KM.

We have created an evidence-based guide for clinicians to the relative utility of nonpharmacologic treatments for attention-deficit/hyperactivity disorder (ADHD). This article uses the term evidence-based in

the sense applied by the Oxford Center for Evidenced-Based Medicine to help readers understand the degree to which nonpharmacologic treatments are supported by the scientific literature. This article also reviews the magnitude of the treatment effect expressed as the standardized mean difference effect size (also known as Cohen D). It then describes a meta-algorithm to describe how to integrate pharmacologic and nonpharmacologic treatments for ADHD.

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Clin Neurophysiol. 2014.

SUBCORTICAL ENCODING OF SPEECH CUES IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Jafari Z, Malayeri S, Rostami R.

Objective: There is little information about processing of nonspeech and speech stimuli at the subcortical level in individuals with attention deficit hyperactivity disorder (ADHD). The auditory brainstem response (ABR) provides information about the function of the auditory brainstem pathways. We aim to investigate the subcortical function in neural encoding of click and speech stimuli in children with ADHD.

Methods: The subjects include 50 children with ADHD and 34 typically developing (TD) children between the ages of 8 and 12. years. Click ABR (cABR) and speech ABR (sABR) with 40. ms synthetic /da/ syllable stimulus were recorded.

Results: Latencies of cABR in waves of III and V and duration of V-Vn (P (less-than or equal to). 0.027), and latencies of sABR in waves A, D, E, F and O and duration of V-A (P (less-than or equal to). 0.034) were significantly longer in children with ADHD than in TD children. There were no apparent differences in components the sustained frequency following response (FFR).

Conclusions: We conclude that children with ADHD have deficits in temporal neural encoding of both nonspeech and speech stimuli.

Significance: There is a common dysfunction in the processing of click and speech stimuli at the brainstem level in children with suspected ADHD.

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Clin Neurophysiol. 2014;125:S225-S226.

TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) IN THE TREATMENT OF ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Sotnikova A, Soff C, Becker K, et al.

Question: The stimulation of the brain with weak direct current through the scalp (tDCS) is a safe, well tolerable and effective procedure which allows a focal modification of cortical excitability in brain areas of interest and causes changes of corresponding neurophysiological functions associated with the stimulated brain areas. In our study we investigated the influences of the anodal tDCS of the prefrontal cortex on the clinical symptoms of adolescent ADHD as well as on the neuropsychological parameters: working memory, executive functions and attention.

Methods: Sixteen adolescents with ADHD (12-16 years old) were treated according to the double-blind sham controlled cross-over design with anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC, 1mA, 20 min) and with the sham protocol (impedance control, no direct current, 20 min) 5 days each with a 2 weeks pause between these conditions. The first tDCS and sham stimulation were performed in the MR scanner combined with the working memory task during the fMRI (3 Tesla Siemens Trio). The influence of tDCS on the neuronal networks of attention, impulse inhibition and working memory was investigated. The clinical effects were evaluated by patients and their parents in standardized questionnaires (FBB-ADHS). The dynamik of neuropsychological parameters was studied using a computerized continuous working memory test (QbTest, QbTech, Sweden) each day during the treatment and one week after.

Results: All 16 Patients tolerated the tDCS well. 5 Patients reported local sensation such as itching under the stimulation electrode, which occured during the tDCS as well as during the sham condition. A significant improvement of the reaction time variability was observed in tDCS and not in the sham condition. Corresponding activation of attention/working memory network was registered in the tDCS condition compared with sham stimulation. This activation was observed not ony in der brain area under

the stimulating electrode (DLPFC) but also in brain areas remote from the stimulated region (inferior frontal gyrus, anterior cingulate).
Conclusion: Anodal tDCS revealed significant clinical effects in ADHD. The neuropsychological changes in RT variability correlated with an activation of attention/working memory networks. This project expandes the perspective of a possible use of tDCS on the treatment of ADHD and other psychiatric disorders such as tics, anorexia and depression in children and adolescents.

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Clin Neurophysiol. 2014;125:S157.

EEG ANALYSIS OF CHILDREN WITH ATTENTION DEFICIT AND AUTISM.

Yavlal F, Bebek N, Abali O, et al.

Question: Autism is accepted as a neuropsychiatric disorder that begins at early ages and causes retarded and deviated communication, social, cognitive and behavioral development. We aim to evaluate the EEG findings of children with attention deficit and autism.
Methods: Retrospective analysis of electroencephalographic (EEG) findings obtained from children diagnosed with autism and attention deficit by Child Psychiatry Clinic was performed. Cases were evaluated according to age, gender, clinical diagnosis and detailed EEG findings.
Results: Total of 20 subjects consisting of 14 males (64.7%) and 6 females (35.2%) between the ages of 2 -15 years were evaluated. EEG findings were normal in 10 (50%) out of 20 patients with autism and/or attention deficit. Focal epileptiform anomaly was found in six cases (30%) which was localized to central area in four, temporoparietal area in one patient. Besides in five cases, one of which has also epileptic anomaly, mild and diffuse slowing was found. None of these cases had epilepsy history.
Conclusions: It was reported that EEG anomaly rates were 10-83% and epilepsy history was 4-32% in patients with autism and attention deficit. We found 30% of epileptic abnormality without any history of epilepsy. Further prospective studies are needed to enlighten these differences and related patho-physiological mechanisms and to understand the prognostic value of the EEG.

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Clin Neurophysiol. 2014;125:S159.

TEMPORAL VARIABILITY IN EEG FUNCTIONAL CONNECTIVITY IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Alba G, Mendez LD, Manas S, et al.

Question: In a previous work, our group has demonstrated an increasing in the EEG cortical connectivity in children with Attention Deficit Hyperactivity Disorder (ADHD) when compared with healthy children (Gonzalez et al., Clin Neurophysiol 124 (6), 1139-1150, 2013). In this work, the temporal variability of EEG functional connectivity in ADHD children is analyzed.
Methods:
Signals: digitised EEGs (sampling rate: 256 Hz) from an ADHD of mixed type (11-males, 10-15 years) and a control (CONT) group (13-males, 10-15 years). EEG recording were from 16 monopolar EEG channels using the international 10/20 system (Fp1-2/F3-4/F7-8/T3-4/T5-6/C3-4/P3-4/O1- 2, reference: linked A1-A2 mastoid). Pairwise interdependence between EEG channels was assessed through two measures: the covariance and the nonlinear synchronization. Thus, EEG functional connectivity was estimated by averaging the corresponding intra&interhemispheric interdependence measures for each electrode. Temporal variability (TVA) of EEG connectivity was assessed through the standard deviation of interdependence measures from 30 EEG artifact-free segments of 5 s each.
Conditions were: basal, eyes-closed (EC) and eyes-open. ANOVA test for repeated was used for between-group comparisons.
Results: a) As to covariance measures: TVA of EEG connectivity was greater for ADHD group than for CONT group ($p<0.05$) and only during EC; this result was clearer for the connectivity of O1 and O2 ($p<0.001$) and for that of F7, F8, T3, T4 and T6 regions ($p<0.01$); b) As for the nonlinear synchronization, the TVA was also greater for ADHD than for CONT in EC condition ($p<0.001$) and this result was true for

the connectivity of most channels of the right and left hemisphere (Fp1,T3, T5, C4, T4 with p<0.01 and F7, C3, P3, P4, O1, O2, F4, F8, P4, T6 with p<0.001).
Conclusions: Children with ADHD of mixed type show increased the temporal variability of the EEG functional connectivity of certain cortical regions compared with CONT. This result is evident primarily when the connectivity of each region is estimated through measures of nonlinear synchronization with eyes closed.

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Clin Neurophysiol. 2014;125:S235.
ADHD AWARENESS, QUALITY OF LIFE AND TREATMENT ACCEPTANCE.
Santos MV, Romano-Silva MA.
The attention deficit hyperactivity disorder (ADHD) has a high prevalence (5%) in school-age children. If on the one hand the literature shows that information enables conscious decision making, recent research shows there is a lot of misinformation about ADHD, even among health and teaching professionals. The main objective of our study was to determine whether knowledge about ADHD found in parents of brazilian children and adolescents diagnosed with this disorder had a significant relationship with treatment acceptance. The sample consisted of 101 parents or caregivers (94 women and 7 men) of children and adolescents treated for ADHD at the Hospital das Clinicas, Universidade Federal de Minas Gerais. The profile was composed of young, low-income (52.5%), students, aged 4 to 18 years old, in the majority boys (76.2%). The instrument used consisted of a structured questionnaire with 100 questions, with six different scales, assessing the general knowledge about ADHD and quality of life. The results showed there is no statistical significance between any of the variables tested. However, individuals classified as the inattentive subtype showed significant differences in appearance greater acceptance of the treatment of the hyperactive or combined subtypes. While individuals with higher scores for quality of life showed intermediate treatment acceptance, the group with the lowest quality of life scores showed high treatment acceptance. We suggest that further studies should be conducted to better understand the relationship between ADHD awareness and its influence on individual behavior. These results could be useful for improved health education, including the development of prevention campaigns to promote effective health.

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Clin Neurophysiol. 2014;125:S324.
NOCTURNAL POLYSOMNOGRAPHY AND SLEEP ARCHITECTURE CHARACTERIZATION IN CHILDREN WITH BIPOLAR DISORDER VERSUS ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.
Alvarez G, I, Estrada P, X, Principe A, et al.
Introduction: Sleep complaints in children with Bipolar Disorder (BD) and Attention Deficit and Hyperactivity Disorder (ADHD) have been widely described. Conversely, some reports point on the role of sleep disturbances in BD and ADHD physiopathology. Clinically, pediatric BD and ADHD comorbidity is not infrequent. Nocturnal Polysomnography (PSG) could be a useful tool in order to specify the sleep disorders and to establish a differential diagnosis upon these patients.
Aim: To compare sleep architectures and other PSG data in children with BD and ADHD.
Materials and methods: 5 BD and 5 ADHD patients aged from 7 to 18 years were recruited from the Child and Adolescent Mental Health Services. International Neuropsychiatric Interview for Kids and Adolescents (MINI-Kid) was used for diagnostic purposes. BEARS Algorithm and Sleep Disturbance Scale for Children (SDSC) were applied for screening of sleep disorders. The same day of nocturnal PSG performance Child Depression Inventory (CDI), Child Mania Rating Scale (CMRS) and Parent Version of the Young Mania Rating Scale (p-YMRS) were measured, as well as 15 days sleep calendar recording was collected. PSGs were manually scored by a blinded investigator (American Academy of Sleep Medicine, 2007 criteria). NoREM and REM Sleep Latencies, Sleep Efficiency, Sleep Time in N1, N2, N3 and REM stages, duration and number of REM cycles and REM density values were analyzed.
Results: Sleep architecture showed a wide diversity among individuals, regardless the belonging group. Significant differences in PSG values according to BD or ADHD conditions were not found. Only REM

density showed a higher mean value on BD than on ADHD children. No correlation between scales for the assessment of mood and sleep variables was found. Correlations between sleep architecture and current medical treatments could not be established.
Conclusions: Sleep architectures in BD and ADHD children present heterogeneous patterns. REM density seems to play an important role in the differential diagnosis of BD and ADHD. PSG may be used for an early detection of sleep disturbances in pediatric psychiatric disorders.

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Clin Pediatr. 2014;53:943-48.
PARENTING TEENS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: CHALLENGES AND OPPORTUNITIES.
Modesto-Lowe V, Chaplin M, Godsay V, et al.
Attention-deficit/hyperactivity disorder (ADHD) presents in childhood with inattention, hyperactivity, and impulsivity and is associated with functional impairments. These children tend to display a variety of disruptive behaviors, which may worsen in adolescence. Teens with ADHD may show high levels of defiance, posing significant challenges for parents. Early efforts to understand parenting in the context of teen ADHD reveal high levels of parental stress and reactivity in response to the teen's ADHD symptoms. Subsequent research recognized that some of these parents have ADHD or other psychopathology that may contribute to maladaptive parenting. However, some parents adjust and demonstrate optimism and resilience in the face of their teens' ADHD. Recent research has identified parental factors (eg, emotional intelligence) and interventions (eg, mindfulness training) that may improve parenting/teen relationships and the developmental outcomes of teens. This article explores parenting teens with ADHD with a focus on these novel interventions.

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Clin Pediatr. 2014;53:949-59.
PARENTS' GOALS FOR ADHD CARE IN A CLINICAL PEDIATRIC SAMPLE.
McGoron L, Sturner R, Howard B, et al.
Objective. This report describes goals parents have for their children with attention deficit/hyperactivity disorder (ADHD) when coming for a pediatric visit.
Method. Data were collected from 441 parents of children presenting to either a primary care pediatric practice or a developmental behavioral pediatric practice. Parents were asked to report their top 1 or 2 goals for improvement for their children, and responses were coded into 17 categories. These categories were further grouped into 7 goal composites and examined in relation to demographic characteristics of the families, office type, and symptomology.
Results. Goals related to reducing symptoms of inattention were most common, but goals were heterogeneous in nature. Goals were meaningfully, but modestly, related to symptomology. In several instances, symptoms of comorbid conditions interacted with symptoms of ADHD in relation to specific goals being reported.
Conclusions. Parents' goals extended beyond ADHD symptoms. Pediatricians need an array of resources to address parents' goals.

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CNS Drugs. 2014.
EFFECT OF EXTENDED-RELEASE DEXMETHYLPHENIDATE AND MIXED AMPHETAMINE SALTS ON SLEEP: A DOUBLE-BLIND, RANDOMIZED, CROSSOVER STUDY IN YOUTH WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Santisteban JA, Stein MA, Bergmame L, et al.
Objective We sought to determine the dose-response effects of extended-release (ER) dexmethylphenidate (d-MPH) and ER mixed amphetamine salts (MAS) on objective measures of sleep.
Methods This was an 8-week, double-blind, placebo-controlled, randomized, two period, crossover study of youth with attention-deficit hyperactivity disorder (ADHD) as confirmed by the Kiddie Schedule for

Affective Disorders for School-Age Children-Present and Lifetime version (K-SADS-PL). Children aged 10-17 years were recruited from clinical practice, colleague referrals, and flyers. Participants were randomized to initially receive either d-MPH or MAS. During each 4-week drug period, children received three dose levels (10, 20, and 25/30 mg) in ascending order, with placebo substituted for active medication in a randomized fashion during 1 week of the study. After 4 weeks, participants were switched to the alternative medication for another 4 weeks of treatment. The main outcome measure was sleep duration as measured by actigraphy. Children, parents, and researchers were blinded to drug, dose, and placebo status.
Results Sixty-five participants met the inclusion criteria and were enrolled in the study. Of these, 37 participants with sufficient sleep data for analysis were included. Sleep schedule measures showed a significant effect for dose on sleep start time ($F(1,36) = 6.284$; $p < 0.05$), with a significantly later sleep start time when children were receiving 20- or 30-mg doses, compared with placebo ($p < 0.05$). A significant dose effect was found on actual sleep duration ($F(1,36) = 8.112$; $p < 0.05$), with significantly shorter actual sleep duration for subjects receiving 30 mg compared with those receiving placebo ($p < 0.05$). There were no significant differences on sleep duration or sleep schedule between the two stimulant medications. The trial is complete and closed to follow-up.
Conclusions Higher stimulant doses were associated with reduced sleep duration and later sleep start times, regardless of medication class. Trial registration
ClinicalTrials.gov: NCT00393042.

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Cogn Behav Pract. 2014.
CHANGING ACADEMIC SUPPORT IN THE HOME FOR ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A FAMILY-BASED CLINICAL PROTOCOL FOR IMPROVING SCHOOL PERFORMANCE.
Hogue A, Bobek M, Evans SW.
Attention-deficit/hyperactivity disorder (ADHD) is highly prevalent among adolescent clinical populations and associated with myriad deficits in school functioning. Yet, behavior therapists have few developmentally appropriate tools for addressing school problems in this group. This article introduces a behavioral protocol designed to fill the gap: Changing Academic Support in the Home for Adolescents With ADHD (CASH-AA). CASH-AA is a family-based intervention that targets home environment, adolescent skills, and family-school partnership characteristics in order to improve school performance. Protocol components are derived from three evidence-based approaches for adolescent behavior problems: family psychoeducation, clinical family interventions to heighten adolescent and caregiver motivation to change, and training interventions for homework planning and organization skills. CASH-AA contains four treatment modules: (1) Psychoeducation: ADHD and Academic Functioning; (2) Motivation and Preparation: Home Academic Environment; (3) Behavior Change: School Attendance and Homework Plan; (4) Collaboration: Therapist-Family-School Partnership. The protocol can be implemented as a stand-alone intervention for ADHD or an adjunct to other behavioral interventions for co-occurring disorders. Two case examples with markedly different treatment profiles are presented to illustrate the utility and flexibility of the protocol.

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Curr Med Res Opin. 2014;30:1687-99.
PHARMACOTHERAPY FOR INCIDENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: PRACTICE PATTERNS AND QUALITY METRICS.
Bussing R, Narwaney KJ, Winterstein AG, et al.
Introduction: This study examines incident treatment patterns for attention-deficit/hyperactivity disorder (ADHD) in children seen in eight integrated healthcare delivery systems and identifies factors associated with adherence to Healthcare Effectiveness Data and Information Set (HEDIS) quality measures developed by the National Committee for Quality Assurance (NCQA).
Method: A retrospective cohort analysis using electronic healthcare data from children aged 3 through 17 years with newly diagnosed ADHD between January 1, 2009 and December 31, 2010 was conducted. NCQA quality definitions for initiation and for continuation and maintenance (C&M) of ADHD medications

were expanded to include preschoolers and adolescents. Poisson regression models with robust error variance were used to evaluate the association between NCQA HEDIS adherence measures, provider type, patient characteristics and care process measures.
Results: Of 6864 children aged 3-17 years old qualifying for incident treatment analyses, 5538 (80.7%) were started on ADHD medication within a year of diagnosis. Adherence to NCQA HEDIS measures was 49.8% for initiation and 45.8% for C&M, with adherence rates higher for mental health than non-mental health providers, school-aged children than adolescents, and for patients concurrently on other psychotropic medications than those who were not. Of those started on ADHD medication, 62.3% were not eligible for C&M analyses according to HEDIS guidelines, because they did not receive continuous (210 of 300 days) ADHD medication treatment, with adolescents less likely than school-aged children to persist with medications.
Conclusion: Study limitations must be considered, including reliance on electronic medical record data, absence of patient race and sociodemographic data, and limited generalizability to other care contexts. Nevertheless, findings suggest novel strategies are needed to improve the quality of ADHD care processes for children of all ages, because even within integrated delivery systems less than half of children with ADHD received care consistent with NCQA HEDIS standards for initiation and C&M care. Results suggest the need to refine quality measures by including follow-up care in those children not receiving or discontinuing medication treatment, a considerable quality concern not currently captured in NCQA HEDIS standards.

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Curr Psychiatry Rep. 2014;16.
DELIVERING EVIDENCE-BASED TREATMENTS FOR CHILD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN THE CONTEXT OF PARENTAL ADHD.
Wang CH, Mazursky-Horowitz H, Chronis-Tuscano A.
Behavioral parent training (BPT) and stimulant medications are efficacious treatments for child attention-deficit/hyperactivity disorder (ADHD); however, there is some evidence to suggest that parental ADHD may reduce the efficacy of both treatment modalities. This review paper summarizes the literature related to the evidence-based behavioral and pharmacological treatment of child ADHD in the context of parental ADHD. We also review the literature on the effects of treating parents' ADHD symptoms on parenting and child behavior outcomes. Although the literature is small and inconsistent, studies suggest that medicating parents' ADHD symptoms may or may not be sufficient in demonstrating desired improvements in parenting and child behavioral outcomes. Therefore, interventions targeting both parent and child ADHD, when both are present, are likely needed to improve parent-child interactions and family functioning. Ongoing studies using a multimodal approach are discussed.

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Curr Psychiatry Rep. 2014;16.
USING STIMULANTS TO TREAT ADHD-RELATED EMOTIONAL LABILITY.
Posner J, Kass E, Hulvershorn L.
Emotional lability, or sudden strong shifts in emotion, commonly occurs in youth with attention-deficit/hyperactivity disorder. Although these symptoms are impairing and disruptive, relatively little research has addressed their treatment, likely due to the difficulty of reliable and valid assessment. Promising signals for symptom improvement have come from recent studies using stimulants in adults, children and adolescents. Similarly, neuroimaging studies have begun to identify neurobiological mechanisms underlying stimulants' impact on emotion regulation capacities. Here, we review these recent clinical and neuroimaging findings, as well as neurocognitive models for emotional lability in ADHD, issues of relevance to prescribers and the important role of psychiatric comorbidity with treatment choices.

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Drug Saf. 2014.

COMPARISON OF PREGNANCY AND LACTATION LABELING FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER DRUGS MARKETED IN AUSTRALIA, THE USA, DENMARK, AND THE UK.

Warrer P, Aagaard L, Hansen EH.

Background Pregnancy and lactation labeling is presented in the officially recognized product information (PI) accompanying prescription drugs to ensure appropriate prescribing in pregnant and breastfeeding women.

Objective The aim of this study was to analyze pregnancy and lactation labeling in PI for attention-deficit hyperactivity disorder drugs marketed across countries and to compare this information with respect to consistency and discrepancy.

Methods We manually surveyed PI for atomoxetine, methylphenidate, and modafinil marketed by the same pharmaceutical companies in Australia, the USA, Denmark, and the UK. We extracted information regarding data sources (animal and human data), risk to the fetus or breastfed child, excretion in breast milk, and recommendations for use. The extracted information was then analyzed and compared with respect to consistency and discrepancy. Results Inter-country discrepancies were identified with respect to both animal and human data sources presented, types of risks listed in association with exposure during pregnancy and lactation, information regarding excretion of the drug in breast milk, and recommendations for use. Consistency was identified between PI for drugs marketed in the EU.

Conclusion The study suggests that pregnancy and lactation labeling in PI for drugs marketed by the same pharmaceutical companies depend on the country of marketing; this raises concern about the reliability of PI documents as a useful source of information for appropriate prescribing during pregnancy and lactation. Discrepancies in this information can potentially lead to inappropriate prescribing in pregnant and breastfeeding women, who may expose their fetuses and breastfed children to unnecessary risks. At the same time, unjustified warnings against breastfeeding may result in children being unnecessarily weaned from being breastfed.

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Drug Saf. 2014.

CARDIOVASCULAR EFFECTS OF METHYLPHENIDATE, AMPHETAMINES AND ATOMOXETINE IN THE TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER: AN UPDATE.

Awudu GAH, Besag FMC.

Several million children and a growing number of adults are currently being treated for attention-deficit hyperactivity disorder (ADHD) worldwide. Concerns have been expressed about possible cardiac effects of the common treatments, namely methylphenidate, amphetamines and atomoxetine. Small increases in mean heart rate (HR) and mean blood pressure (BP) have been reported for all three drugs, but most of the studies have not yielded statistically significant results. These studies also have limitations, particularly regarding the lack of accepted and standardised measurement methods. Several large studies of the very rare phenomenon of sudden death in children have failed to show any convincing association with ADHD treatment. Whether minor increases in HR and BP have a cumulative effect over many years and have a long-term adverse effect on cardiovascular health remains undetermined.

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Drugs in R&D. 2014.

SHOPPING BEHAVIOR FOR ADHD DRUGS: RESULTS OF A COHORT STUDY IN A PHARMACY DATABASE.

Cepeda MS, Fife D, Berwaerts J, et al.

Objective Attention-deficit hyperactivity disorder (ADHD) medications are subject to abuse, misuse, and diversion. Obtaining ADHD prescriptions from multiple prescribers or filled across multiple pharmacies, known as 'doctor shopping', may reflect such unsanctioned use. We sought to create a definition of shopping behavior that differentiated ADHD medications from medications with low risk of diversion, i.e. asthma medications, and describe the incidence, frequency, and demography of shopping behavior.

Methods This was a retrospective cohort study in a pharmacy database-LRx-covering 65 % of US retail pharmacies. Subjects had ADHD or asthma medication dispensed between February 2011 and January 2012. We followed subjects for 18 months to assess the number with overlapping dispensings from different prescribers, and the number of prescribers and pharmacies involved in those dispensings.
Results We included 4,402,464 subjects who were dispensed ADHD medications, and 6,128,025 subjects who were dispensed asthma medications. Overlapping prescriptions from two or more prescribers dispensed by three or more pharmacies was four times more frequent in the ADHD cohort than in the asthma cohort. Using this definition, ADHD medication shopping behavior was more common among experienced users than naive users, and was most common in subjects aged 10-39 years. Among subjects who shopped, 57.4 % shopped only once (accounting for 22.4 % of episodes), and 9.2 % shopped six or more times (accounting for 42.0 % of episodes). Shoppers more often received stimulant ADHD drugs than non-stimulants.
Conclusions Overlapping prescriptions by different prescribers and filled at three or more pharmacies defines ADHD medication shopping. Shopping behavior is most common in adolescents and younger adults. A small proportion of shoppers is responsible for a large number of shopping episodes.

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Emot Behav Difficulties. 2014;19:245.
THE PRACTICES OF DEALING WITH CHILDREN IN NEED OF SPECIAL SUPPORT: A NORDIC PERSPECTIVE.
Daniels H.

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Eur Child Adolesc Psychiatry. 2014;23:531-37.
ON THE LINK BETWEEN ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND OBESITY: DO COMORBID OPPOSITIONAL DEFIANT AND CONDUCT DISORDER MATTER?
Pauli-Pott U, Neidhard J, Heinzel-Gutenbrunner M, et al.
The link between attention deficit/hyperactivity disorder (ADHD) and elevated body weight/obesity can be regarded as well established. Because oppositional defiant disorder (ODD)/conduct disorder (CD) has also been found to be associated with these characteristics and ADHD and ODD/CD often occur comorbidly, we investigated whether ODD/CD and ADHD are independently linked with body weight and obesity. The clinical records of 360 children, 257 (6-12 years) with diagnoses of ADHD, ODD/CD, or comorbid ADHD and ODD/CD and 103 children with adjustment disorder (as a control group) constituted the database. All children were seen for the first time in two outpatient psychiatric clinics. Associations of the psychiatric diagnoses (ADHD present vs. not present; ODD/CD present vs. not present) with the standard deviation scores (according to German reference data) of the child's body mass index (BMI-SDS) and presence of obesity were analyzed by ANCOVA and hierarchical logistic regression analysis, respectively. Children with ODD/CD showed higher BMI-SDS ($F = 7.67$, $p < 0.006$) and rate of obesity (Wald = 4.12, $p < 0.05$, OR = 2.43) while controlling for ADHD comorbidity. While adjusting for ODD/CD comorbidity, the links between ADHD and BMI-SDS or obesity did not reach statistical significance. Given a cross validation of these findings, future (preferably prospective longitudinal) research should analyze the mediating mechanism between the psychiatric conditions and obesity. This knowledge could be helpful for preventive interventions.

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Europ J Spec Needs Educ. 2014.
CYBERBULLYING INVOLVEMENT AMONG STUDENTS WITH ADHD: RELATION TO LONELINESS, SELF-EFFICACY AND SOCIAL SUPPORT.
Heiman T, Olenik-Shemesh D, Eden S.
Cyberbullying is defined as an intentional online act via electronic media, to harm, embarrass and/or humiliate another person. As adolescents with attention deficit hyperactivity disorder (ADHD) are at a

higher risk in being involved in bullying behaviour as perpetrators or victims, the main purpose of this study is to examine the prevalence of their cyber experience and its impact on loneliness, perceived self-efficacy and social support. The study population included 140 adolescent students with ADHD taking part in general classes and 332 students without disabilities, all of whom completed four self-report questionnaires (cyberbullying, perceived feelings of loneliness, self-efficacy and social support). The findings show no significant differences between students with or without ADHD regarding the time spent on the net and their perceived usage expertise. Most participants with ADHD were familiar with the internet and spent a similar amount of time surfing as the adolescents without ADHD. Results revealed significant differences between the student groups (ADHD/Non-ADHD) and some of the social-emotional measures: students with ADHD who were cybervictims and students with ADHD who were cyberwitnesses reported on greater feelings of emotional loneliness and a lower belief in their social self-efficacy than the non-ADHD students. Furthermore, ADHD student cyberwitnesses also reported on feelings of greater social loneliness. Findings revealed that girls were significantly more often cybervictims than boys. However, boys reported on significantly more involvement as cyberperpetrators than girls.

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Europ J Spec Needs Educ. 2014.

BIRTH MONTH AS PREDICTOR OF ADHD MEDICATION USE IN DUTCH SCHOOL CLASSES.

Krabbe EE, Thoutenhoofd ED, Conradi M, et al.

Several international studies have shown that pupils who are comparatively young within their year group have a greater likelihood of being diagnosed with ADHD and receiving ADHD medication. The findings suggest that comparatively young but age-appropriate behaviour some pupils show in school may be confused with ADHD. This study investigates whether this noted association between birth month and ADHD medication is also found in the Netherlands; and if so, whether GPs (general practitioners) and teachers are aware of this association. Over 2000 birth dates of children between the ages of 5 and 12 were collected from GP client files. The data included whether children are prescribed methylphenidate, the most commonly used medication for ADHD. These data were analysed by descriptive statistics (graphs) and evaluative statistics (logistic regression analysis and relative risk). GPs and teachers were invited by questionnaire to report whether they knew of the association between birth month and ADHD. A significant correlation between birth month and methylphenidate prescription are found. Relatively young pupils are 2.43 times more likely to be prescribed methylphenidate than their older classmates. A majority of GPs and teachers report not being aware of an association between birth month and ADHD medication.

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Eur Neuropsychopharmacol. 2014.

GUANFACINE FOR ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN PEDIATRICS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Ruggiero S, Clavenna A, Reale L, et al.

To review the evidence from randomized controlled trials (RCTs) on the safety and efficacy of guanfacine in pediatric attention deficit hyperactivity disorder (ADHD), a bibliographic search up to May 2014 was performed using the Cochrane Library's Central Register of Controlled Trials, the Embase, PsycINFO, and Medline databases, and clinical trials registers. The search terms used were: ["guanfacine"] and ["child" or "adolescent" or "pediatrics"] and ["randomized controlled trial"] and ["Attention Deficit Disorder with Hyperactivity" or "Attention Deficit Disorder" or "Attention Hyperactivity Disorder" or "Hyperactivity" or "ADHD"]. A meta-analysis was performed using response, defined as a score(less-than or equal to)2 on the Clinical Global Impression Improvement score, as the outcome measure. In all, 7 out of 48 studies were included, for a total of 1752 participants. All studies compared guanfacine versus placebo, with a duration ranging from 6 to 16 weeks. In all, the Clinical Global Impression Improvement score was reported as a secondary measure. Overall, 694/1177 (59.0%) participants in the guanfacine group benefited from the treatment compared to 192/575 (33.3%) in the placebo group (pooled OR 3.2; 95%CI 2.4-4.1). The participants with at least one adverse event were 948 (82.4%) in the guanfacine and 376 (67.9%) in the

placebo group (OR 2.6; 95%CI 1.6-4.4). Somnolence (OR 4.9), sedation (OR 2.8), and fatigue (OR 2.2), were the adverse events with the greatest risk of occurrence in the guanfacine versus the placebo group. On the basis of seven randomized, placebo controlled trials guanfacine resulted safe and effective in treating children and adolescents with ADHD.

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Eur Neuropsychopharmacol. 2014.

INFLUENCE OF STIMULANT AND NON-STIMULANT DRUG TREATMENT ON DRIVING PERFORMANCE IN PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.

Gobbo MA, Louza MR.

Adults with Attention Deficit Hyperactivity Disorder (ADHD), especially teenagers and young adults, show important car driving impairments, including risky driving, accidents, fines and suspension of driver's license. We systematically reviewed the efficacy of stimulant and non-stimulant drugs on driving performance of ADHD patients. We searched several databases for randomized controlled trials (RCTs) published through March, 2013. Fifteen RCTs (the majority with crossover design) evaluated methylphenidate (MPH) immediate-release (MPH-IR), MPH osmotic-controlled oral system (MPH-OROS), MPH transdermal system (MTS), extended-release mixed amphetamine salts (MAS-XR); atomoxetine (ATX) and lisdexamfetamine (LDX). Methods varied widely; including simulators and/or cars and different courses and scenarios. Various outcomes of driving performance, including a 'composite' or 'overall' driving score were considered. In general, stimulants improved driving performance in ADHD patients (either in RCTs conducted in simulators and/or cars). MPH-OROS improved driving performance compared with MAS-XR, placebo, or no-drug conditions. Although MPH-OROS and MPH-IR produced similar improvements during the day, MPH-IR lost its efficacy in the evening. MAS-XR also improved driving performance, but worsened driving performance in the evening. MTS (one study) showed a positive effect, but drug compliance varied widely across patients. LDX had positive effect on driving (two studies with the same sample). Studies with ATX report conflicting results. Improvement was more consistent in teenagers and young adults. In general, treatment with psychostimulants or ATX in therapeutic dosages had no negative impact on driving performance of ADHD patients. To conclude, treatment with stimulants in therapeutic doses improves driving performance in ADHD patients, especially teenagers and young adults.

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Eur Psychiatry. 2014.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER INCREASES THE RISK OF DELIBERATE SELF-POISONING: A POPULATION-BASED COHORT.

Chou I-C, Lin C-C, Sung F-C, et al.

Background: Children with attention-deficit hyperactivity disorder (ADHD) may suffer marked impairment in early adulthood, increasing their risk for serious self-harmful behaviors. Deliberate self-poisoning (DSP) is the most common form of deliberate self-harm. An association may exist between ADHD diagnosis and subsequent DSP events. The purpose of study was to determine whether children and adolescents with ADHD are at a greater risk for DSP than are age-matched controls.

Methods: Claims data from the Taiwan National Health Insurance Database were used to conduct a retrospective cohort analysis of emergency department visits. The study cohort contained 3685 patients with ADHD (< 8 years old). Each ADHD patient was frequency matched based on sex, age, urbanization, parental occupation, and index year to 10 control patients without ADHD. A Cox proportional-hazards regression model was used to estimate the risk of DSP in the ADHD and comparison cohorts.

Results: The risk of developing DSP was significantly higher in the ADHD cohort than in the comparison cohort (P < .0001 for log-rank test). After adjusting for potential confounders, the regression model showed that the ADHD patients were at a 4.65-fold greater risk of developing DSP than the control patients were (HR = 4.65, 95% CI: 2.41-8.94).

Conclusion: Children with ADHD are at greater risk of developing DSP. Identifying risk factors of DSP is crucial efforts to implement prevention strategies. The identification of the underlying cause of increased DSP among ADHD patients warrants further investigation.

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Expert Opinion on Drug Metabolism and Toxicology. 2014;10:1289-99.

A PHARMACOKINETIC EVALUATION OF ORAL EDIVOXETINE HYDROCHLORIDE FOR THE TREATMENT OF ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Markowitz JS, Brinda BJ.

Introduction: The majority of available therapeutics to treat attention-deficit/hyperactivity disorder (ADHD) are formulations of either methylphenidate or amphetamine. However, psychostimulants may not be suitable options for many patients. The availability of novel pharmacological agents to treat ADHD is highly desirable. Edivoxetine hydrochloride (LY2216684) is a highly selective and potent norepinephrine reuptake inhibitor under clinical development for ADHD.

Areas covered: This paper provides an overview of what is presently known of the pharmacokinetics (PK) of edivoxetine based on available studies in healthy volunteers, in subjects with compromised renal and hepatic functioning and in children and adolescents.

Expert opinion: Available data suggest edivoxetine is safe and well tolerated. Edivoxetine is readily absorbed with metabolism proceeding through the CYP hepatic enzyme pathway, with CYP2D6 and CYP3A4 playing the most prominent roles. The tmax is ~ 2 h post-dose, and the plasma t1/2 is ~ 4-6 h irrespective of the dose. Pharmacokinetic parameters are not substantially different between children and adults. Edivoxetine may be a promising non-stimulant therapeutic agent. However, at present, there is insufficient data available to permit a thorough analysis of its potential place in ADHD pharmacotherapy, or how its PK and pharmacodynamics may differ in clinically meaningful ways from existing agents.

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Expert Rev Neurother. 2014;14:849-65.

THE USE OF LISDEXAMFETAMINE DIMESYLATE FOR THE TREATMENT OF ADHD AND OTHER PSYCHIATRIC DISORDERS.

Roncero C, Alvarez FJ.

Lisdexamfetamine dimesylate (LDX) is a long-acting oral prodrug stimulant. It is inactive until enzymatically hydrolyzed in the blood to active d-amphetamine. The pharmacological action of this compound involves blocking norepinephrine (NE) and dopamine reuptake into presynaptic neurons and promoting the release of NE and dopamine into the extraneuronal space. LDX has been approved for treating ADHD, which is the most common psychiatric disorder in children and adolescents. Also, LDX has been proposed for other psychiatric conditions related with dopaminergic and NE CNS. LDX is the first long-acting oral prodrug indicated for the treatment of ADHD in children (6-12 years), adolescents (13-17 years) and in adults in the USA and Canada, whereas, in Europe, LDX is licensed in several countries for the treatment of children and adolescents with ADHD who have had a clinically inadequate response to methylphenidate. This article covers the most important pharmacological aspects of LDX as well as data on the efficacy, tolerability and safety of this long-acting amphetamine prodrug collected from clinical studies recently published in the literature.

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Hum Brain Mapp. 2014;35:4693-705.

DISRUPTED NETWORK ARCHITECTURE OF THE RESTING BRAIN IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sripada C, Kessler D, Fang Y, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders of childhood. Neuroimaging investigations of ADHD have traditionally sought to detect localized abnormalities in discrete brain regions. Recent years, however, have seen the emergence of

complementary lines of investigation into distributed connectivity disturbances in ADHD. Current models emphasize abnormal relationships between default network-involved in internally directed mentation and lapses of attention-and task positive networks, especially ventral attention network. However, studies that comprehensively investigate interrelationships between large-scale networks in ADHD remain relatively rare.
Methods: Resting state functional magnetic resonance imaging scans were obtained from 757 participants at seven sites in the ADHD-200 multisite sample. Functional connectomes were generated for each subject, and interrelationships between seven large-scale brain networks were examined with network contingency analysis.
Results: ADHD brains exhibited altered resting state connectivity between default network and ventral attention network [P<0.0001, false discovery rate (FDR)-corrected], including prominent increased connectivity (more specifically, diminished anticorrelation) between posterior cingulate cortex in default network and right anterior insula and supplementary motor area in ventral attention network. There was distributed hypoconnectivity within default network (P=0.009, FDR-corrected), and this network also exhibited significant alterations in its interconnections with several other large-scale networks. Additionally, there was pronounced right lateralization of aberrant default network connections.
Conclusions: Consistent with existing theoretical models, these results provide evidence that default network-ventral attention network interconnections are a key locus of dysfunction in ADHD. Moreover, these findings contribute to growing evidence that distributed dysconnectivity within and between large-scale networks is present in ADHD.

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Indian Pediatr. 2014;51:457-62.

INCLEN DIAGNOSTIC TOOL FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (INDT-ADHD): DEVELOPMENT AND VALIDATION.

Mukherjee S, Aneja S, Russell PSS, et al.

Objective: To develop and validate INCLEN Diagnostic Tool for Attention Deficit Hyperactivity Disorder (INDT-ADHD).
Design: Diagnostic test evaluation by cross sectional design.
Setting: Tertiary care pediatric centers.
Participants: 156 children aged 65-117 months.
Methods: After randomization, INDT-ADHD and Connor's 3 Parent Rating Scale (C3PS) were administered, followed by an expert evaluation by DSM-IV-TR diagnostic criteria.
Main outcome measures: Psychometric evaluation of diagnostic accuracy, validity (construct, criterion and convergent) and internal consistency.
Results: INDT-ADHD had 18 items that quantified symptoms and impairment. Attention deficit hyperactivity disorder was identified in 57, 87 and 116 children by expert evaluation, INDT-ADHD and C3PS, respectively. Psychometric parameters of INDT-ADHD for differentiating attention deficit hyperactivity disorder and normal children were: sensitivity 87.7%, specificity 97.2%, positive predictive value 98.0% and negative predictive value 83.3%, whereas for differentiating from other neuro-developmental disorders were 87.7%, 42.9%, 58.1% and 79.4%, respectively. Internal consistency was 0.91. INDT-ADHD has a 4-factor structure explaining 60.4% of the variance. Convergent validity with Conner's Parents Rating Scale was moderate (r =0.73, P= 0.001).
Conclusions: INDT-ADHD is suitable for diagnosing attention deficit hyperactivity disorder in Indian children between the ages of 6 to 9 years.

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Indian Pediatr. 2014;51:550-54.

COMPARATIVE SHORT TERM EFFICACY AND TOLERABILITY OF METHYLPHENIDATE AND ATOMOXETINE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Garg J, Arun P, Chavan BS.

Objective: To compare the short term efficacy and tolerability of methylphenidate and atomoxetine in children with Attention deficit hyperactivity disorder (ADHD).
Design: Open label randomized parallel group clinical trial.
Setting: Child Guidance Clinic of a tertiary care hospital of Northern India from October 2010 to June 2012.
Participants: 69 patients (age 6-14 y) with a diagnosis of ADHD receiving methylphenidate or atomoxetine.
Intervention: Methylphenidate (0.2-1 mg/kg/d) or atomoxetine (0.5-1.2 mg/kg/d) for eight weeks.
Main outcome measures: Treatment response (>25% change in baseline Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS); Vanderbilt ADHD Diagnostic Teacher Rating Scale (VADTRS); Clinical Global Impression Severity Scale (CGI-S) at eight weeks and adverse effects.
Results: Treatment response was observed in 90.7% patients from methylphenidate group and 86.2% patients of atomoxetine group at an average dose of 0.45 mg/kg/d and 0.61 mg/kg/d, respectively. The patients showed comparable improvement on VADPRS (P=0.500), VADTRS (P=0.264) and CGI-S (P=0.997). Weight loss was significantly higher in methylphenidate group (-0.57(plus or minus)0.78 kg; P=0.001), and heart rate increase was observed at higher rate in atomoxetine group (7(plus or minus) 9 bpm; P=0.021).
Conclusion: Methylphenidate and atomoxetine are efficacious in Indian children with ADHD at lesser doses than previously used. Their efficacy and tolerability are comparable.
Trial Registration No.: CTRI/2011/08/001981.

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Int Clin Psychopharmacol. 2014;29:274-78.

THE BENEFICIAL EFFECT OF METHYLPHENIDATE IN ADHD WITH COMORBID SEPARATION ANXIETY.

Golubchik P, Golubchik L, Sever JM, et al .

The objective of this study was to assess the response of subsyndromal separation anxiety (SSSA) symptoms to methylphenidate (MPH) treatment in patients with attention-deficit/hyperactivity disorder (ADHD). A group of patients with ADHD and SSSA (n=42), aged 8-17 years, received 12 weeks of MPH treatment. The severity of SSSA symptoms was assessed using appropriate scales including the Screen for Child Anxiety Related Emotional Disorders and the specially designed Child and Adolescent Separation Anxiety Scale (CASAS). The severity of ADHD symptoms was assessed using the ADHD Rating Scale. The severity of ADHD and separation anxiety reduced significantly and significant positive correlations were found between the changes in ADHD Rating Scale and the total CASAS scores (P=0.012), as well as other relevant subscales of Screen for Child Anxiety Related Emotional Disorders and CASAS. The MPH-related attenuation in the severity of ADHD was associated with a corresponding improvement in separation anxiety related to school. SSSA symptomatology may be secondary to ADHD and thus the alleviation in ADHD symptoms achieved by MPH treatment results in corresponding relief in separation anxiety.

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International Journal of Developmental Disabilities. 2014;60:184-97.

CONTEXT-SPECIFIC MEMORY IN CHILDREN WITH ADHD .

Kerns KA, Macoun SJ.

Objectives: Memory for where and when information is learned, or contextual aspects of memory, as opposed to fact or item memory, has been suggested to be more dependent on frontal brain and related executive control systems. Children with neurodevelopmental disorders involving frontal brain systems have been noted to have problems on contextual memory tasks. Children with attention deficit hyperactivity disorder (ADHD) have difficulties with forgetfulness and are known to have deficits in aspects of executive

control with associated dysfunction in frontal brain systems; therefore, while their item memory is not typically impaired, they may have difficulty on tasks requiring contextual memory abilities. The goal of this study was to compare children with ADHD to typically developing children, on two different contextual memory tasks (source memory and memory for temporal recency) and to compare this with their respective performance on traditional fact/item memory tasks.
Methods: Participants included 36 children with combined type ADHD and 36 typically developing controls ages 6-13 years, matched by age and gender. In addition to a measure of intellectual ability, children completed two different contextual memory tasks; one assessing recall for the source of new information and one assessing recall of the temporal context of information (recency). Incorporated into these tasks were standard measures of item/fact memory recall.
Results: Results revealed that children with ADHD performed similarly to control participants on memory recognition tasks, but differed from controls on the contextual memory tasks. Children with ADHD outperformed control participants when recalling the source from which they had learned information, but performed more poorly than control on a task that required them to make a recency/temporal order judgment.
Conclusion: The data suggest that while children with ADHD may have somewhat similar capacity to recognise new information, they differ in aspects of their performance on contextual aspects of memory. These differences are not uniform and mirror neuroscience findings supporting dissociable contextual memory systems. Potential theoretical explanations for the dissociations seen are discussed.

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International Journal of Developmental Disabilities. 2014;60:163-73.

ON THE ROLE OF NON-SHARED ENVIRONMENT FOR EXECUTIVE FUNCTIONING IN ADHD: A TWIN-DIFFERENCES DESIGN STUDY.

Willfors C, Poltrago L, Berggren S, et al.

Introduction: The study of differences between monozygotic (MZ) twin pairs with respect to ADHD may provide novel leads to disentangle the environmental contribution driving its phenotypes.
Objectives: To examine non-shared environmental influences on executive function in dimensionally defined ADHD.
Methods: This study included 27 MZ twin pairs (7 female) aged 11-20 years being moderately to substantially discordant for ADHD traits as assessed by the Attention Problem (AP) scale of the Child Behavior Checklist/Adult Behavior Checklist. The twins completed the Wisconsin Card Sorting Test (WCST) for cognitive flexibility and the Tower Test (TT) for foresighted planning. Two statistical approaches were used to analyze the data. First, correlations between ADHD trait intra-pair differences and WCST and TT scores were calculated. Second, the significance of those intra-pair differences on WCST and TT, using ADHD as categorical variable in clinically discordant pairs, was tested.
Results: Both analysing strategies revealed a link between ADHD on one hand, and foresighted planning and inhibitory control on the other hand mediated by non-shared environmental factors. The first statistical approach yielded positive correlations between intra-pairs differences on the AP scale and intra-pair differences on two subscales of the TT: total rule violation (r s=0.41) and rule-violation-per-item-ratio (rs=0.38). Findings in categorically discordant pairs were consistent, showing within-pair differences on the same subtests (z-1.63, P=0.05, one-tailed and z=-1.60, P=0.05, one-tailed).
Conclusions: Findings confirm previous research suggesting ADHD to be a quantitative extreme on a continuum with executive functions being a cognitive marker of ADHD traits. Non-shared environmental factors appear to influence planning skills and inhibitory control.

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International Journal of Developmental Disabilities. 2014;60:144-54.

EXECUTIVE FUNCTION AND ATTENTION PROFILES IN PRESCHOOL AND ELEMENTARY SCHOOL CHILDREN WITH AUTISM SPECTRUM DISORDERS OR ADHD.

Sinzig J, Vinzelberg I, Evers D, et al.

Both autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) show executive function and attention problems. By now, these are well described in school children and adolescents, but not in preschool or elementary school children. The goal of this study was to compare the neuropsychological profiles of executive and attention functions in an ADHD, an ASD, and a typically-developing group. Eighty-five children aged 4-9 years old with ADHD (n=30) or ASD (n=26) and healthy children (n=29) were included consecutively. Psychopathology was evaluated using the KIDDIE-SADS, the Child Behaviour Checklist (CBCL), and symptom checklists for ADHD according to DSM-IV. Assessment of neuropsychological functioning included tasks from the Amsterdam Neuropsychological Tasks (ANT), namely, inhibition (GoNoGo), flexibility (shifting attentional set visual), and sustained attention (sustained attention objects). A MANOVA with age and IQ as covariates revealed statistically significant group effects for the variable 'flexibility errors compatible'. Effect sizes showed clear deficits of children with ASD and ADHD in inhibition and, furthermore, impairments in sustained attention in ASD children. Pearson correlations revealed associations between social problems and aggressive behaviour with all three tasks in the ADHD group and between thought problems and sustained attention in the ASD group. Our hypothesis was partly confirmed as ADHD children showed more deficits in inhibition tasks than healthy children. However, there was no evidence that children with ASD have a specific profile in comparison to ADHD children.

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Int J Eating Disord. 2014.

ASSOCIATION BETWEEN BINGE EATING AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN TWO PEDIATRIC COMMUNITY MENTAL HEALTH CLINICS.

Reinblatt SP, Leoutsakos J-M, Mahone EM, et al.

Objective: Attention-Deficit/ Hyperactivity Disorder (ADHD) has been linked with obesity; however its relationship with binge eating (BE) is less clear. We aimed to explore the associations among ADHD, weight, and BE in pediatric mental health clinics.

Method: We retrospectively reviewed consecutive intakes in two pediatric mental health clinics (N=252). BE was assessed using the C-BEDS scale. Associations between ADHD, BE, and BMI-z score were assessed via regression.

Results: Mean age was 10.8 (3.7 SD) years. Twelve percent (n=31) had BE. The association between ADHD and BE was statistically significant (OR 16.1, p<.001), and persisted after adjusting for comorbid diagnoses, medications, demographic variables, and clinic. There was a statistically significant association between ADHD and BMI z-scores ((beta)=0.54, p<.001). After adjusting for BE, the relationship between ADHD and BMI z-scores was attenuated ((beta)=0.35, p=.025), and the coefficient for BE was decreased ((beta)=0.75, p=.001). Although stimulant use was associated with a three-fold increase in odds of BE (OR 3.16, p=.006), stimulants were not associated with greater BMI-z scores ((beta)=0.18, p=.32).

Discussion: There was a significant association between ADHD and BE in two pediatric mental health clinics. Although these data are cross-sectional, and cannot be used to make causal inferences, these findings are compatible with the hypothesis that BE partially mediates the association between ADHD and BMI z-scores. In mental health clinics, children with ADHD may present as overweight or obese. Further, children with ADHD may exhibit BE. Future prospective studies should elucidate the complex relationships among ADHD, weight, stimulants, and BE.

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Int J Neuropsychopharmacol. 2012;15:223.

IDENTIFICATION AND MANAGEMENT OF ADULT ATTENTION DEFICIT DISORDER: CASE DISCUSSIONS AND BRIEF LITERATURE REVIEW.

Pattanayak S, Bhimwal N.

Objective:

Introduction: Not all children with ADHD remit in adolescence and many continue to manifest a host of behavioral and lifestyle problems, and are often treated as 'lazy/disorganized' by family members. Adult ADD needs more clinical and research attention.

Objective: To describe the case histories and management of three patients diagnosed as Adult ADHD and present a brief review of relevant literature.

Methods: The case details of three adult male patients (Mr A, 25 yrs ; Mr B 30 years and Mr C 34 years) presenting to the out-patient psychiatric clinic of V.I.M.H.A.N.S., New Delhi are being presented. All three patients reported long standing histories of difficulties experienced in organizing work or home affairs, poor time management/ inability to keep appointments, at times not even making it on time for examinations/interviews, tendency to delay/procrastinate important things, frequent inattention towards the work at hand affecting the academic/job performance, multiple changes of job, considered to be 'chronically lazy' and ' inattentive' by family members. All three patients had childhood histories of ADHD.

Results: After a careful history and assessments, and ruling out any other psychiatric/medical comorbidity, a diagnosis of Adult ADHD was considered. They were initiated on stimulants and were carefully monitored. Al the three patients responded well to Atomoxetine 15 mg, Methylphenidate 40 mg/day and Atomoxetine 58 mg/day respectively, with a considerable improvement in symptoms of inattention and improved socio-occupational performance. The findings from the cases are being discussed in light of available literature.

Conclusion: The diagnosis of adult ADD should be considered in all patients presenting with chronic histories of inattention. The childhood history of ADHD should be enquired from family members and if positive, these patients can be considered for an adequate trial of stimulant-based pharmacotherapy.

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Int J Neuropsychopharmacol. 2012;15:222.

ADHERENCE TO OROS METHYLPHENIDATE AND SYMPTOMS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kim S-H, Yang J, Lee M-S, et al.

Objective: The goal of this study was to examine medication adherence to Osmotic-controlled Release Oral delivery System methylphenidate using electronic measurements and other measures of adherence in children with attention-deficit hyperactivity disorder (ADHD). The relationship between adherence and other clinical factors was also analyzed.

Methods: Thirty-nine children diagnosed with ADHD were monitored over the course of eight weeks. Medication adherence was assessed using patient self-report, a clinician rating scale, pill counts, and the Medication Event Monitoring System (MEMS), which is a medication bottle cap with a microprocessor that records the time and date every time the bottle is opened. Agreement among the adherence measures and the relationships between adherence and other factors, including ADHD rating scores of children and their parents, were assessed.

Results: The rate of non-adherence measured by the MEMS was found to be 46.2 %, which was considerably higher than the clinician scale (31.7 %), patient self-report (17.9 %), and pill count (12.8%) rates of non-adherence. The rate of adherence measured by the MEMS was not significantly associated with baseline symptom severity or symptom changes over a short-term period, though non-adherent group experienced more severe symptoms in children with ADHD.

Conclusion: Adherence to OROS methylphenidate varied depending on the method used to measure adherence. There was a discrepancy between adherence measures according to clinician rating and the MEMS. Further studies are needed to evaluate the variables that may impact medication adherence in ADHD.

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Int J Neuropsychopharmacol. 2012;15:223.

CONVERSION OF LISDEXAMFETAMINE DIMESYLATE TO D-AMFETAMINE: LOW VARIABILITY IN EXPOSURE TO D-AMFETAMINE AFTER ADMINISTRATION OF LISDEXAMFETAMINE DIMESYLATE TO CHILDREN WITH ADHD.

Pennick M, Ermer J.

Objective: Lisdexamfetamine dimesylate (LDX, Vyvanse1, Shire US Inc) is a long-acting prodrug stimulant that requires hydrolytic cleavage to generate active d-amfetamine. Preclinical studies indicate that LDX is rapidly absorbed via active transport, and is a likely substrate for PepT1 in the small intestine. Here, we describe the formation of d-amfetamine from LDX in human tissues maintained in vitro, and the low variability in d-amfetamine exposure in children with ADHD treated with LDX.

Methods: Studies on LDX hydrolysis were performed in homogenized tissues and fractions of blood obtained from human donors. Tissues were incubated (37 xC) with 1 mg/mL LDX, and samples were collected for <4 hrs. Variability in systemic exposure of d-amfetamine following administration of LDX 30 mg, 50 mg and 70 mg was examined in a single-dose, randomized, crossover study in boys and girls (6-12 years) with ADHD severe enough to require a treatment change.

Results: Half-lives for the disappearance of LDX were 1.6 h, 2.3 h and 9.7 h in whole blood, kidney and liver, respectively ; LDX was stable in homogenates of upper and lower intestines, pancreas and plasma. When incubated with red blood cells (RBC), the half-life for the disappearance of LDX was 1.0 h; and there was still substantial conversion at 10-15% of normal haematocrit. In children with ADHD (17 completed the study ; mean age 9.6 years), exposure (AUC0-1) of d-amfetamine increased proportionally with increasing LDX dose (mean [standard deviation] ng.h/mL: 30 mg, 844.6 [116.7] ; 50 mg, 1510.0 [241.6] ; 70 mg, 2157.0 [383.3]). The variability (percent coefficient of variation) in d-amfetamine AUC0-1 was below 20% for all three doses of LDX (30 mg, 13.8%; 50 mg, 16.0%; 70 mg, 17.8 %).

Conclusion: LDX was converted to d-amfetamine primarily in RBC. In children with ADHD, exposure to d-amfetamine increased in proportion to dose, and variability in exposure was low, within the therapeutic dose range (30-70 mg).

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J Abnorm Child Psychol. 2014 Aug;42:1033-42.

ADHD SYMPTOMS AND ATTACHMENT REPRESENTATIONS: CONSIDERING THE ROLE OF CONDUCT PROBLEMS, COGNITIVE DEFICITS AND NARRATIVE RESPONSES IN NON-ATTACHMENT-RELATED STORY STEMS.

Scholtens S, Rydell AM, Bohlin G, et al.

The overall aim of the present study was to investigate ADHD symptoms in relation to attachment representations. We used both attachment- and non-attachment-related story stems, which allowed us to investigate whether problems with narrative production can explain the relation between ADHD symptoms and attachment representations. We also investigated the role of cognitive deficits and conduct problems in these relations. The sample consisted of 89 children (27 % girls) between 6 and 10 years old, with an oversampling of children with high levels of ADHD symptoms. ADHD symptoms and conduct problems were rated by parents and teachers. Cognitive functioning was investigated using laboratory tests of inhibition, working memory and sustained attention. Attachment representations were coded as secure, organized insecure and disorganized categories. Narrative responses to non-attachment-related story stems were coded for incoherence and negative content. Results showed that children in the disorganized attachment category had significantly higher levels of ADHD symptoms compared to those in the secure category. Both ADHD symptoms and disorganized attachment were related to incoherence and negative content. Attachment representations were not associated with ADHD symptoms when controlling for negative content in response to non-attachment-related story stems. These results suggest that the associations between attachment security and ADHD are yet to be fully understood. Importantly, a propensity to envisage negative events seems to characterize children with high levels of ADHD symptoms.

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J Abnorm Child Psychol. 2014 Aug;42:993-1004.

CHANGES IN ADHD SYMPTOM ENDORSEMENT: PRESCHOOL TO SCHOOL AGE.

Curchack-Lichtin JT, Chacko A, Halperin JM.

To investigate endorsement patterns among the 18 DSM-IV symptoms of ADHD in a longitudinal sample of children with and without ADHD (n=144), as assessed at ages 4-5, 5-6, and 6-7 years. Symptom endorsements and diagnoses were determined at all time-points via K-SADS-PL interview administered to parents and supplemented by teacher questionnaires and clinician observations. Changes in endorsement patterns over time for each of the 18 DSM-IV symptoms were ascertained. Several symptoms, particularly those of inattention, were infrequently endorsed and of apparently limited diagnostic utility at ages 4-5; hyperactive/impulsive symptoms were more frequently endorsed among young children with ADHD than were inattentive symptoms. However, by ages 6-7, inattention items were somewhat superior at discriminating ADHD from Non-ADHD children. Several DSM-IV and now DSM-V symptoms provide limited diagnostic differentiation prior to school-age, particularly those most commonly observed in the context of formal schooling. Consideration should be made in future iterations of the DSM that account for such developmental and contextual differences.

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J Adolesc. 2014;37:1003-09.

SINGLE NIGHT VIDEO-GAME USE LEADS TO SLEEP LOSS AND ATTENTION DEFICITS IN OLDER ADOLESCENTS.

Wolfe J, Kar K, Perry A, et al.

The present study investigated adolescent video-game use prior to bedtime and subsequent sleep, working memory and sustained attention performance. Participants were 21 healthy, good-sleeping adolescents (16 male) aged between 15 and 20 years (M=17.6 years, SD=1.8). Time spent video-gaming and subsequent sleep was measured across one night in the sleep laboratory. There were significant correlations between time spent video-gaming and sleep and between video-gaming and sustained attention, but not working memory. Sleep duration, in turn, had a significant negative association with sustained attention performance. Mediation analyses revealed that the relationship between video-gaming and sustained attention was fully mediated by sleep duration. These results indicate that video-gaming affected the ability to sustain attention only in as much as it affected sleep. In order to minimise negative consequences of video-game playing, video-games should be used in moderation, avoiding use close to the sleep period, to obviate detriments to sleep and performance.

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Journal of Attention Disorders. 2014 Aug;18:521-31.

PARENT-OF-ORIGIN EFFECTS IN ADHD: DISTINCT INFLUENCES OF PATERNAL AND MATERNAL ADHD ON NEUROPSYCHOLOGICAL FUNCTIONING IN OFFSPRING.

Thissen AJAM, Rommelse NNJ, Altink ME, et al.

Objective: The authors examined parent-of-origin effects in transmission of ADHD and neuropsychological functioning. Proof of these effects can identify more etiologically homogeneous ADHD subgroups and facilitate genetic studies.

Method: The authors included 238 ADHD and 147 control families. ADHD in children was assessed using parent and teacher ratings, while parents completed self-reports. Children were assessed with neuropsychological paradigms measuring IQ, motor, timing, and executive functions.

Results: Paternal and maternal ADHD were equally positively related to ADHD in offspring. Paternal ADHD was related to poorer time reproduction in offspring and to lower verbal and total IQ in daughters. Maternal ADHD was related to poorer inhibition and motor control in offspring. No mediating effects of neuropsychological functions were found between parent and offspring ADHD symptoms.

Conclusion: Neuropsychological functions may be more sensitive to parent-of-origin effects than ADHD symptoms and possibly useful in detecting the transmission of different gene-brain network pathways depending on parental sex.

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Journal of Attention Disorders. 2014 Aug;18:542-50.

VIDEO GAME PERFORMANCES ARE PRESERVED IN ADHD CHILDREN COMPARED WITH CONTROLS.

Bioulac S, Lallemand S, Fabrigoule C, et al.

Objective: Although ADHD and excessive video game playing have received some attention, few studies have explored the performances of ADHD children when playing video games. The authors hypothesized that performances of ADHD children would be as good as those of control children in motivating video games tasks but not in the Continuous Performance Test II (CPT II).

Method: The sample consisted of 26 ADHD children and 16 control children. Performances of ADHD and control children were compared on three commercially available games, on the repetition of every game, and on the CPT II.

Results: ADHD children had lower performances on the CPT II than did controls, but they exhibited equivalent performances to controls when playing video games at both sessions and on all three games.

Conclusion: When playing video games, ADHD children present no difference in inhibitory performances compared with control children. This demonstrates that cognitive difficulties in ADHD are task dependent.

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Journal of Attention Disorders. 2014 Jul;18:402-11.

THE MULTIDIMENSIONAL ANXIETY SCALE FOR CHILDREN: A FURTHER VALIDATION WITH AUSTRALIAN ADOLESCENTS WITH AND WITHOUT ADHD.

Houghton S, Hunter SC, Trewin T, et al.

Objective: To examine the factor structure of the Multidimensional Anxiety Scale for Children (MASC) with Australian adolescents with and without ADHD.

Method: The MASC was administered to 210 high school–aged adolescents (109 males, 101 females), 115 of whom were clinically diagnosed as ADHD (86 males, 29 females). The remaining 95 were non-ADHD community comparisons.

Results: Analyses supported a three-factor model, with a reduced item pool, which combined the Harm Avoidance and Separation Anxiety scales together. This model was invariant across younger and older participants, and across boys and girls. The model was largely invariant across ADHD and non-ADHD groups. The ADHD group had significantly higher Physical Symptom factor scores than the non-ADHD group.

Conclusion: The MASC is useful for assessing anxiety in adolescents with and without ADHD, but items reflecting the Harm Avoidance and Separation Anxiety scales may need revising.

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Journal of Attention Disorders. 2014 Jul;18:447-55.

ASSOCIATION BETWEEN ADHD SYMPTOMS AND ANXIETY SYMPTOMS IN TAIWANESE ADOLESCENTS.

Liu TL, Yang P, Ko CH, et al.

Objective: The aims of this cross-sectional study were to examine the association between significant ADHD symptoms and the four domains of anxiety symptoms on the Taiwanese version of Multidimensional Anxiety Scale for Children (MASC-T) and to examine the moderating effects of sociodemographic characteristics on this association among Taiwanese adolescents in the community.

Method: A total of 4,716 adolescents in Grades 7 through 12 in southern Taiwan completed the MASC-T, the ADHD Self-Rated Scale, the Mandarin Chinese version of the Center for Epidemiological Studies Depression Scale, the Rosenberg Self-Esteem Scale, and a questionnaire about sociodemographic characteristics. Multiple regression analysis was used to examine both the association of significant ADHD symptoms with four domains of anxiety symptoms on the MASC-T and the moderating effects of sociodemographic characteristics on this association.

Results: The adolescents with significant ADHD symptoms had more severe total anxiety symptoms, physical symptoms, social anxiety symptoms, and separation/panic symptoms for three domains of the

MASC-T but less harm avoidance than did those without significant ADHD symptoms. Age, gender, and low self-esteem had moderating effects on the association between significant ADHD symptoms and anxiety symptoms for some domains of the MASC-T.
Conclusion: The results of this study suggest a significant association between significant ADHD symptoms and the severity of anxiety symptoms in adolescents. Clinicians must evaluate anxiety symptoms among adolescents with ADHD and arrange comprehensive treatment programs.

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Journal of Attention Disorders. 2014 Aug;18:551-59.
AN OPEN TRIAL OF A METACOGNITIVE EXECUTIVE FUNCTION TRAINING FOR YOUNG CHILDREN WITH ADHD.
Tamm L, Nakonezny PA, Hughes CW.
Objective: Executive functioning is impaired in children with ADHD and putatively related to the pathogenesis of ADHD. The authors developed an innovative treatment teaching parents to administer a metacognitive executive function training intervention with children, promoting positive interactions during activities designed to improve attention and self-regulation.
Method: A total of 24 young children with ADHD and their parents participated in an 8-week open trial of the intervention designed to assess feasibility and initial efficacy.
Results: The intervention is feasible and accepted by parents as shown by high attendance/adherence, low attrition, and satisfaction ratings. Improvements in executive functions (visual/auditory attention, working memory, and cognitive flexibility) with corresponding improvements in parent ratings of executive functioning were observed. Reduced inattention symptoms were reported.
Conclusion: Executive functioning training is a promising approach to treating young children with ADHD and holds promise for generalizability because parents are trained to be interventionists and coached to apply the strategies to alternative domains.

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Journal of Attention Disorders. 2014 Jul;18:466-78.
DEVELOPMENTAL DELAYS IN CHILDREN WITH ADHD.
Dyck MJ, Piek JP.
Objective: ADHD is often comorbid with other disorders, but it is often assumed that academic, language, or motor ? skills problems are secondary to ADHD rather than that attention problems are secondary to the other disorder or both disorders have a shared etiology. We assessed for comorbid developmental disorders and which cognitive processes were impaired in children with ADHD.
Method: Measures of intelligence, language, motor skills, social cognition, and executive functions were administered to children with ADHD (n=53) and age/sex-matched typical children.
Results: Clinically significant deficits were 2 to 7 times as common in children with ADHD as in typical children, and the structure of ability differed in the two groups. Abilities were less differentiated in children with ADHD.
Conclusion: The results indicate a need for comprehensive screening for developmental disorders in children with ADHD and imply that research needs to focus on how ADHD and developmental disorders may share an etiology.

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Journal of Attention Disorders. 2014 Jul;18:434-46.
INCREASED RESPONSE-TIME VARIABILITY ACROSS DIFFERENT COGNITIVE TASKS IN CHILDREN WITH ADHD.
Adamo N, Di Martino A, Esu L, et al.
Objective: Increased response-time (RT) fluctuations below 0.2 Hz have been reported as characteristic of ADHD in some but not all studies, possibly due to methodological differences. Accordingly, We contrasted two tasks and two analytical approaches in the same sample of children with ADHD.

Method: Fifty-two children with ADHD and 49 typically developing children completed an Eriksen Flanker Task and a fixed-sequence version of the sustained attention to response task. RT fluctuations with two different frequency analyses were examined.
Results: Robust ADHD-related increases of slow RT fluctuations within all frequencies were found in both tasks. Tasks were significantly correlated in both groups for frequencies above 0.07 Hz. RT fluctuations across all frequencies were greatest in children with ADHD with abnormally elevated omissions.
Conclusion: We observed significantly increased fluctuations of RT in children with ADHD across two different tasks and methods supporting the hypothesis that slow frequency RT fluctuations reflect neurophysiological processes underlying ADHD.

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Journal of Attention Disorders. 2014 Aug;18:511-20.
VOLUMETRIC MRI DIFFERENCES IN TREATMENT NAÏVE AND CHRONICALLY TREATED ADOLESCENTS WITH ADHD-COMBINED TYPE.
Semrud-Clikeman M, Pliszka SR, Bledsoe J, et al.
Objective: The purpose of this study was to determine whether there are differences in the volume of specific brain regions using magnetic resonance imaging (MRI) between children and adolescents with ADHD and controls and whether such differences are related to the participants' history of stimulant treatment.
Method: A total of 16 healthy controls, 16 children, and adolescents with ADHD-combined (ADHD-C) type with a history of stimulant treatment, and 13 children and adolescents with ADHD-C type treatment naïve participated.
Results: Total frontal, prefrontal, and caudate volumes were larger for children and adolescents with ADHD compared with controls with no differences based on medication history with larger right gray and white matter prefrontal volumes in the ADHD groups. A medication difference was found with the right anterior cingulate cortex smaller in children and adolescents without a treatment history.
Conclusion: These findings suggest that aberrant prefrontal and caudate volumes in ADHD-C may compromise functioning of the frontostriatal circuitry.

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Journal of Attention Disorders. 2014 Aug;18:483-95.
COGNITIVE BEHAVIORAL TREATMENT OUTCOMES IN ADOLESCENT ADHD.
Antshel KM, Faraone SV, Gordon M.
Objective: To assess the efficacy of cognitive behavioral therapy (CBT) for managing adolescent ADHD.
Method: A total of 68 adolescents with ADHD and associated psychiatric comorbidities completed a manualized CBT treatment protocol. The intervention used in the study was a downward extension of the Safren et al. program for adults with ADHD who have symptoms unresolved by medication. Outcome variables consisted of narrow band (ADHD) and broadband (e.g., mood, anxiety, conduct) symptom measures (Behavior Assessment System for Children–2nd edition and ADHD–Rating Scales) as well as functioning measures (parent/teacher ratings and several ecologically real-world measures).
Results: Treatment effects emerged on the medication dosage, parent rating of pharmacotherapy adherence, adolescent self-report of personal adjustment (e.g., self-esteem), parent and teacher ratings of inattentive symptoms, school attendance, school tardiness, parent report of peer, family and academic functioning and teacher report of adolescent relationship with teacher, academic progress, and adolescent self-esteem. Adolescents with ADHD with oppositional defiant disorder were rated by parents and teachers as benefiting less from the CBT intervention. Adolescents with ADHD and comorbid anxiety/depression were rated by parents and teachers as benefiting more from the CBT intervention.
Conclusion: A downward extension of an empirically validated adult ADHD CBT protocol can benefit some adolescents with ADHD.

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Journal of Attention Disorders. 2014 Aug;18:496-503.

SYMPTOM DIMENSIONS OF DISRUPTIVE BEHAVIOR DISORDERS IN ADOLESCENT DRIVERS.

Garner AA, Gentry A, Welburn SC, et al .

Objective: Adolescents with disruptive behavior disorder, including ADHD, are more likely to engage in risky driving practices and, consequently, are more likely to be involved in a motor vehicle crash (MVC) than their non-ADHD peers. It is unclear whether symptoms of inattention, hyperactivity/impulsivity, or oppositional defiant disorder (ODD) increase risk of poor driving outcomes.

Method: A total of 41 participants (16-19 years old) reported their ADHD and ODD symptoms and risky driving practices (errors and violations). History of citations and MVCs were acquired from state records. Relative predictive utility of symptom dimensions was assessed using multiple regressions.

Results: Inattention solely predicted driving variables of interest: Greater levels of inattention were predictive of more citations, MVCs, and self-reported errors and violations.

Conclusion: Findings suggest that symptoms of inattention play a primary role in driving-related problems among adolescents. Implications for future research and practice are discussed.

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Journal of Attention Disorders. 2014 Aug;18:504-10.

HANDWRITING IN CHILDREN WITH ADHD.

Langmaid RA, Papadopoulos N, Johnson BP, et al.

Objective: Children with ADHD–combined type (ADHD-CT) display fine and gross motor problems, often expressed as handwriting difficulties. This study aimed to kinematically characterize the handwriting of children with ADHD using a cursive letter l's task.

Method: In all, 28 boys (7-12 years), 14 ADHD-CT and 14 typically developing (TD), without developmental coordination disorder (DCD) or comorbid autism, wrote a series of four cursive letter l's using a graphics tablet and stylus.

Results: Children with ADHD-CT had more inconsistent writing size than did TD controls. In addition, ADHD-CT symptom severity, specifically inattention, predicted poorer handwriting outcomes.

Conclusion: In a sample of children with ADHD-CT who do not have DCD or autism, subtle handwriting differences were evident. It was concluded that handwriting might be impaired in children with ADHD in a manner dependent on symptom severity. This may reflect reports of underlying motor impairment in ADHD.

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Journal of Attention Disorders. 2014 Jul;18:456-65.

THE INFLUENCE OF PARENT BEHAVIORS ON POSITIVE ILLUSORY BIAS IN CHILDREN WITH ADHD.

Emeh CC, Mikami AY.

Objective: To explore the relationship between parental feedback and the accuracy of children's self-perceptions. Children with ADHD have been demonstrated to overestimate their own competence, a phenomenon known as positive illusory bias (PIB).

Method: Participants were families of 56 children (41 male) ages 7 to 10, half of whom had clinical diagnoses of ADHD. PIB was assessed by comparing children's self-ratings of their competence relative to teachers' ratings. Laboratory interactions were observed where parental feedback to children was coded.

Results: Parental warmth was associated with lower PIB about social competence in children with ADHD, but greater PIB in comparison children. Parent criticism was positively correlated with greater PIB about social competence in children with ADHD, but the relationship was nonsignificant for comparison children. Parent praise was associated with lower PIB about behavioral conduct in comparison children.

Conclusion: Results support the self-protective hypothesis of PIB, and implications for interventions are discussed.

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Journal of Child Psychology and Psychiatry. 2014 Aug;55:905-13.
RACIAL/ETHNIC DISPARITIES IN ADHD DIAGNOSIS BY KINDERGARTEN ENTRY.
Morgan PL, Hillemeier MM, Farkas G, et al.
Background: Whether and to what extent racial/ethnic disparities in attention-deficit/hyperactivity disorder (ADHD) diagnosis occur by kindergarten entry is currently unknown. We investigated risk factors associated with an ADHD diagnosis by kindergarten entry generally, and specifically whether racial/ethnic disparities in ADHD diagnosis occur by this very early time period.
Methods: Secondary analysis of data from children enrolled in the Early Childhood Longitudinal Study-Birth Cohort (ECLS-B), a large, nationally representative cohort of US children born in 2001. Data include information from birth certificates, parent and teacher questionnaires, and in-person developmental assessments conducted with children at intervals from 9 months through kindergarten entry. The analytic sample included children enrolled in the ECLS-B at the 60-month assessment (N=6,550).
Results: Black children in the United States were 70% (1 – OR of .30) less likely to receive an ADHD diagnosis than otherwise similar White children. Hispanic children initially appeared to be underdiagnosed for ADHD. However, their disparity with Whites became statistically nonsignificant after controlling for whether a language other than English was primarily spoken in the home. Analyses of kindergarten teacher-reported classroom behavior indicated that neither Black nor Hispanic children displayed less frequent ADHD-related behaviors than Whites.
Conclusions: Although they are not less likely to display ADHD-related behaviors, children who are Black or being raised in households where non-English is primarily spoken are less likely than otherwise similar White children to be diagnosed with ADHD in the US.

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Journal of Child Psychology and Psychiatry. 2014 Aug;55:878-85.
STIMULANT ADHD MEDICATION AND RISK FOR SUBSTANCE ABUSE.
Chang Z, Lichtenstein P, Halldner L, et al.
Background: There are persistent concerns of long-term effects of stimulant ADHD medication on the development of substance abuse.
Methods: Using Swedish national registers, we studied all individuals born between 1960 and 1998 and diagnosed with ADHD (26,249 men and 12,504 women). We investigated the association between stimulant ADHD medication in 2006 and substance abuse during 2009. Substance abuse was indexed by substance-related death, crime, or hospital visits.
Results: ADHD medication was not associated with increased rate of substance abuse. Actually, the rate during 2009 was 31% lower among those prescribed ADHD medication in 2006, even after controlling for medication in 2009 and other covariates (hazard ratio: 0.69; 95% confidence interval: 0.57–0.84). Also, the longer the duration of medication, the lower the rate of substance abuse. Similar risk reductions were suggested among children and when investigating the association between stimulant ADHD medication and concomitant short-term abuse.
Conclusions: We found no indication of increased risks of substance abuse among individuals prescribed stimulant ADHD medication; if anything, the data suggested a long-term protective effect on substance abuse. Although stimulant ADHD medication does not seem to increase the risk for substance abuse, clinicians should remain alert to the potential problem of stimulant misuse and diversion in ADHD patients.

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Journal of Child Psychology and Psychiatry. 2014 Aug;55:897-904.
RELATIVE IMMATURITY AND ADHD: FINDINGS FROM NATIONWIDE REGISTERS, PARENT- AND SELF-REPORTS.
Halldner L, Tillander A, Lundholm C, et al.
Background: We addressed if immaturity relative to peers reflected in birth month increases the likelihood of ADHD diagnosis and treatment.
Methods: We linked nationwide Patient and Prescribed Drug Registers and used prospective cohort and nested case–control designs to study 6–69 year-old individuals in Sweden from July 2005 to December

2009 (Cohort 1). Cohort 1 included 56,263 individuals diagnosed with ADHD or ever used prescribed ADHD-specific medication. Complementary population-representative cohorts provided DSM-IV ADHD symptom ratings; parent-reported for 10,760 9-year-old twins born 1995–2000 from the CATSS study (Cohort 2) and self-reported for 6,970 adult twins age 20–47 years born 1959–1970 from the STAGE study (Cohort 3). We calculated odds ratios (OR:s) for ADHD across age for individuals born in November/December compared to January/February (Cohort 1). ADHD symptoms in Cohorts 2 and 3 were studied as a function of calendar birth month.
Results: ADHD diagnoses and medication treatment were both significantly more common in individuals born in November/December versus January/February; peaking at ages 6 (OR: 1.8; 95% CI: 1.5–2.2) and 7 years (OR: 1.6; 95% CI: 1.3–1.8) in the Patient and Prescribed Drug Registers, respectively. We found no corresponding differences in parent- or self-reported ADHD symptoms by calendar birth month.
Conclusion: Relative immaturity compared to class mates might contribute to ADHD diagnosis and pharmacotherapy despite absence of parallel findings in reported ADHD symptom loads by relative immaturity. Increased clinical awareness of this phenomenon may be warranted to decrease risk for imprecise diagnostics and treatment. We speculate that flexibility regarding age at school start according to individual maturity could reduce developmentally inappropriate demands on children and improve the precision of ADHD diagnostic practice and pharmacological treatment.

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Journal of Child Psychology and Psychiatry. 2014 Aug;55:914-23.

GENETICS OF PREPARATION AND RESPONSE CONTROL IN ADHD: THE ROLE OF DRD4 AND DAT1.

Albrecht B, Brandeis D, von Sandersleben HU, et al.

Background: Difficulties with performance and brain activity related to attentional orienting (Cue-P3), cognitive or response preparation (Cue-CNV) and inhibitory response control (Nogo-P3) during tasks tapping executive functions are familial in ADHD and may represent endophenotypes. The aim of this study was to clarify the impact of dopamine receptor D4 (DRD4) and dopamine transporter (DAT1) gene polymorphisms on these processes in ADHD and control children.
Methods: Behavioural and electrophysiological parameters from cued continuous performance tests with low and high attentional load were assessed in boys with ADHD combined type (N = 94) and controls without family history of ADHD (N = 31). Both groups were split for the presence of at least one DRD4 7-repeat allele and the DAT1 10-6 haplotype.
Results: Children with ADHD showed diminished performance and lower Cue-P3, CNV and Nogo-P3 amplitudes. Children with DRD4 7R showed similar performance problems and lower Cue-P3 and CNV, but Nogo-P3 was not reduced. Children with the DAT1 10-6 haplotype had no difficulties with performance or Cue-P3 and CNV, but contrary to expectations increased Nogo-P3. There were no Genotype by ADHD interactions.
Conclusions: This study detected specific effects of DRD4 7R on performance and brain activity related to attentional orienting and response preparation, while DAT1 10-6 was associated with elevated brain activity related to inhibitory response control, which potentially compensates increased impulsivity. As these genotype effects were additive to the impact of ADHD, the current results indicate that DRD4 and DAT1 polymorphisms are functionally relevant risk factors for ADHD and presumably other disorders sharing these endophenotypes.

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Journal of Inherited Metabolic Disease. 2012;35:S167.

RELATIONSHIPS BETWEEN SYMTOMS OF ATTENTION DEFICIT AND HYPERACTIVITY DISORDER AND BLOOD LEVELS OF LEAD AND PHENYLALANINE IN SCHOOL CHILDREN.

Kirli, Bulbul, Kurt.

Background: Attention Deficit and Hyperactivity Disorder (ADHD) can occur by the interactions of genetic factors, diet and social/physical environment where lead plays an important role among all. This study was

planned to determine association between ADHD symptoms and blood lead level and to examine whether serum phenylalanine level effects this assosication.
Methods: The study group was consisted of 1413 primary school children. 55 students with mean age of 8.86(plus or minus)1.60 years were selected by using the DSM-IV Based child and adolescent behavior rating scale. 55 matched controls for age, gender and socioeconomic strata were enrolled.
Results: Serum lead, phenylalanine, tyrosine levels, and phenylalanine/ tyrosine ratio (Phe/tyr) were measured. Mean blood lead level (4.00(plus or minus) 1.93 (mu)g/dL) and Phe/tyr (0.91(plus or minus)0.37) of the case group were significantly higher than the control group [blood lead level (3.11(plus or minus)1.99 (mu)g/dL) and Phe/ tyr 0.75(plus or minus)0.32)], (p=0.019 and p=0.018, respectively). There were weak positive correlations between both blood lead level and Phe/tyr with the scores of attention deficit subscales(r=0.431 and r=0.384 respectively, p<0.001)and hyperactivity/impulsivity subscale (r=0.267, p=0.005).
Conclusion: Because symptoms of ADHD is associated with phenylalanine/ tyrosine ratio which is used for follow-up of individuals diagnosed with hyperphenylalaninemia, it is suggested that phenylalanine metabolism may have a role in relationship between lead exposure and ADHD.

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Journal of Inherited Metabolic Disease. 2012;35:S130.

(ALPHA)-METHYL-COA RACEMASE DEFICIENCY: REPORT OF A NEW MUTATION AND RESPONSE TO TREATMENT IN A PATIENT WITH NEONATAL CHOLESTATIC LIVER DISEASE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Ersoy M, Cakir N, Balci MC, et al.

Background: (alpha)-Methyl-acyl-CoA-racemase (AMACR) deficiency (OMIM 604489), a rare peroxisomal disorder, may present with cholestatic liver disease in the first months of life and with neuropsychiatric disorders such as development delay, encephalopathy, demyelinating polyneuropathy, schizophrenia from childhood to late adult life.
Objectives: AMACR could be in the aetiology of attention deficit hyperactivity disorder (ADHD) and can benefit from diet therapy.
Case report: 10-month-old girl presented with bleeding tendency with elevated prothrombin time (PT), international normalized ratio (INR) and 5-fold raised transaminases. Liver biopsy showed mild hepatocellular degeneration. Vitamin-K treatment normalised PT, INR, transaminases within 6 months. Elevation of C27-bile acids and pristanic acid raised the suspect of peroxisomal dysfunction. The absence of the S-isomers and accumulation of the R-isomers of bile acid intermediates led to the diagnosis of AMACR deficiency. Sequence analysis of the AMACR gene showed a new homozygous mutation, c.59 G>A. On follow up although neurocognitive development was normal ADHD was diagnosed at the age of three years. After phytanic acid restricted diet pristanic acid levels decreased half-fold and patient showed improvement on ADHD symptoms.
Conclusion: AMACR is a rare disorder that should be considered in the differential diagnosis of ADHD and implementation of dietary treatment should be evaluated.

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Journal of Inherited Metabolic Disease. 2014;37:S64.

A BOY WITH DYSLEXIA AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Sivri HS, Yildiz Y, Tokatli A, et al.

Case report: A thirteen-day-old boy was referred to our clinic upon detection of positive screening test for phenylketonuria (PKU) through nationwide screening programme. He was found to have a blood phenylalanine level of 669 (mu)mol/l, diagnosed with mild phenylketonuria and started on a phenylalanine-restricted diet. Family history revealed an eight-year-old brother with dyslexia and attention-deficit hyperactivity disorder currently on methylphenidate and a distant relative with classical phenylketonuria. The elder brother was summoned to our clinic and was discovered to have mild phenylketonuria with a blood phenylalanine level of 860 (mu)mol/l. He was found to be tetrahydrobiopterin (BH4)-responsive based on BH4 loading test and started on sapropterin. Their genetic analyses revealed compound

heterozygous mutations on the PAH gene, one of which was known to be responsive to BH4. As of now, both brothers have good metabolic control with sapropterin alone on an unrestricted diet.
Conclusions: This case underlines the importance of investigating phenylketonuria in patients with mild cognitive and behavioural problems, especially in countries where nationwide neonatal screening was started realtively late or has poor coverage rate.

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J Neurosci Methods. 2014;235:181-88.

DYSFUNCTIONAL CORTICAL INHIBITION IN ADULT ADHD: NEURAL CORRELATES IN AUDITORY EVENT-RELATED POTENTIALS.

Schubert JK, Gonzalez-Trejo E, Retz W, et al.

In recent times, the relevance of an accurate diagnosis of attention-deficit/hyperactivity disorder (ADHD) in adults has been the focus of several studies. No longer considered a pathology exclusive to children and adolescents, and taking into account its social implications, developing enhanced support tools for the current diagnostic procedure becomes a priority. Here we present a method for the objective assessment of ADHD in adults using chirp-evoked, paired auditory late responses (ALRs) combined with a two-dimensional ALR denoising scheme to extract correlates of intracortical inhibition. Our method allows for an effective single-sweep denoising, thus requiring less trials to obtain recognizable physiological features, useful as pointers of cortical impairment. Results allow an optimized diagnosis, reduction of data loss and acquisition time; moreover, they do not account exclusively for critical elements within clinical evaluations, but also allow studying the pathophysiology of the condition by providing objective information regarding impaired cortical functions.

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J Popul ther Clin Pharmacol. 2014;21:e303.

LARGE EARS DISTINGUISH ADHD CHILDREN FROM NON-FAS, FASD CHILDREN.

Kapalanga J, Laufer B, Nwebube N, et al.

Background/Objectives: Individuals diagnosed with FASD or ADHD share a certain behavioral phenotype characterized by executive function difficulties and often varying degrees of cognitive and other developmental deficits. Children with severe FASD (or FAS) have distinctive craniofacial features. However children with ADHD and many with less severe FASD putatively do not have distinctive physical features. The objectives of this study are to determine whether or not certain craniofacial features could distinguish FASD from ADHD children. We report that large ear size can distinguish children with ADHD from children with non-FAS, FASD.
Methods: Ear length and ear width were measured during clinical assessment of 59 children with non-FAS, FASD, 67 ADHD and 61 control age and sex null matched children aged 3 to 17 years. Study participants were categorized into four age groups, viz; 3-6, 7-10, 11-14 and 15-17 years. Ear length and width were measured along the greatest vertical and horizontal axes, respectively, by a self-retracting plastic tape measure marked on one side in imperial units with the inch markings in sixteenths and on the other side in metric units with the centimeter markings in elevenths. Both right and left ears were measured and the mean measurements were calculated, respectively. Ear size was estimated as a product of ear length and ear width.
Results: The product of the mean ear length and ear width was 22.9 in ADHD children, 17.9 in controls and 16.1 in FASD children. The differences were significant ($p<0.05$) across age groups even when adjusted for head size.
Conclusions/Discussion: These results demonstrate that ear size is significantly larger in children with ADHD compared to controls and to children with FASD. Large ear size is a common clinical feature in certain neurobehavioral and neurodevelopmental syndromes (example Fragile X syndrome) that share the behavioural phenotype observed in ADHD and FASD. As alcohol is a teratogen, smaller ear size in children with FASD could be attributed to the teratogenic effect of alcohol. Further, these observations also suggest

that ear morphogenesis is related to neurobehavioural and cognitive development. In conclusion ear size can be used as a clinical feature for distinguishing ADHD from FASD patients.

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J Psychopathol Behav Assess. 2014.

SUICIDE IDEATION AND ATTEMPTS ARE ASSOCIATED WITH CO-OCCURRING OPPOSITIONAL DEFIANT DISORDER AND SADNESS IN CHILDREN AND ADOLESCENTS WITH ADHD.

Mayes SD, Calhoun SL, Baweja R, et al.

Mothers rated the frequency of suicide ideation and attempts in 925 children and adolescents with ADHD (3-16 years). Ideation and attempts were more than twice as common in ADHD-Combined type than in ADHD-Inattentive type. Ideation occurred in 19 % with ADHD-C and in 7 % with ADHD-I. Percentages for attempts were 7 % and 3 %. For children and adolescents with co-occurring sadness and oppositional defiant disorder (ODD), 46 % had ideation and 21 % had attempts (vs. 6 and 2 % for ADHD alone). For those with ideation, 78 % had ODD or sadness. For those with attempts, 84 % had ODD or sadness. Maternal ratings of aggressive, explosive, sad, and moody were significant independent predictors of suicide behavior for ADHD-C, and sad and moody were predictors for ADHD-I. All children and adolescents with ADHD should be screened for suicide ideation and attempts, and co-occurring ODD and sadness should be treated to prevent suicide behavior.

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J Am Acad Child Adolesc Psychiatry. 2014.

RISPERIDONE ADDED TO PARENT TRAINING AND STIMULANT MEDICATION: EFFECTS ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, OPPOSITIONAL DEFIANT DISORDER, CONDUCT DISORDER, AND PEER AGGRESSION.

Gadow KD, Arnold LE, Molina BSG, et al.

Objective: In this study, we aimed to expand on our prior research into the relative efficacy of combining parent training, stimulant medication, and placebo (Basic therapy) versus parent training, stimulant, and risperidone (Augmented therapy) by examining treatment effects for attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) symptoms and peer aggression, symptom-induced impairment, and informant discrepancy.

Method: Children (6-12 years of age; N=168) with severe physical aggression, ADHD, and co-occurring ODD/CD received an open trial of parent training and stimulant medication for 3 weeks. Participants failing to show optimal clinical response were randomly assigned to Basic or Augmented therapy for an additional 6 weeks.

Results: Compared with Basic therapy, children receiving Augmented therapy experienced greater reduction in parent-rated ODD severity (p=.002, Cohen's d=0.27) and peer aggression (p=.02, Cohen's d=0.32) but not ADHD or CD symptoms. Fewer children receiving Augmented (16%) than Basic (40%) therapy were rated by their parents as impaired by ODD symptoms at week 9/endpoint (p=.008). Teacher ratings indicated greater reduction in ADHD severity (p=.02, Cohen's d=0.61) with Augmented therapy, but not for ODD or CD symptoms or peer aggression. Although both interventions were associated with marked symptom reduction, a relatively large percentage of children were rated as impaired for at least 1 targeted disorder at week 9/endpoint by parents (Basic 47%; Augmented 27%) and teachers (Basic 48%; Augmented 38%).

Conclusion: Augmented therapy was superior to Basic therapy in reducing severity of ADHD and ODD symptoms, peer aggression, and symptom-induced impairment, but clinical improvement was generally context specific, and effect sizes ranged from small to moderate.

Clinical trial registration information-Treatment of Severe Childhood Aggression (The TOSCA Study); http://clinicaltrails.gov/; NCT00796302.

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J Am Acad Child Adolesc Psychiatry. 2014.

REDUCED PREFRONTAL EFFICIENCY FOR VISUOSPATIAL WORKING MEMORY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Bedard A-C, Newcorn JH, Clerkin SM, et al.

Objective: Visuospatial working memory impairments have been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). However, most ADHD research has focused on the neural correlates of nonspatial mnemonic processes. This study examined brain activation and functional connectivity for visuospatial working memory in youth with and without ADHD.

Method: Twenty-four youth with ADHD and 21 age- and sex-matched healthy controls were scanned with functional magnetic resonance imaging while performing an N-back test of working memory for spatial position. Block-design analyses contrasted activation and functional connectivity separately for high (2-back) and low (1-back) working memory load conditions versus the control condition (0-back). The effect of working memory load was modeled with linear contrasts.

Results: The 2 groups performed comparably on the task and demonstrated similar patterns of frontoparietal activation, with no differences in linear gains in activation as working memory load increased. However, youth with ADHD showed greater activation in the left dorsolateral prefrontal cortex (DLPFC) and left posterior cingulate cortex (PCC), greater functional connectivity between the left DLPFC and left intraparietal sulcus, and reduced left DLPFC connectivity with left midcingulate cortex and PCC for the high load contrast compared to controls ($p < .01$; $k > 100$ voxels). Reanalysis using a more conservative statistical approach ($p < .001$; $k > 100$ voxels) yielded group differences in PCC activation and DLPFC-midcingulate connectivity.

Conclusion: Youth with ADHD show decreased efficiency of DLPFC for high-load visuospatial working memory and greater reliance on posterior spatial attention circuits to store and update spatial position than healthy control youth. Findings should be replicated in larger samples.

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Klin Psikofarmakol Bul. 2014;24:139-45.

SERUM COPPER AND CERULOPLASMIN LEVELS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kul M, Kara M, Unal F, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder seen in childhood. It is characterized by inattention, hyperactivity, and impulsivity that is inappropriate for the age and developmental level of the child. Although the number of studies investigating the neurobiological basis of ADHD is increasing, there is still no clear understanding of the mechanisms of the disorder. Serum copper and ceruloplasmin levels may play a role in the neurobiology of ADHD due to their effects on oxidative mechanisms and the dopaminergic-catecholaminergic system. However, the results of studies investigating the serum levels of copper in patients with ADHD are contradictory. Moreover, serum ceruloplasmin levels have not yet been studied. The aim of the current study was to compare the serum copper and ceruloplasmin levels in children and adolescents with ADHD to the levels found in healthy controls.

Method: This study included 43 children and adolescents (32 males, 11 females) with ADHD, who did not have any neurological, systemic, or comorbid psychiatric disorders, except for oppositional defiant disorder (ODD), and 32 gender and age-matched healthy controls (23 males, 9 females). Levels of serum copper and ceruloplasmin were compared between the two groups. Approximately 47% of the children with ADHD had comorbid ODD. The level of serum copper was measured using atomic absorption spectrophotometry, and serum ceruloplasmin was measured using nephelometry.

Results: The mean level of serum copper was 17.3(plus or minus)3.2 (mu)g/ dL in the ADHD group, and 16.9(plus or minus)2.6 in the control group. This difference was not significant (p=0.538). The mean serum ceruloplasmin level was 37.6 (plus or minus) 6.9 (mu)g/dL in the group with ADHD, and 36.9(plus or minus)6.4 (mu)g/dL in the control group; this difference between groups was not significant (p=0.685). Moreover, no significant difference was observed between the groups with ADHD with or without ODD comorbidities and the control group for either levels of serum copper (p=0.845), or ceruloplasmin (p=0.878).

Conclusion: This study showed that serum copper and ceruloplasmin levels do not differ between children and adolescents with ADHD compared with controls. Although our results suggest that serum ceruloplasmin and copper do not have a direct role in the neurobiology of ADHD, there is a need for future studies with larger patient groups.

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Klin Psikofarmakol Bul. 2014;24:168-71.

CHIN TREMBLING INDUCED BY COMBINED USE OF OROS METHYLPHENIDATE AND PROCATEROL HYDROCHLORIDE IN A BOY WITH ADHD.

Yang R, Feng J, Zhang S, et al.

Recently, asthma has been reported to be a potential comorbidity of attention deficit hyperactivity disorder (ADHD). It is, therefore, possible to have combined use of medications for both ADHD and asthma although, potential adverse reactions are unknown. The case presented here is that of a 61/2-year-old boy diagnosed as having both ADHD and asthma. He presented with chin trembling after the first administration of OROS methylphenidate and procaterol hydrochloride. This is the first report of an adverse event in patients using a combination of these two types of drugs. It raises an awareness of chin trembling as an adverse effect in patients using a combination of methylphenidate and procaterol hydrochloride, especially among those who are younger and underweight.

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Klin Psikofarmakol Bul. 2014;24:146-57.

EFFECTS OF LONG ACTING METHYLPHENIDATE ON GHRELIN LEVELS IN MALE CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: AN OPEN LABEL TRIAL.

Yalcin O, Iseri E, Bukan N, et al.

Objective: The most commonly reported side effects of methylphenidate, which is generally used for attention deficit hyperactivity disorder, are loss of appetite, decrease of body weight and initial growth retardation. Ghrelin, which is dominantly released by the stomach, promotes feeding, decreases energy expenditure and locomotor activity, enhances weight gain and fat mass deposition and also effects gastrointestinal motility. Ghrelin may be related to the metabolic and anorexigenic effects of methylphenidate in children. The aim of this study was to investigate methylphenidate's effect on fasting serum active Ghrelin levels in prepubertal children with attention deficit hyperactivity disorder. We expected to find a difference between pre- and post-treatment ghrelin levels with 18 mg/day methylphenidate administered via an osmotic-controlled release oral delivery system in prepubertal boys.
Methods: Thirty-three boys with attention deficit hyperactivity disorder between the ages of 6-12 were recruited for this investigation. In addition to Ghrelin levels, other laboratory findings, body mass index, body mass index percentiles, body weight-height measures and attention deficit-hyperactivity disorder symptom severity findings were analyzed before and after the 60 days of methylphenidate treatment.
Results: We could not find a significant alteration in serum active Ghrelin levels with methylphenidate. Methylphenidate improved core inattention, hyperactivity and impulsivity symptoms of attention deficit hyperactivity disorder with no significant alteration in height, body weight and body mass index, without serious side effects.
Conclusion: This is the first study which directly aims to determine methylphenidate's effect on serum active Ghrelin levels. Further research with higher methylphenidate doses and/or other stimulants such as atomoxetine and amphetamine should be done as Ghrelin is also associated with obesity, alcohol and drug addiction and reward system pathologies, which are also closely related to attention deficit hyperactivity disorder.

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Mol Psychiatry. 2014.

PRENATAL ANTIDEPRESSANT EXPOSURE IS ASSOCIATED WITH RISK FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER BUT NOT AUTISM SPECTRUM DISORDER IN A LARGE HEALTH SYSTEM.

Clements CC, Castro VM, Blumenthal SR, et al.

Previous studies suggested that risk for Autism Spectrum Disorder (ASD) may be increased in children exposed to antidepressants during the prenatal period. The disease specificity of this risk has not been addressed and the possibility of confounding has not been excluded. Children with ASD or attention-deficit hyperactivity disorder (ADHD) delivered in a large New England health-care system were identified from electronic health records (EHR), and each diagnostic group was matched 1:3 with children without ASD or ADHD. All children were linked with maternal health data using birth certificates and EHRs to determine prenatal medication exposures. Multiple logistic regression was used to examine association between prenatal antidepressant exposures and ASD or ADHD risk. A total of 1377 children diagnosed with ASD and 2243 with ADHD were matched with healthy controls. In models adjusted for sociodemographic features, antidepressant exposure prior to and during pregnancy was associated with ASD risk, but risk associated with exposure during pregnancy was no longer significant after controlling for maternal major depression (odds ratio (OR) 1.10 (0.70-1.70)). Conversely, antidepressant exposure during but not prior to pregnancy was associated with ADHD risk, even after adjustment for maternal depression (OR 1.81 (1.22-2.70)). These results suggest that the risk of autism observed with prenatal antidepressant exposure is likely confounded by severity of maternal illness, but further indicate that such exposure may still be associated with ADHD risk. This risk, modest in absolute terms, may still be a result of residual confounding and must be balanced against the substantial consequences of untreated maternal depression.

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Neurochem Res. 2014.

A PILOT STUDY ON THE CONTRIBUTION OF FOLATE GENE VARIANTS IN THE COGNITIVE FUNCTION OF ADHD PROBANDS.

Saha T, Dutta S, Rajamma U, et al.

Genetic abnormalities in components important for the folate cycle confer risk for various disorders since adequate folate turnover is necessary for normal methylation, gene expression and chromosome structure. However, the system has rarely been studied in children diagnosed with attention deficit hyperactivity disorder (ADHD). We hypothesized that ADHD related cognitive deficit could be attributed to abnormalities in the folate cycle and explored functional single nucleotide polymorphisms in methylenetetrahydrofolate dehydrogenase (rs2236225), reduced folate carrier (rs1051266), and methylenetetrahydrofolate reductase (rs1801131 and rs1801133) in families with ADHD probands (N = 185) and ethnically matched controls (N = 216) recruited following the DSM-IV. After obtaining informed written consent for participation, peripheral blood was collected for genomic DNA isolation and PCR-based analysis of target sites. Data obtained was analyzed by UNPHASED. Interaction between sites was analyzed by the multi dimensionality reduction (MDR) program. Genotypic frequencies of the Indian population were strikingly different from other ethnic groups. rs1801133 "T" allele showed biased transmission in female probands ($p < 0.05$). Significant difference in genotypic frequencies for female probands was also noticed. rs1801131 and rs1801133 showed an association with low intelligence quotient (IQ). MDR analysis exhibited independent effects and contribution of these sites to IQ, thus indicating a role of these genes in ADHD related cognitive deficit.

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Neurol Sci. 2014;35:1189-96.

GENOME-WIDE PATHWAY ANALYSIS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lee YH, Song GG.

This study aimed to (1) to identify candidate single-nucleotide polymorphisms (SNPs) and mechanisms of attention-deficit/hyperactivity disorder (ADHD) and (2) to generate SNP-to-gene-to-pathway hypotheses. An ADHD genome-wide association study (GWAS) dataset that included 428,074 SNPs in 924 trios (2,758

individuals) of European descent was used in this study. The Identify candidate Causal SNPs and Pathways (ICSNPathway) analysis was applied to the GWAS dataset. ICSNPathway analysis identified 11 candidate SNPs, 6 genes, and 6 pathways, which provided 6 hypothetical biological mechanisms. The strongest hypothetical biological mechanism was that rs2532502 alters the role of CD27 in the context of the pathways of positive regulation of nucleocytoplasmic transport [nominal p < 0.001; false discovery rate (FDR) = 0.028]. The second strongest mechanism was the rs1820204, rs1052571, rs1052576 -> CASP9 -> mitochondrial pathway (nominal p < 0.001; FDR = 0.032). The third mechanism was the rs1801516 -> ATM -> CD25 pathway (nominal p < 0.001; FDR = 0.034). By applying the ICSNPathway analysis to the ADHD GWAS data, 11 candidate SNPs, 6 genes that included CD27, CASP9, ATM, CD12orf65, OXER1, and ACRY, and 6 pathways were identified that may contribute to ADHD susceptibility.

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Neuropsychiatr Dis Treat. 2014;10:1439-49.

A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS OF BUPROPION VERSUS METHYLPHENIDATE IN THE TREATMENT OF ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER.

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

Background: Some trials have suggested that bupropion, as well as methylphenidate, is beneficial in the treatment of attention-deficit/hyperactivity disorder (ADHD).

Objectives: The purpose of this systematic review was to summarize the efficacy, acceptability, and tolerability of bupropion in comparison with methylphenidate for ADHD treatment. Included studies were randomized controlled trials (RCTs) that compared bupropion and methylphenidate. Clinical studies conducted between January 1991 and January 2014 were reviewed.

Data sources: MEDLINE(registered trademark), EMBASE(trademark), CINAHL, PsycINFO(registered trademark), and the Cochrane Controlled Trials Register were searched in January 2014. Additionally, clinical trials were identified from the databases of ClinicalTrials.gov and the EU Clinical Trials Register.

Study eligible criteria, participants, and interventions: All RCTs of bupropion and methylphenidate reporting final outcomes relevant to 1) ADHD severity, 2) response or remission rates, 3) overall discontinuation rate, or 4) discontinuation rate due to adverse events. Language restriction was not applied.

Study appraisal and synthesis methods: The relevant clinical trials were examined and the data of interest were extracted. Additionally, the risks of bias were also inspected. The efficacy outcomes were the mean changed scores of ADHD rating scales, the overall response rate, and the overall remission rates. The overall discontinuation rate and the discontinuation rate due to adverse events were determined. Relative risks and weighted mean differences or standardized mean differences with 95% confidence intervals were estimated using a random effect model.

Results: A total of 146 subjects in four RCTs comparing bupropion with methylphenidate in the treatment of ADHD were included. The pooled mean changed scores of the Iowa-Conner's Abbreviated Parent and Teacher Questionnaires and the ADHD Rating Scale-IV for parents and teachers of children and adolescents with ADHD in the bupropion and methylphenidatetreated groups were not significantly different. Additionally, the pooled mean changed score in adult ADHD between the two groups, measured by the ADHD Rating Scale-IV and the Adult ADHD Rating Scale, was also not significantly different. The pooled rates of response, overall discontinuation, and discontinuation due to adverse events between the two groups were not significantly different.

Conclusion: Based on limited data from this systematic review, bupropion was as effective as methylphenidate for ADHD patients. Additionally, tolerability and acceptability were also comparable. However, these findings should be considered as very preliminary results. To confirm this evidence, further studies in this area should be conducted.

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Pediatr Blood Cancer. 2014;61:S29.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH SICKLE CELL DISEASE.

Acquazzino M, Myrvik M, Scott J.

Background: Neurocognitive deficits, including difficulties with attention and executive function, as well as poor school performance, are well described in children and adolescents with sickle cell disease (SCD). Given such deficits, individuals with SCD appear at particular risk for attention deficit/hyperactivity disorder (ADHD), a neurobiological disorder characterized by persistent, pervasive, impairing and developmentally excessive levels of hyperactivity, impulsivity and inattention. Currently, there is a paucity of data examining ADHD within SCD beyond the known neurocognitive deficits. As such, additional research is needed to learn more about ADHD in children and adolescents with SCD.

Objectives: To determine the prevalence and characterize the type of ADHD and corresponding treatment in a cohort of children and adolescents with SCD referred for neuropsychological testing.

Design/Method: A retrospective chart review was conducted of children with SCD ages 4-18 years who were referred for complete neuropsychological evaluation due to academic or behavioral concerns. 96 patients with SCD (66 HgbSS, 19 HgbSC, 9 HgbSb+, 1 Hgb G-Philadelphia, and 1 HgSb0) met inclusion criteria. A diagnosis of ADHD was determined using diagnostic criteria from the Diagnostic Statistical Manual -Fourth Edition -Text Revised (DSM-IV-TR). Patients with a known history of stroke, silent stroke or other neurologic disorder were excluded.

Results: 23 patients (24%) met the diagnostic criteria for ADHD (16 HgbSS, 6 HgbSC and 1 HgbSb+). Of the patients diagnosed with ADHD, 52% were male and 48% were female. In terms of ADHD subtypes, 13 patients (56.5%) were diagnosed with ADHD primarily inattentive type, 7 (30.5%) with ADHD combined type and 3 (13%) with ADHD primarily hyperactive-impulsive type. Only 8.7% of patients diagnosed with ADHD were found to be taking medication for ADHD.

Conclusion: We found a high rate of ADHD (24%) in patients with SCD referred for neuropsychological evaluation. The most common subtype of ADHD was inattentive type. Despite the high risk for academic underachievement, patients with SCD and ADHD were rarely found to be taking medication for ADHD.

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Psychiatr Invest. 2014;11:258-65.

THE VALIDITIES AND EFFICIENCIES OF KOREAN ADHD RATING SCALE AND KOREAN CHILD BEHAVIOR CHECKLIST FOR SCREENING CHILDREN WITH ADHD IN THE COMMUNITY.

Park J-I, Shim S-H, Lee M, et al.

Objective The purpose of this study is to examine the validity of primary screening tools for attention deficit hyperactivity disorder (ADHD) in a community-based sample of children using the Korean version of the Child Behavior Checklist (K-CBCL) and the Korean version of the ADHD Rating Scale (K-ARS).

Methods A large-scale community-based study for ADHD screening was conducted in the Jeollabuk province in the Republic of Korea. In 2010-2011, we surveyed a total of 49,088 first- and fourth-grade elementary school students. All of the participants in this study were assessed by the K-ARS-Parent version (K-ARS-P) and the K-ARS-Teacher version (K-ARS-T) as the primary screening instruments. The Diagnostic Interview Schedule for Children Version IV (DISC-IV) was used for confirming the diagnosis of ADHD. DISC-IV was administered to subjects who received top 10% scores in the K-ARS-P or K-ARS-T tests.

Results Of the 3,085 subjects who completed the DISC-IV, 1,215 were diagnosed as having ADHD. A reasonable level of sensitivity, specificity, and negative predictive value were obtained when the total K-ARS-P scores were (greater-than or equal to)90th percentile. The positive predictive value and specificity increased significantly when the total K-ARS-P scores were (greater-than or equal to)90th percentile, T scores were (greater-than or equal to)60 in the attention problems of K-CBCL, and T scores were (greater-than or equal to)63 in the total problems of K-CBCL

Conclusion These results suggested that the K-ARS-P could effectively serve as a primary screening tool to identify elementary school children with ADHD in the community. Also, there might be some increment in the effectiveness of K-ARS-P when combined with KCBCL-A and K-CBCL-T as a secondary screening tool.

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Psychiatr Invest. 2014;11:223-27.

MOTOR FUNCTION IN SCHOOL-AGED CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN KOREA.

Cho H, Ji S, Chung S, et al.

Objective Motor function critically influences daily activities and academic performance. We compared motor function in schoolaged children with Attention-Deficit/ Hyperactivity Disorder (ADHD) to that of normal children.

Methods Participants were 58 children with ADHD [51 males, 7 females; mean age 9 years 6 months(plus or minus)2 years 0 months (SD)] and 70 normal controls [56 males, 14 females; mean age 9 years 2 months(plus or minus)1 years 7 months (SD)]. We assessed motor function with the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition.

Results The ADHD group had a significantly lower total motor composite score (t=-9.32, p<0.001) than that of the control group. Standard scores of four motor-area composites such as fine manual control (t=-3.76, p<0.001), manual coordination (t=-6.87, p<0.001), body coordination (t=-7.14, p<0.001), and strength and agility (t=-8.54, p<0.1) were significantly lower in the ADHD group than those in the control group. Among the subtests, scores on fine motor precision, fine motor integration, manual dexterity, bilateral coordination, balance, running speed and agility, and strength were significantly lower in the ADHD group than those in the controls, whereas upper-limb coordination was not significantly different between the groups.

Conclusion School-aged children with ADHD in Korea had significantly lower motor function compared to that of controls. Thus, it is suggested that appropriate target intervention for motor function is important in children with motor impairment in addition to pharmacotherapy or psychosocial therapy for improving the core symptoms.

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Psychiatr Invest. 2014;11:266-71.

ATTENTION DEFICIT HYPERACTIVITY DISORDER LIKE BEHAVIORAL PROBLEMS AND PARENTING STRESS IN PEDIATRIC ALLERGIC RHINITIS.

Lee YS, Kim SH, You JH, et al.

Objective Previous studies have reported comorbidity of attention deficit and hyperactivity disorder (ADHD) and allergic diseases. The current study investigated ADHD like behavioral symptoms and parenting stress in pediatric allergic rhinitis.

Methods Eighty-seven children (6-13 years old) with allergic rhinitis and 73 age- and sex-matched children of control group were recruited. Diagnosis and severity assessments of allergic rhinitis were determined by a pediatric allergist. The Parenting Stress Index-Short Form (PSI-SF), ADHD Rating Scale (ARS), and Child Behavior Checklist (CBCL) were completed by their mothers.

Results In the allergic rhinitis group, the total PSI-SF score (p<0.01), ARS score (p<0.01), the subscale scores of the CBCL including somatization, attentional problems and emotional instability (p=0.01; p<0.01; p<0.01) and prevalence of ADHD (p=0.03) were significantly higher than those of the control group. Among mothers of children with allergic rhinitis, those of children with comorbid ADHD demonstrated significantly higher parenting stress than those without comorbid ADHD (p<0.01). Parenting stress was correlated with severity of child's allergic symptoms and the ARS total score (beta=0.50, p<0.01; beta=0.39, p<0.01). There was a significant correlation between allergic symptom severity and the ARS total score (B=8.4, SD=2.5, t=3.3, p<0.01).

Conclusion This study demonstrated that ADHD symptoms were common in children with allergic rhinitis, and this factor increased parenting stress and disrupted the parent-child relationship. Routine evaluation

and early management of ADHD symptoms in pediatric allergic rhinitis may benefit families of children with allergic rhinitis.

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Psychiatry Res. 2014.

ODD IRRITABILITY IS ASSOCIATED WITH OBSESSIVE-COMPULSIVE BEHAVIOR AND NOT ADHD IN CHRONIC TIC DISORDERS.

Theriault MCG, Lesperance P, Achim A, et al.

Gilles de la Tourette syndrome (TS) and chronic tic disorder (CT) are often associated with a variety of behavioral comorbidities including attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive behavior (OCB), oppositional-defiant disorder (ODD) and temper outbursts. ODD is often associated with ADHD but its links to other symptoms of TS/CT is not as clear. This study examined whether the various symptoms of ODD were differentially linked to the various comorbidities in TS. A clinical sample of 135 children diagnosed with TS was evaluated through parent questionnaires and semi-structured interviews. Regressions and structural equation modeling confirmed that ODD is multidimensional in a TS/CT sample and showed that OCB was associated with the irritability symptoms of ODD whereas ADHD was associated with the Headstrong symptoms of ODD. Results suggest that increased attention to the different facets of ODD may help improve our understanding of emotional symptoms in TS/CT.

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Psychiatry Res. 2014.

BLOOD MANGANESE LEVELS IN RELATION TO COMORBID BEHAVIORAL AND EMOTIONAL PROBLEMS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hong S-B, Kim J-W, Choi B-S, et al.

Patients with attention-deficit/hyperactivity disorder (ADHD) appear to be more vulnerable to the development of other psychiatric disorders than the general population. The proposed neurotoxic mechanisms of manganese involve striatal dopamine neurotransmission, implicated in the pathophysiology of ADHD. We investigated whether the adverse impact of manganese is particularly pronounced in children with ADHD. Blood manganese concentration and diagnosis of ADHD were assessed in a general population of 890 children, aged 8-11 years. The main outcome measure was the Child Behavior Checklist (CBCL). A significant interaction was found between ADHD status and blood manganese level in predicting CBCL total problems score as well as anxiety/depression, social problems, delinquent behavior, aggressive behavior, internalizing problems, and externalizing problems. The directions of the interactions indicated that blood manganese level was more positively correlated with CBCL scores in ADHD children than in the healthy population. In ADHD children, only the fifth quintile of blood manganese concentration was significantly associated with the CBCL total problems score. ADHD children may be more vulnerable than the general school-age population to the neurotoxic effects of manganese exposure, which lead to an elevated risk of developing comorbid mental conditions.

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Psychiatry Res Neuroimaging. 2014.

CORTICAL THINNING OF TEMPORAL POLE AND ORBITOFRONTAL CORTEX IN MEDICATION-NAIVE CHILDREN AND ADOLESCENTS WITH ADHD.

Fernandez-Jaen A, Lopez-Martin S, Albert J, et al.

Structural and functional brain studies on attention deficit/hyperactivity disorder (ADHD) have primarily examined anatomical abnormalities in the prefronto-striatal circuitry (especially, dorsal and lateral areas of the prefrontal cortex and dorsal striatum). There is, however, increased evidence that several temporal lobe regions could play an important role in ADHD. The present study used MRI-based measurements of cortical thickness to examine possible differences in both prefrontal and temporal lobe regions between medication-naive patients with ADHD (N=50) and age- and sex-matched typically developing controls

(N=50). Subjects with ADHD exhibited significantly decreased cortical thickness in the right temporal pole and orbitofrontal cortex (OFC) relative to healthy comparison subjects. These differences remained significant after controlling for confounding effects of age, overall mean cortical thickness and comorbid externalizing conditions, such as oppositional defiant and conduct disorders. These results point to the involvement of the temporal pole and OFC in the neuropathology of ADHD. Moreover, present findings add evidence to the assumption that multiple brain regions and psychological processes are associated with ADHD.

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Radiology. 2014;272:514-23.

INTRINSIC BRAIN ABNORMALITIES IN ATTENTION DEFICIT HYPERACTIVITY DISORDER: A RESTING-STATE FUNCTIONAL MR IMAGING STUDY.

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

Purpose: To explore alterations of regional and network-level neural function using resting-state functional magnetic resonance (MR) imaging in children and adolescents with attention deficit hyperactivity disorder (ADHD) and to assess the association between these alterations of intrinsic neural activity and executive dysfunction in ADHD.

Materials and Methods: This prospective study was approved by the local ethical committee, and written informed consent was obtained from guardians of all participants. Thirty-three boys with ADHD who were not receiving medication and who were without comorbidity (aged 6-16 years) and 32 healthy control subjects (aged 8-16 years) underwent imaging by using resting-state functional MR imaging. Amplitude of low-frequency fluctuation (ALFF) and seed-based functional connectivity (FC) were calculated to examine regional neural function and functional integration, respectively, and were compared between patients and control subjects by using the voxel-based two-sample t test, while Pearson correlation analyses were performed to identify neural correlates of executive function measured with the Wisconsin Card Sorting Test and the Stroop Color-Word Test.

Results: Relative to healthy control subjects, patients with ADHD showed impaired executive function ($P < .05$), along with the following: lower ALFF in the left orbitofrontal cortex ($P = .004$) and the left ventral superior frontal gyrus ($P = .003$); higher ALFF in the left globus pallidus ($P = .004$), the right globus pallidus ($P = .002$), and the right dorsal superior frontal gyrus ($P = .025$); lower long-range FC in the frontoparietal and frontocerebellar networks; and higher FC in the frontostriatal circuit that correlated across subjects with ADHD with the degree of executive dysfunction ($P < .05$).

Conclusion: These findings of focal spontaneous hyper- and hypofunction, together with altered brain connectivity in the large-scale resting-state networks, which correlates with executive dysfunction, point to a connectivity-based pathophysiologic process in ADHD.

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Radiology. 2014;272:524-32.

MULTIMODAL MR IMAGING OF BRAIN IRON IN ATTENTION DEFICIT HYPERACTIVITY DISORDER: A NONINVASIVE BIOMARKER THAT RESPONDS TO PSYCHOSTIMULANT TREATMENT?

Adisetiyo V, Jensen JH, Tabesh A, et al.

Purpose: To comprehensively assess brain iron levels in typically developing control subjects and patients with attention deficit hyperactivity disorder (ADHD) when psychostimulant medication history is accounted for. Materials and This prospective study was approved by the institutional.

Methods: review board, and informed consent was obtained. Brain iron was indexed noninvasively by using magnetic resonance (MR) imaging relaxation rates (R2, R2*, R2') and magnetic field correlation (MFC) in the globus pallidus, putamen, caudate nucleus, and thalamus for 22 patients with ADHD (12 medication-naive patients and 10 with a history of psychostimulant treatment) and 27 control subjects (age range, 8-18 years). Serum iron measures were also collected. Subgroup differences were analyzed with data-appropriate omnibus tests followed by post hoc pairwise comparisons; false discovery rate correction was conducted to control for multiple comparisons.

Results: Medication-naive ADHD patients had significantly lower striatal and thalamic MFC indexes of brain iron than did control subjects (putamen, P = .012; caudate nucleus, P = .008; thalamus, P = .012) and psychostimulant-medicated ADHD patients (putamen, P = .006; caudate nucleus, P = .010; thalamus, P = .021). Conversely, the MFC indexes in medicated patients were comparable to those in control subjects. No significant differences were detected with R2, R2*, R2', or serum measures.
Conclusion: Lower MFC indexes of striatal and thalamic brain iron in medication-naive ADHD patients and lack of differences in psychostimulant-medicated patients suggest that MFC indexes of brain iron may represent a noninvasive diagnostic biomarker that responds to psychostimulant treatment.

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Res Autism Spectr Disord. 2014;8:1333-38.

AUTISTIC SPECTRUM DISORDER, ATTENTION DEFICIT HYPERACTIVITY DISORDER, AND ALLERGY: IS THERE A LINK? A NATIONWIDE STUDY.

Lin T-Y, Lin P-Y, Su T-P, et al.

Previous studies showed that both attention deficit hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD) were associated separately with a higher risk of allergic diseases. However, the comorbid effect of ADHD and ASD on the risk of allergic diseases is still unknown. Using the Taiwan National Health Insurance Research Database, 5386 children aged less than 18 years with ADHD alone, 578 with ASD alone, 458 with ADHD + ASD, and 25,688 non-ADHD/ASD age- and sex-matched (1:4) controls were enrolled in our study. The prevalence of allergic diseases, including asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis, was evaluated among the four groups. Logistic regression analysis showed that the ADHD + ASD group (odds ratio [OR]: 2.26, 95% confidence interval [CI]: 1.83-2.79), ADHD-alone group (OR: 1.81, 95% CI: 1.70-1.93), and ASD-alone group (OR: 1.24, 95% CI: 1.04-1.48) had an increased risk of allergic comorbidities compared to the control after adjusting age, sex, and level of urbanization. ASD children with more allergic comorbidities ((greater-than over equal to)3: OR: 2.57, 95% CI: 1.74-3.79; 2: OR: 2.00, 95% CI: 1.41-2.84; 1: OR: 1.60, 95% CI: 1.16-2.22) were associated with a greater likelihood of ADHD. Children with ADHD or ASD had an increased risk of allergic comorbidities,

and those with both ADHD and ASD had the highest. These results may inspire more research to clarify the underlying mechanisms among ASD, ADHD, and allergic diseases.

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Res Dev Disabil. 2014;35:3046-56.

CONTRASTING DEFICITS ON EXECUTIVE FUNCTIONS IN CHINESE DELINQUENT ADOLESCENTS WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER SYMPTOMS AND/OR READING DISABILITY .

Poon K, Ho CSH.

Many studies reported high prevalence of reading disability (RD) and attention deficit hyperactivity disorder (ADHD) among delinquent adolescents. Very few have examined their cognitive profile. The present study compared the executive functions (EFs) and severity of delinquency in delinquent adolescents with RD and/or ADHD symptoms (AS). Delinquents with AS (n= 29), RD (n= 24), comorbidity AS. +. RD (n= 35) were recruited from juvenile institutions along with typically developing controls (n= 29) from local schools; all completed EF assessments and self-report questionnaires on delinquency. Results showed that pure AS group exhibited impaired inhibition while the pure RD group was weak in processing speed and visual memory. The comorbidity group showed unique impairments in interference control and significantly higher delinquency severity. The present findings suggest that comorbidity AS. +. RD may influence delinquency severity. It also provides a more comprehensive picture of the unique EF deficits associated with different groups, allowing for better matching for future identification and intervention programme.

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Rev Psiquiatr Salud Ment. 2014;7:104-12.

PREVALENCE OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN OUTPATIENT ADOLESCENTS AND YOUNG ADULTS WITH OTHER PSYCHIATRIC DISORDERS REFRACTORY TO PREVIOUS TREATMENTS.

Vidal R, Barrau V, Casas M, et al.

Introduction The aim of the current study was to assess the prevalence of symptoms of attention deficit/hyperactivity disorder (ADHD) in adolescents and young adults diagnosed with other primary psychiatric disorders, who had not responded to previous treatments.

Material and methods A total of 795 outpatients aged 15 to 24 years were included. The presence of ADHD was studied using DSM-IV criteria and the frequency of symptoms using the 18 item DuPaul ADHD Rating Scale.

Results ADHD (DSM-IV criteria) was present in 48 patients (6%), none of whom had previously received the diagnosis. A total of 260 patients (32.7%) met the criteria for moderate ADHD and between them, severity of primary psychiatric disorder was higher according to the CGI-S (P =.007). Risk factors for moderate ADHD symptoms were the presence of substance use disorders (SUD) (odds ratio = 1.543, P =.01) and borderline personality disorders (odds ratio = 2.173, p =.0001).

Conclusion Unrecognized ADHD was present in 6% of patients; moreover 32.7% of the sample also presented moderate symptoms of the disorder. Screening for ADHD in young patients with refractory response to primary disorder treatment, mainly those with substance use disorders, conduct and personality disorders is highly advisable, due to the high frequency of ADHD comorbidity in these psychiatric disorders.

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Seminars in Hearing. 2014;35:193-205.

USE OF WIRELESS TECHNOLOGY FOR CHILDREN WITH AUDITORY PROCESSING DISORDERS, ATTENTION-DEFICIT HYPERACTIVITY DISORDER, AND LANGUAGE DISORDERS.

Schafer EC, Traber J, Layden P, et al.

There are several populations of children who have normal hearing but exhibit auditory listening difficulties in the classroom. Recent publications will be reviewed to support the use of wireless, remote microphone technology for improving speech-recognition performance in noise and classroom-listening abilities in children diagnosed with auditory processing disorders (APDs), attention-deficit hyperactivity disorder (ADHD), and autism spectrum disorders (ASDs). In addition, a series of case studies on children diagnosed with APDs, ADHD, ASDs, and/or language disorders will be presented to (1) support specific remote microphone-fitting procedures and (2) to report speech-recognition performance in noise; listening comprehension; and participant-, parent-, and teacher-rated listening behaviors following a trial period with the technology. The results of these case studies will validate fitting procedures for these populations with auditory listening difficulties and will provide additional, evidence-based support for the use of remote microphone technology for children diagnosed with APDs, ADHD, ASDs, and/or language disorders.

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Tropical Journal of Pharmaceutical Research. 2014;13:1157-62.

PRESCRIBING PATTERNS OF METHYLPHENIDATE AND ATOMOXETINE FOR PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Truter I.

Purpose: To determine the prescribing pattern of methylphenidate and atomoxetine to patients with Attention-Deficit/Hyperactivity Disorder (ADHD) in South Africa.

Methods: A retrospective, cross-sectional pharmacoepidemiological study was conducted based on the data from a medical aid administrator in South Africa for 2011. All records for ADHD patients who received one or more prescriptions for methylphenidate and/or atomoxetine (ATC Code N06BA) were extracted for analysis.

Results: A total of 455 patients (mean age: 16.5 (plus or minus) 11.56 yr) received 1653 prescriptions for methylphenidate and/or atomoxetine at a total cost of South AfricanRand 554,915.84 (US dollar 1.0 = Rand

6.76). A majority of these patients (70.34 %) were males and 21.10 % were older than 18 yr (25.76 % of females and 19.81 % of males). About a third of the prescriptions (30.44 %) were dispensed to children younger than 12 years while 25.88 % were dispensed to adolescents (12 to 18 years). Most prescriptions (92.01 %) were for methylphenidate while atomoxetine accounted for 7.99 % of the prescription. A majority of the prescriptions for methylphenidate (47.86 %) were for children younger than 12 yr, and most prescriptions for atomoxetine (52.27 %) were for adolescents.
Conclusion: Methylphenidate is the mainstay in the treatment of ADHD in South Africa, with atomoxetine prescribed more often to older patients. Drug use is rational and dosages are within the recommended dosage ranges. As expected, older patients are receiving treatment for ADHD.

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Twin Res Hum Genet. 2014 Jun;17:164-76.
THE ROOTS OF AUTISM AND ADHD TWIN STUDY IN SWEDEN (RATSS).
Bölte S, Willfors C, Berggren S, et al.
Neurodevelopmental disorders affect a substantial minority of the general population. Their origins are still largely unknown, but a complex interplay of genetic and environmental factors causing disturbances of the central nervous system's maturation and a variety of higher cognitive skills is presumed. Only limited research of rather small sample size and narrow scope has been conducted in neurodevelopmental disorders using a twin-differences design. The Roots of Autism and ADHD Twin Study in Sweden (RATSS) is an ongoing project targeting monozygotic twins discordant for categorical or dimensional autistic and inattentive/hyperactive-impulsive phenotypes as well as other neurodevelopmental disorders, and typically developing twin controls. Included pairs are 9 years of age or older, and comprehensively assessed for psychopathology, medical history, neuropsychology, and dysmorphology, as well as structural, functional, and molecular brain imaging. Specimens are collected for induced pluripotent (iPS) and neuroepithelial stem cells, genetic, gut bacteria, protein-/monoamine, and electron microscopy analyses. RATSS's objective is to generate a launch pad for novel surveys to understand the complexity of genotype-environment-phenotype interactions in autism spectrum disorder and attention-deficit hyperactivity disorder (ADHD). By October 2013, RATSS had collected data from 55 twin pairs, among them 10 monozygotic pairs discordant for autism spectrum disorder, seven for ADHD, and four for other neurodevelopmental disorders. This article describes the design, recruitment, data collection, measures, collected pairs' characteristics, as well as ongoing and planned analyses in RATSS. Potential gains of the study comprise the identification of environmentally mediated biomarkers, the emergence of candidates for drug development, translational modeling, and new leads for prevention of incapacitating outcomes.

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World J Biol Psychiatry. 2014;15:499-504.
HUMAN ENDOGENOUS RETROVIRUSES AND ADHD.
Balestrieri E, Pitzianti M, Matteucci C, et al.
Objectives. Several lines of evidences suggest that human endogenous retroviruses (HERVs) are implicated in the development of many complex diseases with a multifactorial aetiology and a strong heritability, such as neurological and psychiatric diseases. Attention deficit hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that results from a complex interaction of environmental, biological and genetic factors. Our aim was to analyse the expression levels of three HERV families (HERV-H, K and W) in patients with ADHD.
Methods. The expression of retroviral mRNAs from the three HERV families was evaluated in peripheral blood mononuclear cells (PBMCs) from 30 patients with ADHD and 30 healthy controls by quantitative RT-PCR.
Results. The expression levels of HERV-H are significantly higher in patients with ADHD compared to healthy controls, while there are no differences in the expression levels of HERV-K and W.
Conclusions. Since the ADHD aetiology is due to a complex interaction of environmental, biological and genetic factors, HERVs may represent one link among these factors and clinical phenotype of ADHD. A

future confirmation of HERV-H overexpression in a larger number of ADHD patients will make possible to identify it as a new parameter for this clinical condition, also contributing to deepen the study on the role of HERVs in the neurodevelopment diseases.

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REVIEW

Guanfacine for attention deficit and hyperactivity disorder in pediatrics: A systematic review and meta-analysis

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KEYWORDS
Attention deficit disorder with hyperactivity;
Child;
Guanfacine;
Meta-analysis;
Systematic review

Abstract
To review the evidence from randomized controlled trials (RCTs) on the safety and efficacy of guanfacine in pediatric attention deficit hyperactivity disorder (ADHD), a bibliographic search up to May 2014 was performed using the Cochrane Library's Central Register of Controlled Trials, the Embase, PsycINFO, and Medline databases, and clinical trials registers. The search terms used were: ["guanfacine"] and ["child" or "adolescent" or "pediatrics"] and ["randomized controlled trial"] and ["Attention Deficit Disorder with Hyperactivity" or "Attention Deficit Disorder" or "Attention Hyperactivity Disorder" or "Hyperactivity" or "ADHD"]. A meta-analysis was performed using response, defined as a score ≤ 2 on the Clinical Global Impression Improvement score, as the outcome measure. In all, 7 out of 48 studies were included, for a total of 1752 participants. All studies compared guanfacine versus placebo, with a duration ranging from 6 to 16 weeks. In all, the Clinical Global Impression Improvement score was reported as a secondary measure. Overall, 694/1177 (59.0%) participants in the guanfacine group benefited from the treatment compared to 192/575 (33.3%) in the placebo group (pooled OR 3.2; 95%CI 2.4-4.1). The participants with at least one adverse event were 948 (82.4%) in the guanfacine and 376 (67.9%) in the placebo group (OR 2.6; 95%CI 1.6-4.4). Somnolence (OR 4.9), sedation (OR 2.8), and fatigue (OR 2.2), were the adverse events with the greatest risk of

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occurrence in the guanfacine versus the placebo group. On the basis of seven randomized, placebo controlled trials guanfacine resulted safe and effective in treating children and adolescents with ADHD

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in children and adolescents that comprises core symptoms of developmentally inappropriate levels of inattention and/or hyperactivity and impulsivity. (American Psychiatric Association.Task force on DSM-IV., 2010) Recommendations in the international guidelines on the treatment of ADHD vary. However, there is a general consensus on recommending psychostimulant drugs as first line treatment because of their documented efficacy in about 80% of children. (American Academy of Pediatrics, 2011; National Collaborating Centre For Mental Health, 2008) In particular, methylphenidate is preferred to amphetamines, which are generally less used in Europe. Atomoxetine is a non-stimulant medication that, although generally less effective than stimulants, is also widely available and may be recommended as an alternative to methylphenidate (Hanwella et al., 2011; National Collaborating Centre For Mental Health, 2008; Newcorn et al., 2008). Since their approval, several issues have affected the use of ADHD medications, such as tolerability, comorbidity, and potential substance abuse risk.. This has enhanced the need for alternative treatment options, such as the α2 adrenergic receptor agonists, clonidine and guanfacine. Clonidine and guanfacine are two older antihypertensive drugs, licensed for use in adults, that induce peripheral sympatho-inhibition via the stimulation of receptors located in the brainstem. (van Zwieten and Chalmers, 1994) Despite their proven efficacy in lowering blood pressure, these two drugs are no longer widely used as antihypertensive agents. Nevertheless, they have been found to be useful in the treatment of different neuropsychiatric disorders, including ADHD, with the first studies in ADHD dating back to 30 years ago. (Hunt et al., 1985; Hunt et al., 1995) For a long time these drugs have been used as off-label alternatives to stimulant therapies, in particular in children and adolescents who continued to show behavioral problems, tics, or sleep disturbances during treatment with stimulants or atomoxetine. (Posey and McDougle, 2007) Although clonidine, used alone or in combination with methylphenidate, has been shown to be effective in reducing symptoms of ADHD in children, its clinical usefulness is limited by adverse effects, including sedation, bradycardia, and hypotension, especially at the start of treatment. (Hunt et al., 1990) Guanfacine is a more selective α 2-adrenoceptor agonist than clonidine. (Horrigan and Barnhill, 1995) Whereas clonidine binds equally to α 2A-, α 2B-, and α 2C-adrenoceptors (as well as to α 1-adrenoceptors, β-adrenoceptors, histamine receptors, and possibly dopamine receptors), guanfacine binds preferentially to postsynaptic α 2A-adrenoceptors in the prefrontal cortex (PFC), which have been implicated in attentional and organizational functions. (Wang et al., 2007) The mechanism through which α 2-adrenoceptor agonists works in ADHD patients is unclear, but abnormal PFC functioning is posited to be a key contributor to the impairments observed in ADHD. (Arnsten and Li, 2005; Arnsten et al., 2007; Franowicz et al., 2002) The guanfacine selectivity for α 2A receptors in PFC may more efficiently target ADHD symptoms while minimizing the risk of adverse effects. Compared with clonidine, guanfacine has less central nervous system depressant and less hypotensive activity (Yamadera et al., 1985; Kugler et al., 1980) and may have a more favorable pharmacokinetic profile. (Newcorn et al., 1998; Sorkin and Heel, 1986) In USA, a long acting formulation of guanfacine was approved in February 2009 by the Food and Drug Administration (FDA) for the treatment of ADHD in the pediatric population aged 6 to 7 years as monotherapy, and in 2011 as adjunctive therapy to psychostimulant treatment. In 2013 the drugs was approved also in Canada for use in children 6-12 years old. In Europe, a Pediatric Investigation Plan was submitted to the EMA from the drug company (EMEA-000745-PIP01-09-M01), but, until now the use of guanfacine is still limited to the treatment of hypertension in adults. Given the increasing interest for this drug in the clinical, research and regulatory settings, a review of published and unpublished studies on the safety and efficacy of guanfacine in the treatment of ADHD symptoms in the pediatric population was performed.

2. Experimental procedures

2.1. Definitions and inclusion/exclusion criteria

The systematic review was restricted to studies evaluating guanfacine therapy in children and adolescents with a diagnosis of ADHD. The search was limited to humans and only original articles were considered. Studies were eligible if they were randomized controlled trials. Studies involving adults, reviews, letters, editorials, follow-up studies, n-of-1 studies (i.e. studies in which random allocation is used to determine the order in which an experimental and a control intervention are given to a single patient who represents the trial population), comments, or published errata were excluded.

2.2. Search strategy

The search was performed independently by 2 reviewers (SR, AC) using the Medline (1950-May 2014), Embase (1974-May 2014), and PsycINFO (1967-May 2014) databases, and the Cochrane Central Register of Controlled Trials (Issue 5 of 12, May 2014).

The search strategy used both terms included in the title/abstract and in the subject headings, i.e. Medical Subject Headings (MeSH) for Medline and Cochrane, Emtree for Embase, and thesaurus for PsycINFO. The search terms used were: ["guanfacine"]

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and ["child" or "adolescent" or "pediatrics"] and ["randomized controlled trial"] and ["Attention Deficit Disorder with Hyperactivity" or "Attention Deficit Disorder" or "Attention Hyperactivity Disorder" or "Hyperactivity" or "ADHD"]. No language restriction was applied. The assessors independently screened the title, abstract, and keywords of each citation to determine its relevance. In case of disagreement, the opinion of a third assessor (MB) was sought.

Moreover, two international clinical trials registers (clinicaltrials.gov, clinicaltrialsregister.eu) were searched up to 12 June 2014 to retrieve pertinent unpublished studies.

Complete references were downloaded and stored using Reference Manager 2011.0.1 software (Thompson ResearchSoft, Carlsbad, CA, USA).

2.3. Quality assessment

Two reviewers (SR and ACI) independently assessed each study for methodological quality. In case of disagreement, the opinion of a third assessor (MB) was sought.

The included articles were assessed using the Cochrane Collaboration's tool for risk of bias,(Higgins et al., 2011) which classifies risk of bias into six different domains:

- method used to generate the sequence of randomization (sequence randomization);
- method used to mask the sequence of allocation to treatment (allocation concealment);
- measures used to ensure the "blindness" of the study participants and medical staff and not with respect to treatment assignment (blinding of participants, personnel and outcome assessors);
- completeness of the data for each outcome considered (incomplete outcome data);
- selective description of the results (selective outcome reporting);
- other sources of bias (e.g. bias due to the early interruption of the study because of the benefits) (other sources of bias).

For each domain assessors were expected to judge the risk of bias ("high risk", "low risk", or "unclear") on the basis of the information retrieved from the papers.

2.4. Outcome measurement

For each study data concerning the primary and secondary endpoints were extracted end evaluated. For the meta-analysis, the treatment response, defined as Clinical Global Impression Improvement (CGI-I) score of ≤ 2 (reflecting much improved or very much improved ADHD symptoms), was used as primary outcome measure.

None of the retrieved studies defined response on the basis of a predefined percentage reduction of ADHD-RS score. It was not possible to pool ADHD-RS score data retrieved from the published papers.

2.5. Statistical analysis

Inter-reviewer reliability was measured using Cohen's Kappa statistics.

For the meta-analysis, data from studies based on treatment response were pooled.

Data were analyzed using Review Manager (RevMan) 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2012). A random effects model was used to calculate pooled Odds Ratios and 95% confidence intervals.(Fleiss, 1981). The sample size chosen for statistical analysis on efficacy was the randomized population. A sensitivity analysis using a fixed effects model and one considering only patients who completed the studies were also performed.

The sample for the statistical analysis on tolerability was the safety population as reported in each study (defined as the subjects who received at least 1 dose of study drug). Data concerning children with at least one treatment emergent adverse events (TEAE) were pooled. Sub-analyses were performed pooling data based on children reporting each of the most common AEs.

Heterogeneity was examined using the Q and I^2 statistics. (DerSimonian and Laird, 1986; Fleiss, 1981)

Cochran's Q (distributed as a Chi-square statistic) is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance.(Higgins et al., 2003)

3. Results

3.1. Systematic review

3.1.1. Search results

A trial flow diagram is shown in Fig. 1. The electronic search strategy, after accurate evaluation of the abstracts, identified 48 potentially relevant published studies. Nineteen of these were duplicate titles indexed in multiple databases and were excluded. No additional studies were retrieved via the manual search of reference lists of identified papers. Of the 29 resulting studies, 23 were excluded. In particular, 10 studies were not randomized controlled trials, 2 were excluded because ADHD was not the primary diagnosis of the enrolled patients, 2 were performed in adults, 1 study did not focus on guanfacine treatment, 1 considered add on therapy, and 1 was a pharmacokinetic trial. Moreover, 2 studies were open-label-extensions of previous short term trials,(Biederman et al., 2008a; Sallee et al., 2009a) 2 were secondary analyses of previous RCTs,(Faraone and Glatt, 2010; Sallee et al., 2012) 1 was a cost effectiveness analysis based on a previously published trial,(Sikirica et al., 2012) and 1 reference was a short-version of another article. (Biederman et al., 2008b) Thus, a total of 6 relevant randomized controlled trials on guanfacine treatment in ADHD children and adolescents met the criteria for inclusion in the systematic review. (Biederman et al., 2008b; Connor et al., 2010; Kollins et al., 2011; Newcorn et al., 2013; Sallee et al., 2009b; Scahill et al., 2001a)

Both reviewers fully agreed on the choice of the pertinent trials (weighted $K=1$).

A total of 25 trials were retrieved from clinical trials registers, 21 of which from clinicaltrials.gov and 4 from clinicaltrialsregister.eu. Four trials were listed in both registers and the duplicates were excluded. Nine out of 21 trials were published (all of which were identified through the bibliographic search). Among the 12 unpublished trials, only 9 met the inclusion criteria (they were randomized and controlled); 4 of these were ongoing and 5 were completed (Table S1). For 2 studies the register did not report the results: one compared guanfacine versus placebo (clinicaltrials.gov NCT 01156051) and one guanfacine versus placebo

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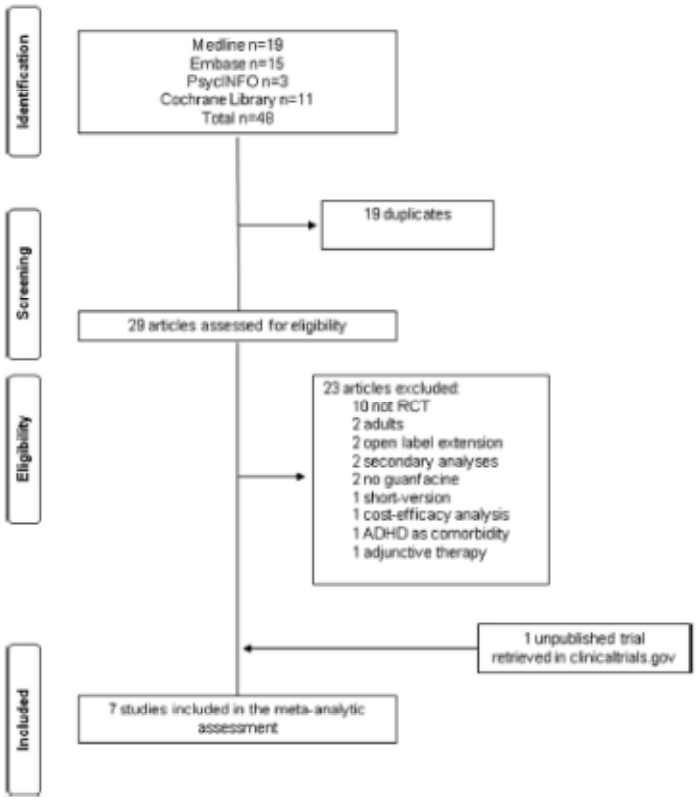

Fig. 1 RCTs identified through database searching and clinical trials registers.

and atomoxetine (NCT01244490). Of the three studies with results, one study focused almost exclusively on electrophysiology (NCT 01069523) and one was a withdrawal trial with an open-label phase preceding the randomized phase (NCT01081145). and both were excluded. It was possible to evaluate the results of an unpublished RCT,(NCT01081132) and a total of 7 studies therefore met the inclusion criteria for the systematic review (Table 1).

3.1.2. Therapeutic dosages in reviewed RCTs

All studies were double blind, parallel group studies comparing guanfacine with placebo. The extended release formulation of guanfacine (GXR) was evaluated in 6 studies, the immediate release (GIR) in one (Scahill et al., 2001a) The guanfacine doses ranged from 1 to 7 mg/day. A guanfacine dose optimization schedule starting from 1.5 or 1 mg/die was used in 5 studies, while 2 used a fixed guanfacine schedule. Treatment duration ranged from 6 to 13 weeks (mean 8.9; SD 2.1).

3.1.3. RCT characteristics

All but one study were multicenter (range 9-54 centers); the only single center study was also the oldest.(Scahill et al., 2001a) Five studies were performed in the USA (Biederman et al., 2008c; Connor et al., 2010; NCT01081132, 2014; Sallee et al., 2009b; Scahill et al., 2001b) and one in the USA and Canada. (Newcorn et al., 2013) In one case the authors did not report the enrollment countries, but it is likely that the study was performed in the USA.(Kollins et al., 2011)

The publication years ranged from 2001-2013. Six out of 7 studies were funded by pharmaceutical industries. One was funded by the Children's Clinical Research Center, Yale Mental Health Research Center, and the Tourette Syndrome Association.(Scahill et al., 2001a)

In all, 1752 children and adolescents (range 34-345; median 314) were randomized, 1177 of whom received guanfacine and 575 placebo.

In all, 1235 (70.5%) patients (mean 206.7; SD 126.2; median 207) completed the studies. The percentage of completers ranged from 62.3 to 100%.

Dropouts were present in all but one study (Scahill et al., 2001a) and ranged from 10 to 130 children. In all, 29.5% (n=517) of the randomized patients did not complete the study they participated in.

The most common reasons for dropping out were lack of efficacy (26.3%) and adverse events (22.4%). Of the 136 children who dropped-out for lack of efficacy, 43% (n=58) were drug treated versus 57% (n=78) placebo treated; while 104 out of 116 (90%) who dropped out for adverse effects were in the guanfacine group (Table 2).

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Table 1 Characteristics of the randomized controlled trials.

Study	Participants randomized (completers) (n)	Age (years)1;*	Drug treatment duration (weeks)	Diagnosis	Mean daily dose	Primary outcome measure	Response rate (CGI-I)		Risk of bias2;**			
							Guanfacine	*Placebo*	*Random*	*Allocation*	*Attrition*	*Reporting*
(Scahill et al., 2001a)	34	10.4 (7-14)	8	ADHD and tics	Dose optimization: GIR 3 mg/d	ADHD-RS	9/17	0/17	U	U	L	U
(Biederman et al., 2008b)	345 (215)	10.5 (6-17)	8	ADHD	Fixed doses: GXR 3 mg	ADHD-RS-IV	141/259	22/86	U	L	L	L
(Sallee et al., 2009b)	324 (211)	11.0 (6-17)	9	ADHD	Fixed doses: GXR 2.5 mg	ADHD-RS-IV	134/258	20/66	U	U	L	L
(Connor et al., 2010)	217 (157)	9.4 (6-12)	9	ADHD and Oppositional Symptoms	Dose optimization: GXR 3 mg	CPRS-R:L	93/138	24/79	L	U	U	U
(Kollins et al., 2011)	178 (168)	12.6 (6-17)	6	ADHD	Dose optimization: GXR 2.5 mg	CRT	69/121	20/57	L	U	L	U
(Newcorn et al., 2013)	340 (243)	9.1 (6-12)	8	ADHD	Dose optimization: GXR 1-4 mg	ADHD-RS-IV	213/227	35/113	U	U	L	L
NCT01081132	314 (207)	14.5(13-17)	13	ADHD	Dose optimization: GXR 1-7 mg	ADHD-RS-IV	104/157	71/157	n.a	n.a	n.a	n.a

ADHD-RS: ADHD Rating Scale; CRT: Choice Reacting Time.
*mean (range);
**L=Low; U=Unclear. "Detection bias" and "other bias" were considered low for all the studies and were therefore not reported in the table. n.a. not applicable.

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Table 2 Reasons for dropping out.

	Placebo $n=184$ (32.0%)[a]	Guanfacine $n=333$ (28.3%)[a]	Total $n=517$ (29.5%)[a]
Lack of efficacy	78 (13.6%)	58 (4.9%)	136 (7.8%)
Adverse events	12 (2.1%)	104 (8.8%)	116 (6.6%)
Consent withdrawn	41 (7.2%)	73 (6.2%)	114 (6.5%)
Lost to follow up	23 (4.0%)	48 (4.1%)	71 (4.1%)
Other	13 (2.3%)	31 (2.6%)	44 (2.5%)
Protocol violation	13 (2.3%)	10 (0.8%)	23 (1.3%)
No compliance	4 (0.7%)	9 (0.8%)	13 (0.7%)

Reasons are mutually exclusive;
[a] *N* (% of total enrolled patients).

Patients age ranged from 6 to 17. Three studies enrolled children of the same age group, and one enrolled only adolescents 13-17 years old.

In only 4 studies the gender distribution in the randomized population was reported, and the male/female ratio was 2.3 (614/264).

The length of the studies ranged from 6 to 16 weeks (mean 11.3; SD 4.0), including the last follow up visit.

A very good agreement between reviewers on the evaluation of the quality of the studies was found (weighted $K=0.842$).

The risk of bias resulted generally low or unclear. For no studies did assessors attribute a low risk for all bias domains considered. Only the risk of detection bias (blinding of participants, personnel, and outcome assessors) was judged to be low in all studies.

All studies were stated to be randomized, but 4 papers did not provided detailed information relative to the random sequence generation procedure (Biederman et al., 2008b; Newcorn et al., 2013; Sallee et al., 2009b; Scahill et al., 2001a). Only Biederman et al. and Sallee et al. studies mentioned adequate concealment of allocation (Biederman et al., 2008b; Sallee et al., 2009b). All studies reported how missing data were managed, with the exception of the trial by Connor et al. (Connor et al., 2010).

3.1.4. Diagnostic tools and inclusion/exclusion criteria used in the reviewed RCTs

All the published studies included children or adolescents with a diagnosis of ADHD based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*). (American Psychiatric Association. Task force on DSM-IV. (2010)) Five out of six studies used at least one other parameter to define the eligible population. In particular, 4 of these studies used the ADHD Rating Scale IV (ADHD-RS-IV) (DuPaul et al., 1998) (total score ≥ 24 or ≥ 28) in association with one or two other scales (Table 3). Four studies used at least three scales. Overall, inclusion criteria varied widely between the six studies.

Children with psychiatric comorbidities (with the exception of oppositional defiant disorder) were excluded in four studies, while Connor et al. included children with oppositional defiant disorder, dysthymia, or simple phobias, (Connor et al., 2010) and Scahill et al. included children with tics, with the exception of those with moderate or severe tics. (Scahill et al., 2001a)

3.2. Analysis of efficacy

A total of 11 different efficacy measures were used (Table 3). The ADHD-RS was used in all selected studies, in 5 of these it was the primary efficacy measure of the improvement from baseline to the endpoint (the last post-randomization treatment week of the treatment period for which a valid ADHD-RS score was obtained). In two studies authors measured the change from baseline of both the inattention and hyperactivity/impulsivity subscales of the ADHD RS-IV. (Biederman et al., 2008b; Kollins et al., 2011) The effect size was reported in four out of six studies. Among these, 2 dose optimization studies reported the total effect size (0.92 and 1.23). Two studies comparing different, fixed guanfacine dosages ranging from 1-4 mg (Sallee et al., 2009b) and from 2-4 mg (Biederman et al., 2008b), reported the effect size by randomized dosage (respectively 0.43-0.62 and 0.64-0.84); and by weight adjusted dosage (range 0.41-0.89, and 0.58-1.34).

The CGI-I was used in all studies as the secondary efficacy measure. In Connor et al. and in Newcorn et al. results from the CGI-I were retrieved from data reported in clinicaltrials.gov (study NCT00367835, and NCT01081132).

In two studies, the Clinical Global Impression of Severity (CGI-S) score was measured, too.

Four studies used the Conners' Parent Rating Scale (CPRS), three of which used only one of the subscales of CPRS (L, S, and hyperactivity index), and one study measured both CPRS-R and Conners' Teacher Rating Scale (CTRS). In one case CPRS was indicated as the primary efficacy measure.

The Physician Global Assessment (PGA) score was used in two studies as the secondary efficacy measure.

Finally, other different scales and questionnaires were used in three studies. Scahill et al. used also the following outcome measures: Yale Global Tic Severity Scale, Children's Yale-Brown Obsessive Compulsive Scale, and Continuous Performance Test. (Scahill et al., 2001a) Moreover, Kollins et al. evaluated psychomotor functioning and alertness through several measures, including the Choice Reaction Time (CRT) test from the Cambridge Neuropsychological Test Automated Battery. (Kollins et al., 2011)

3.2.1. Statistical analysis of efficacy data

All seven studies were included in the analysis of efficacy. Based on all randomized children who received at least

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Table 3 Assessment tools and inclusion criteria used in the reviewed RCTs (published data only).

	Efficacy measure							Study inclusion criteria
	ADHD-RS	CGI-I	CGI-S	CPRS-R	CTRS-R	PGA	Others1;*	
Ref.								
(Scahill et al., 2001a)	□	Δ		Δ[a]	Δ[a]		Δ[b]	DSM-IV diagnosis of ADHD, Conners hyperactivity index ≥ 1,5
(Biederman et al., 2008b)	□1;*	Δ	Δ	Δ	Δ	Δ		DSM-IV diagnosis of ADHD
(Sallee et al., 2009b)	□	Δ		Δ		Δ		DSM-IV diagnosis of ADHD, K-SADS-PL, ADHD-RS ≥ 24
(Connor et al., 2010)	Δ	Δ2;**	Δ	□ [a]				DSM-IV diagnosis of ADHD, K-SADS_PL, ADHD-RS ≥ 24, CPRS ≥ 14 (m) or ≥ 12 (f)
(Kollins et al., 2011)	□1;*	Δ					Δ[c]	DSM-IV diagnosis, ADHD-RS ≥ 24, CGI-S ≥ 4
(Newcorn et al., 2013)	□	Δ2;**						ADHD diagnosis, ADHD-RS-IV ≥ 28, CGI-S ≥ 4

□ used as primary efficacy measure; Δ used as secondary efficacy measure.
DSM-IV-TR= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; K-SADS-PL=Kiddie-Sads-Present and Lifetime Version; ADHD-RS= ADHD Rating Scale; CGI-S= Clinical Global Impression - Severity scale; CGI-I= Clinical Global Impression of Improvement; CPRS =Conners' Parent Rating Scale; CTRS= Conners' Teacher Rating Scale; PGA= Physician Global Assessment.
*studies evaluating also the ADHD-RS Inattention and Hyperactivity/Impulsivity Subscale.
**not reported in the published paper, but available in the clinicaltrials.gov register.
[a]Only a subscale of CPRS was used in these studies (Hyperactivity Index in Scahill et al.; Oppositional Subscale in Connor et al.).
[b]Yale Global Tic Severity Scale, Children's Yale-Brown Obsessive Compulsive Scale, Continuous Performance Test.
[c]Choice Reaction Time (CRT).

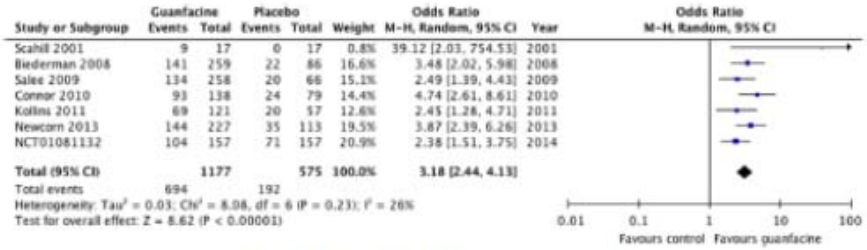

Fig. 2 Meta-analysis of efficacy endpoint (CGI-I).

1 dose of study drug, 59.0% of children in the guanfacine group benefited from the treatment compared with 33.3% in the placebo group. The pooled odds ratio was 3.18 (95%CI 2.44-4.13). The number needed to treat for benefit was 3.9 (95%CI 3.3-4.8). Between-studies heterogeneity accounted for 26% (P=0.23) (Fig. 2).

The results of meta-analysis did not change when using fixed effect model (OR 3.20, 95%CI 2.57-3.98) or when excluding the study by Scahill et al. (small study evaluating immediate release guanfacine), with a pooled odds ratio of 3.11 (95%CI 2.48-3.90). When the sample chosen for statistical analysis was the completer population, the pooled odds ratio increased to 6.28 (95% CI 3.70-10.66).

3.3. Safety

All studies evaluated the safety profile of guanfacine compared with placebo and mentioned safety monitoring in the methods section. Generally, assessments of adverse events (AEs) were performed in all visits and were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Only in Scahill et al. were adverse events systematically assessed using a modified version of the Systematic Assessment for Treatment of Emergent Events (SAFTEE). (Scahill et al., 2001a)

The Pediatric Daytime Sleepiness Scale was used in the Newcorn et al. study (Newcorn et al., 2013)

AEs were classified as treatment-emergent AEs (TEAEs) if they started or worsened between a subject's first dose of medication and the third day (inclusive) after treatment was stopped. Four out of seven trials defined TEAEs in the methods section of the published article. Six out of the seven studies were included in the adverse events' analysis. Scahill et al.'s study was excluded because, differently from the other five studies, authors did not report the number of participants who experienced at least one adverse event, nor the distributions of adverse events in the drug treated

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and placebo groups. (Scahill et al., 2001a) Nevertheless, the most common adverse events reported by Scahill et al. were similar to those reported in the studies considered in our analysis. (Scahill et al., 2001a)

The resulting safety population included a total of 1704 subjects, 1150 (67.5%) of whom were drug treated and 554 (32.5%) of whom received placebo. Two studies considered as their safety population only subjects who received at least 1 dose of study drug.

All six trials reported the number of subjects who experienced at least one TEAE, both in the placebo and the drug treated subjects.

Overall, 948 (82.4%) participants in the guanfacine group experienced at least one TEAE compared with 376 (67.9%) in the placebo group. The pooled Odds Ratio (OR) was 2.62 (95% CI 1.57-4.38). Between-studies heterogeneity accounted for 74% (P=0.002) (Fig. 3).

Five trials reported all the most common TEAEs that occurred in ≥ 5% in either treatment group (safety population), while Kollins et al. only reported the most common TEAEs that were observed at a higher incidence with guanfacine than placebo. (Kollins et al., 2011) Combining data from these 6 articles, the most common TEAEs were somnolence (30.1%), headache (19.4%), fatigue (11.5%), and upper abdominal pain (8.6%) (Table 4). Somnolence, upper abdominal pain, and sedation were reported in all six studies, while headache and fatigue were only in five. Overall, the above TEAEs were more frequent in the guanfacine than in the placebo group.

Based on a sub-analysis of the most frequent TEAE, an increased OR in guanfacine treated patients was found for somnolence (OR 4.86; 95%CI 2.68-8.81), headache (OR 1.60; 95%CI 1.18-2.17), fatigue (OR 2.23; 95%CI 1.50-3.33). upper abdominal pain (OR 1.77;95%CI 1.06-2.95), sedation (OR 2.79; 95%CI 1.22-6.35), and irritability (OR 1.98; 95%CI 1.14-3.44) (Figs. S1-S6).

Many TEAEs were mild and transient. A total of 68 subjects experienced a severe TEAE (4.9%), 64 (6.4%) of whom were drug treated and 4 (1.0%) placebo treated (OR 4.65, 95%CI 1.04-20.81).

Serious AEs (SAEs) occurred in all six studies, for a total of 15 children. Among these 15 children, only 3 received placebo and experienced lower limb fracture (n=1), clavicle and pelvic fracture (n=1), and ovarian cyst rupture (n=1). The 12 drug-treated children experienced the following SAEs: asthma (n=2), syncope (n= 2), loss of consciousness (n=2), concussion and convulsion (n=2), pneumotorax (n=1), self-injurious/suicidal ideation (n=1), suicidal ideation (n=1), homicidal ideation (n=1), and abdominal pain and vomiting (n=1). Three SAEs were judged to be related to the study drug: two cases of syncope and one case of self-injurious/suicidal ideation. (Newcorn et al., 2013) No subjects died during the studies.

Discontinuation rate due to any AEs was reported in all six studies. A total of 104 subjects discontinued for any AE, among which 95 (9.5%) were in the guanfacine and 9 (2%) in the placebo group (OR 4.16; 95%CI 1.10-15.64).

Four out of six studies reported the most common TEAEs leading to discontinuation. Thirty-eight out of 104 (36.5%) subjects who discontinued due to TEAEs experienced somnolence or sedation. All of them were treated with guanfacine. Nevertheless, the risk of discontinuation from the studies in children experiencing somnolence or sedation did not significantly differ from the risk of discontinuation due to other TEAE (Relative Risk 0.85; 95%CI 0.55-1.33; χ^2 0.60 p=0.5).

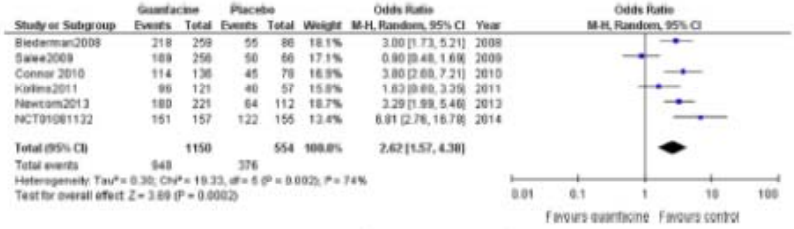

Fig. 3 Meta-analysis of safety endpoint.

Table 4 Most common TEAEs in safety population (listed in at least four studies).

	Placebo			Guanfacine			Total	
	N	%	95%CI	*N*	%	95%CI	*N*	%
Any TEAE	376/554	67.9	64.0-71.8	948/1150	82.4	80.2-84.6	1324/1704	77.7
Somnolence	75/554	13.5	10.7-16.4	438/1550	38.1	35.3-40.9	513/1704	30.1
Headache	72/468	15.4	12.1-18.7	192/891	21.5	18.8-24.3	264/1359	19.4
Fatigue	31/497	6.2	4.1-8.4	145/1029	14.1	12.0-16.2	176/1526	11.5
Upper abdominal pain	30/554	5.4	3.5-7.3	116/1550	10.1	8.3-11.8	146/1704	8.6
Sedation	16/554	2.9	1.5-4.3	125/1550	10.9	9.1-12.7	141/1704	8.3
Dizziness	28/497	5.6	3.6-7.7	76/1029	7.4	5.8-9.0	104/1526	6.8
Nausea	29/497	5.8	3.8-7.9	64/1029	6.2	4.7-7.7	93/1526	6.1
Irritability	17/497	3.4	1.8-5.0	67/1029	6.5	5.0-8.0	84/1526	5.5

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Overall, all studies evaluated the mean change from baseline to endpoint in cardiovascular parameters (ECG, heart rate, rhythm, QT interval for heart rate according to Fridericia factor (QFcT), and diastolic or systolic blood pressure), laboratory results, vital signs, height, and weight. On the whole, these changes were modest and not considered clinically meaningful. With regard to cardiovascular parameters, guanfacine was generally well tolerated. In subjects receiving guanfacine dose escalation, mean heart rate and systolic and diastolic blood pressure decreased as the dose of drug increased and returned toward baseline during the dose maintenance and dose tapering phases of the trial. ECG abnormalities considered clinically significant and possibly related to guanfacine were reported by Salee et al.(Sallee et al., 2009b) A case of first degree atrio-ventricular block and one of symptomatic sinus bradycardia, each occurring in one subject, were described.

No patient had a QRS interval ≥ 120 ms , QTcF interval ≥ 500 ms , or QTcF increase from baseline ≥ 60 ms at any time during 4 studies that monitored these parameters (Biederman et al., 2008b; Connor et al., 2010; Kollins et al., 2011; Sallee et al., 2009b).

Few, but significant ECG abnormalities leading to discontinuation were reported in two studies.(Biederman et al., 2008b; Connor et al., 2010) In the first, 7 children discontinued the study because of ECG abnormalities, one of whom received placebo. Among the 6 children in the guanfacine group, 4 discontinued because of QTc interval prolongation, 1 because of sinus bradycardia, and 1 because of "left anterior hemiblock". The child in the placebo group discontinued because of a QTc of >440 ms at screening. None of these findings were considered clinically meaningful.

In the second study, one child receiving guanfacine 2 mg/day discontinued after exhibiting bradycardia, sinus arrhythmia, sedation, and hypotension. All events resolved without treatment.

4. Discussion

Three papers reviewed trials concerning guanfacine and/or clonidine in the paediatric population,(Faraone et al., 2013; Hirota et al., 2014; Sallee et al., 2013) one of which performed a meta-analysis(Hirota et al., 2014). In our study the bibliographic search was updated to May 2014, and we were able to analyze also the trial by Newcorn et al. (Newcorn et al., 2013) and the NCT01081132 trial, not considered in the previous meta-analysis.

Our results confirm a favorable risk-benefit profile for guanfacine. Most participants in the guanfacine group benefited from the treatment; somnolence, headache, and fatigue were the most common adverse events, which generally resolved either spontaneously or after decreasing the dose of the study medication. Only a small risk of severe TEAEs was reported in guanfacine treated patients, and only three serious adverse events judged to be drug related were reported in one study (Newcorn et al., 2013). Small decreases from baseline in heart rate and blood pressure were noted, but only a few subjects experienced clinically significant ECG abnormalities.

Despite these positive findings, several considerations need to be made.

First of all, guanfacine efficacy was documented only versus placebo. Second, no details were reported in the papers concerning the number of children also receiving non-pharmacological interventions, an essential part of the management of ADHD symptoms (National Collaborating Centre For Mental Health, 2008), such as psychological interventions, parent/caregiver training, or behavioral or educational therapies, and whether these were equally distributed in the active drug versus control groups. From this point of view, it is not possible to evaluate whether groups were comparable. Third, the number of patients needed to be treated with guanfacine to gain one additional improvement was 3.9 (95%CI 3.3-4.8). With respect to other ADHD medications, based on NNT estimates after pooling results of placebo controlled trials, guanfacine seems to be similar to atomoxetine (NNT=3.4, 95%CI 2.79, 4.45),(Cheng et al., 2007) but less effective than methylphenidate (NNT=2.6; 95%CI 2.4-2.8) or amphetamine (NNT=2.0; 95% CI 1.7-2.2) in reducing ADHD symptoms.(Faraone and Buitelaar, 2010)

It is actually difficult to assess the efficacy of different medications in the absence of direct comparisons within the same study. Using the matching-adjusted indirect comparison methodology. Sikirica et al. observed a greater reduction of ADHD-RS-IV total scores from baseline to end of study in patients treated with GXR relative to atomoxetine (mean difference -7.0, standard error 2.2). (Sikirica et al., 2013) Until now, unfortunately, there are no published trials comparing guanfacine with other ADHD medications. On the contrary, when searching the clinical trial registries, two unpublished head to head studies were found: one, still ongoing, was comparing guanfacine, methylphenidate, and guanfacine +methylphenidate (clinicaltrials.gov NCT00429273), and one comparing guanfacine and atomoxetine (NCT01244490), was completed but with no results available. Our review underlines the need for head to head studies. It would be interesting not only to verify whether guanfacine is more or less effective than other medications in ADHD symptom resolution, but also to assess whether it may have some benefit for specific coexisting ADHD diseases. Despite all trials allowed the enrollment of children with ADHD and oppositional defiant disorder, only Sallee et al. study reported the percentage of children with both diseases (5.6%).(Sallee et al., 2009b)

Of interest, in the current review, only two studies took into consideration the effect of guanfacine on ADHD comorbidities, such as tic disorders and oppositional symptoms. Scahill et al., in a double blind, randomized, placebo controlled trial, noted that tic severity decreased by 31% in the guanfacine group, compared to 0% in the placebo group after 8 weeks of treatment.(Scahill et al., 2001a) Moreover, Connor et al. measured a significant reduction from baseline to endpoint (9 weeks) in CPRS-R:L oppositional subscale scores in the guanfacine group compared to placebo (10.9 versus 6.8; $p<0.001$; effect size=0.59). (Connor et al., 2010) Similar results on the improvement of tic disorders and oppositional symptoms in comorbid ADHD children was noted also for clonidine.(Connor et al., 2000; Tourette's-Syndrome-Study-Group, 2002) This finding could be useful for clinicians in choosing the best treatment option for their patients.

An additional consideration about guanfacine efficacy is that, to date, only one randomized controlled study tested

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the potential efficacy of guanfacine in addition to psychostimulant therapy. Wilens et al. evaluated the association guanfacine+psychostimulants versus psychostimulants alone in 461 children and adolescents diagnosed with ADHD who had had a suboptimal response to psychostimulants alone.(Wilens et al., 2012) The addition of guanfacine to psychostimulants achieved a significantly greater response in ADHD symptoms and generated no safety warning signs. The combination of α2-adrenergic agonists and psychostimulants for the management of ADHD is common in clinical practice. This combination has been suggested to have an effect on the underlying neurobiology of ADHD by different, but potentially synergistic, mechanisms.(Sallee, 2010) Despite clinical experience, studies supporting the safety and efficacy of combination therapy were, until recently, generally lacking. As for guanfacine, the addition of extended-release clonidine was associated with significant improvements (vs. placebo) in ADHD symptoms.(Kollins et al., 2011) Also immediate-release formulations of α2-adrenergic agonists, although not approved by the FDA as monotherapy nor in combination with other therapies in ADHD, have been used and studied as adjunctive therapy for ADHD, especially in patients with a coexisting disease (e.g., tic disorder and ODD).(Connor et al., 2000; Hazell and Stuart, 2003; Palumbo et al., 2008; Pohl et al., 2009; Tourette's-Syndrome-Study-Group, 2002) Across multiple studies, the safety and tolerability profile of guanfacine administered adjunctively to psychostimulants has been consistent with the known profiles of each medication. Together, these data support the use of guanfacine as an adjunct to psychostimulants for the treatment of ADHD (as approved in the USA), particularly among those children and adolescents not responding optimally to psychostimulant monotherapy. Additional studies may help identify other patients likely to benefit from such therapy.

In our analysis guanfacine resulted as generally well tolerated. Most TEAEs were mild or moderate, with only 7.1% of them classified as severe. Despite these positive findings, guanfacine's safety profile may generate some concerns. Indeed, a large number of children (about 80%) treated with guanfacine experienced a TEAE, and about 9% of drug treated children withdrew from the studies due to TEAE.

It should be noted that information on TEAE incidence in the monitored population was only reported if the incidence was above 5%. This complies with regulatory agencies' requirements, but details about rarely occurring TEAEs are not available. Another issue is that information on definitions and scales on which to assess and evaluate TEAE was not reported in the articles, making it impossible to examine this data.

Somnolence was the most common TEAE and an increased risk was found in guanfacine treated patients. Several studies were conducted aiming to explain the mechanisms by which somnolence could be triggered by α2 agonists. There is most likely a link between somnolence and the guanfacine affinity for α2a receptor subtypes expressed in neurons in the locus coeruleus and axons throughout the cortex.(Buzsaki et al., 1991) It has been recognized for a long time that the locus coeruleus is a crucial area in the control of the sleep-wake cycle; in particular, it has been suggested that noradrenaline containing neurons present in the locus coeruleus are be involved in initiating or maintaining stages of the sleep-wake cycle.(De Sarro et al., 1987)

All the results were retrieved from only short term studies lasting no more than 13 weeks. During this brief period, trials are able to identify only the most common adverse events. Furthermore, these short trials cannot assess whether guanfacine effects persist over the time. Only two open label extension studies of published trials were found, but did not meet inclusion criteria because they were not randomized trials.(Biederman et al., 2008a; Sallee et al., 2009a) It is interesting to note that results from these studies were similar to those of the current study; indeed, ADHD-RS total score improved significantly from baseline to endpoint, the majority of adverse events were mild to moderate, and only a few patients discontinued early from the study because of an adverse event. Since ADHD symptoms continue into adulthood for more that 50% of children, and ADHD medications need to be prescribed for long term treatment in many patients,(Lara et al., 2009) there is a need for long-term safety and efficacy studies. There is an ongoing clinical trial aimed at assessing the long term efficacy of guanfacine treatment (clinicaltrials.gov NCT 01500694), with a 2 year follow up.

Inclusion criteria and efficacy measures differed among the included studies. Up to four inclusion criteria were used in the studies and none of the studies used the same criteria to define the eligible population. The studies also differ in terms of efficacy measurements in that they were not fully concordant regarding the tools to be used. Among a total of 11 different tools, ADHD-RS and CGI-I were the most frequently used measures of efficacy. Nevertheless, there was great heterogeneity in the methods used to report results based on these tools. For example, some studies reported the percentage of improvement from baseline to endpoint, while others the mean reduction in the total score. Also the effect size was reported differently, depending on the dose optimization or fixed schedule. All studies measured the response to treatment using the CGI-I scale (score ≤ 2). The ADHD-RS seems to be the preferred measure of efficacy in ADHD trials, even if no study defined the response to treatment on criteria based on this endpoint (e.g. based on a predefined percentage reduction of the ADHD-RS score). The heterogeneity in inclusion criteria and efficacy measures is not exclusive of ADHD clinical trials but it was observed in RCTs evaluating treatment for other mental health disorders. (Usala et al., 2008) The research community should nevertheless find a consensus on how to employ these tools.

Some differences between studies were noted also in the dosage schedule; some studies used a dose optimization schedule, others a fixed schedule. As a consequence, the results could not be stratified by dosage. Despite the above mentioned differences, all studies included in this review were similar in design and setting, treatment duration, the mean daily dosage, as well as in number, age, and gender of included patients. Additionally, with the exception of the study by Scahill et al., the first to be published and with a sample size that could make it be considered a kind of "pilot study", the other six RCTs were performed in the last five years and were funded by the manufacturer. It should be noted that the trend in the current literature is still moving towards the replication of similar studies, even if this may

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partly be the consequence of the regulatory requirements for drug approval. Indeed, from searching the clinical trials registers, it was found that, only 2 trials differed from the previously published trials in that they had ADHD standard therapy (methylphenidate or atomoxetine) as a control. From this point of view, a risk of an unnecessary drug experimentation in the pediatric population seems to exist, raising ethical concerns.(Clavenna et al., 2002) Scientific community and regulatory agencies should make every effort to reduce unnecessary replication of trials, in particular in vulnerable populations.(Chalmers et al., 2014; European Commission, 2008) Moreover, the lack of comparative studies may reflect the interests of the market rather than those of patients and health service. (Garattini and Chalmers, 2009)

In conclusion, on the basis of seven randomized, placebo controlled trials, guanfacine resulted safe and effective in the treatment of children and adolescents with ADHD. No published studies have ever compared guanfacine versus other drugs or other, non pharmacological, kinds of treatment, so more evidence is needed to assess the role of guanfacine in ADHD therapy.

Conflict of interest

The authors have no conflict of interest to disclose regarding the content of this manuscript.

Contributors

MB, ACa and FR were responsible for initiation, design and direction of the review.

MB and ACl wrote the protocol. SR, ACl retrieved the studies, extracted and analyzed the data. All authors interpreted and discussed the results. SR, ACl and LR wrote the first draft of themanuscript, which was discussed and implemented by all authors. All authors have approved the final manuscript.

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Appendix A. Supporting information

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BRIEF REPORT

Human endogenous retroviruses and ADHD

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Abstract

Objectives. Several lines of evidences suggest that human endogenous retroviruses (HERVs) are implicated in the development of many complex diseases with a multifactorial aetiology and a strong heritability, such as neurological and psychiatric diseases. Attention deficit hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that results from a complex interaction of environmental, biological and genetic factors. Our aim was to analyse the expression levels of three HERV families (HERV-H, K and W) in patients with ADHD. *Methods.* The expression of retroviral mRNAs from the three HERV families was evaluated in peripheral blood mononuclear cells (PBMCs) from 30 patients with ADHD and 30 healthy controls by quantitative RT-PCR. *Results.* The expression levels of HERV-H are significantly higher in patients with ADHD compared to healthy controls, while there are no differences in the expression levels of HERV-K and W. *Conclusions.* Since the ADHD aetiology is due to a complex interaction of environmental, biological and genetic factors, HERVs may represent one link among these factors and clinical phenotype of ADHD. A future confirmation of HERV-H overexpression in a larger number of ADHD patients will make possible to identify it as a new parameter for this clinical condition, also contributing to deepen the study on the role of HERVs in the neurodevelopment diseases.

Key words: *Human endogenous retrovirus, HERV-H, ADHD, neurodevelopmental diseases, peripheral blood mononuclear cells*

Introduction

Human endogenous retroviruses (HERVs) are considered to be remnants from ancient germ line infections with exogenous retroviruses. In humans HERVs are generally non-functional, although a few proviruses have retained intact genes, and the corresponding proteins can be expressed (de Parseval and Heidmann 2005). During evolution, HERVs were amplified and spread throughout the human genome by repeated events of retrotransposition and/or reinfection and they are integrated as provirus in chromosomal DNA (Bannert and Kurth 2006). Approximately 50% of the human genome derives from unstable retroelements and HERVs represent about 8% of chromosomal DNA (International Human Genome Consortium 2001). Their integration in any location of the human genome may alter the structure and/or function of genes (Bannert and Kurth 2006; Rowe and Trono 2011). Although most HERVs sequences are inactivated by mutations or deletions or silenced by epigenetic modifications (Gogvadze and Buzdin 2009), their potential responsiveness to environmental factors play an important role in gene–environment interactions (Feschotte and Gilbert 2012). Therefore, the inappropriate expression of HERV genes may initiate or maintain pathological processes implicated in many complex diseases with multifactorial aetiology and genetic basis, including neurological and psychiatric disorders such as multiple sclerosis (Christensen 2010), schizophrenia and bipolar disorder (Yolken et al. 2000; Perron et al. 2012). New information on the role of HERVs in the pathogenesis of neurodevelopmental disorders result from our recent study on the

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expression of three HERV families (HERV-H, K and W), selected on the basis of the frequency of their involvement in human diseases, in autism spectrum disorder (ASD). This study demonstrated for the first time the higher expression of HERV-H in patients with ASD compared to healthy controls (Balestrieri et al. 2012). In order to extend the knowledge of the HERVs involvement in the aetiology of neuropsychiatric diseases, we chose to study the expression of the same three HERV families in another neurodevelopmental disorder, attention deficit hyperactivity disorder (ADHD). ADHD is characterized by persistent and pervasive symptoms of inattention, hyperactivity and impulsivity. Current diagnostic criteria require that symptoms appear prior to the age of 7 years and are expressed in at least two settings for at least 6 months (American Psychiatric Association 2000). ADHD affects 3–8% of children world-wide (Steinhausen 2009; Willcutt 2012). Age-inappropriate levels of inattention and hyperactivity/impulsivity in patients with ADHD could reflect an atypical or typical but delayed neurodevelopment (for review see Chandan 2012). As well as ASD, ADHD has also a multifactorial aetiology and a strong heritability and is considered to be the result of a complex interaction of environmental, biological and genetic factors (DasBanerjee et al. 2008; Curatolo et al. 2009; Pluess et al. 2009). Twin family and adoptions studies of ADHD have supported a strong genetic aetiology for the disorder, with a heritability ranging from 60 to 90% (Gize et al. 2009; Sharp et al. 2009). While the high heritability of ADHD is well established, the exact underlying causes and relevant mutations have not yet been clarified. In this framework, HERVs could represent the interface among genes, environment and clinical phenotype of ADHD. The aim of this pilot study is to verify the involvement of HERVs in patients with ADHD. In order to verify this hypothesis we analysed the expression levels of HERV-H, K and W families in blood samples of drug-naive patients with ADHD compared to healthy controls.

Materials and methods

Participants

Participants included 60 drug-naive subjects: 30 patients with ADHD (27 male and three female; age ranging from 6 to 17 years; median: 11.00; interquartile range: 9–12.25) and 30 healthy controls, matched for age and sex (27 male and three female; age ranging from 6 to 17 years; median: 11.00; interquartile range: 8–13.00). All participants were Caucasian and there are no economic, social and cultural differences. Subjects with ADHD were consecutive referrals at the Child Neurology and Psychiatry Unit of "Tor Vergata" University of Rome and they exhibited an IQ ≥ 85 by Wechsler Intelligence Scale for Children – III Edition (Wechsler 1991). In accordance with the DSM-IV-TR criteria (American Psychiatric Association 2000), the diagnosis of ADHD was based on clinical assessment, observations of children and interviews with parents and children, which were carried out by an experienced child psychiatrist. Both the long version of Conners' Parents Rating Scale-Revised (CPRS-R:L; Conners 2007a) and the Conners' Teachers Rating Scale-Revised (CTRS-R:L; Conners 2007b) were used. Interviews from the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997) were used to exclude other comorbidities in patients with ADHD. The healthy controls were recruited among those attending the outpatient facilities of the "Tor Vergata" University Hospital of Rome for routine control visits. None of them had a history of neurological or psychiatric disorders, learning disability or infectious diseases. At the time of the study, no participants were taking medication known to affect the central nervous system. The study procedure was approved by the Child Psychiatry and Neurology Institute Ethical Committee of our University, and before the testing, every parent or legal guardians of the subjects included in the study undersigned a written informed consent.

Samples preparation and RT-PCR analysis

Peripheral blood mononuclear cells (PBMCs) from heparinized blood samples from both ADHD and healthy control groups were analysed immediately after collection. The expression levels of the env sequence from HERV-H, K and W families were quantitatively assessed by real time RT-PCR, as previously described (Balestrieri et al. 2012). Briefly, 250 ng of DNase-treated RNA from ADHD and healthy controls (HC) were reverse-transcribed and amplified using primers specific for each HERV families using SYBR Green chemistry. Each experiment was completed with a melting curve analysis to confirm the specificity of amplification and the lack of non-specific comparative method. The relative expression was calculated as $2^{-[\Delta Ct(sample)-\Delta Ct(calibrator)]} = 2^{-\Delta\Delta Ct}$, where $^{\Delta}Ct(sample) = [Ct(HERVH/K/W\ env) - Ct(house\ keeping\ gene)]$, and $\Delta Ct(calibrator)$ was the mean of ΔCT of all of the controls. The house keeping gene used to normalize the results was the glucoronidase beta gene (GUSB). Real time PCR results were represented by box plots, depicting mild (black dot) and extreme outliers (asterisk) for each group were showed.

Statistical analysis

The Mann–Whitney test was used to compare expression of HERVs families (HERV-H, K and W) between ADHD and HC groups. To determine any correlation between clinical parameters and HERVs expression, Spearman's rho correlation coefficient (Sperman's ρ) was calculated. Statistical analyses were done using the Statistical Package for Social Sciences SPSS software (version 17.0, Inc., Chicago, IL, USA). P values are indicated in the text, and in figures only for statistically significant comparisons (P values ≤ 0.050).

Results

HERV-H, K and W env gene expression levels

The expression levels of env gene of HERV-H, K and W, obtained from PBMCs of patients with ADHD and healthy controls by Real Time PCR were represented by box plot in Figure 1. HERV-H expression (Figure 1, panel A), shown as $2^{-\Delta\Delta Ct}$ in logarithmic scale, was elevated in PBMCs from patients with ADHD (median: 69.19; interquartile range: 39.70–105.08) compared to the healthy controls (median: 0.0212; interquartile range: 2.34–25.07). The analysis of the expression of HERV-K and W showed comparable levels in PBMCs from patients with ADHD compared to healthy controls (Figure 1, panels B and C, respectively). Median value for HERV-K in ADHD group was 9.31 (interquartile range: 0.02–78.53) and in healthy control group was 2.13 (interquartile range: 0.02–98.72); median value for HERV-W in ADHD group was 1.99 (interquartile range: 0.01–14.48) and in healthy control group was 2.37 (interquartile range: 0.01–9.64). The Mann–Whitney U-test revealed a significant difference between ADHD and HC groups in the expression of HERV-H ($P = 0.001$), but not for HERV-K ($P = 0.918$) and HERV-W ($P = 0.976$).

Correlations with Conners' scores

We next evaluated the association of HERV-H, K and W env expression in PBMCs from ADHD patients, with age, sex and the Conners' scores on each subscale obtained from the parents ($n = 30$) and teachers ($n = 26$) in the ADHD group. Spearman's ρ correlation coefficient analysis revealed a significant correlation between HERV-H expression and T score of inattention ($\rho = 0.536$; $P = 0.002$) (Figure 2, panel A) and hyperactivity/impulsivity ($\rho = 0.369$; $P = 0.045$) (Figure 2, panel B) at the Conners' Parent Rating Scale, while no significant correlation was observed with regard to other HERV families with any parameters analysed.

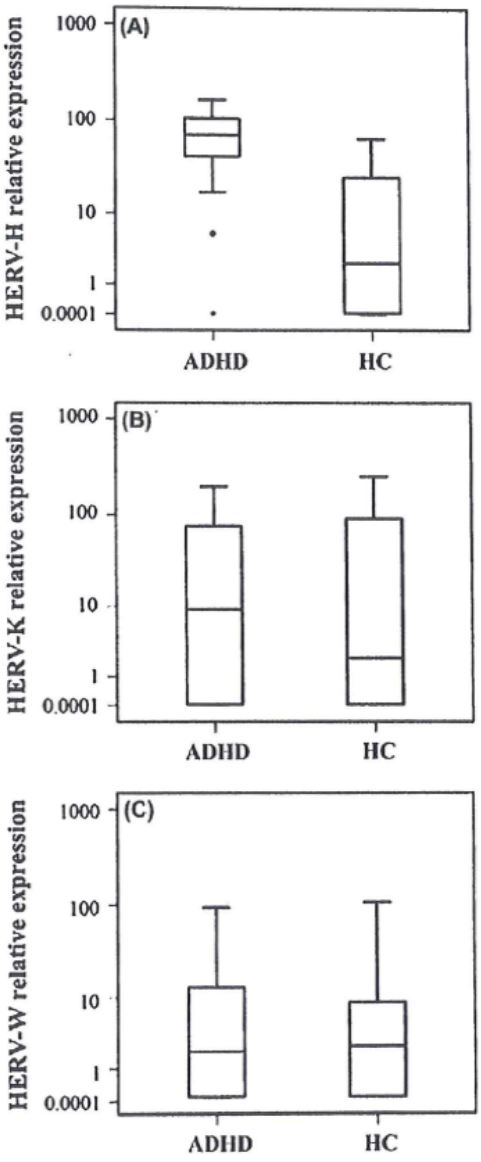

Figure 1. HERV-H, K and W env gene expression levels in PBMCs from patients with ADHD and healthy controls. Results obtained from Real Time PCR were represented as $2^{-\Delta\Delta Ct}$ by box-plot in logarithmic scale. Significant differences in expression levels between patients and healthy controls were observed for HERV-H (panel A), but not for HERV-K (panel B) and HERV-W (panel C).

Discussion

In order to investigate the potential involvement of HERVs in the pathogenesis of ADHD, in this study we analysed the expression of three HERV families (HERV-H, W and K) in blood samples from

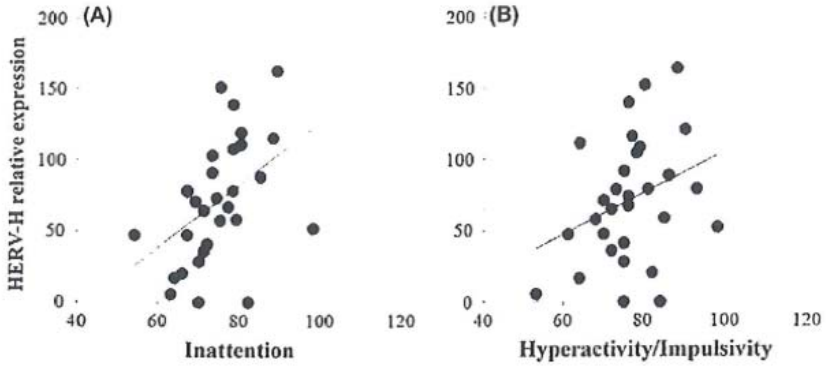

Figure 2. Correlation between HERV-H expression and T score of Inattention and Hyperactivity/Impulsivity. HERV-H mRNA levels, obtained from Real Time PCR, and ADHD symptoms, detected by the Conners' Parents Rating Scale, were represented by scatter plot. Data obtained showed positive significant correlation between the HERV-H expression and T score of inattention (panel A) and Hyperactivity/Impulsivity (panel B).

30 subjects with ADHD and 30 healthy controls. We have demonstrated that PBMCs from patients with ADHD show higher expression of HERV-H compared with healthy controls. We have also shown that expression level of HERV-W and K is comparable in PBMCs from patients with ADHD and healthy controls. The HERV-H overexpression is finally correlated with inattention and hyperactivity symptoms detected with CPRS. Despite the small number of subjects recruited, our findings seem to support the hypothesis that HERV-H overexpression could represent a new possible signature of susceptibility to ADHD. Scientific research has reported that HERVs integration in any location of the human genome may alter the structure and/or function of other genes (Bannert and Kurth 2006; Rowe and Trono 2011). In relation to this ability of HERVs, we hypothesize that they could interfere with the functioning of genes (coding for dopamine, dopamine receptors and the dopamine transporter) known to be involved in the pathogenesis of ADHD (Curatolo et al. 2009), suggesting their possible pathogenetic role in the disease expression. Several lines of evidence support the hypothesis that environmental, biological and genetic factors interact during early development to create a neurobiological susceptibility both to ADHD (Sonuga-Barke and Halperin 2010) and ASD (Lasalle 2013). Epidemiological studies have reported a high rate of ADHD-like symptoms in ASD (Holtmann et al. 2007; Simonoff et al. 2008; Sinzig et al. 2009). Moreover, the ADHD-like symptoms in ASD have been found to be approximately 6 times more frequent than that of ADHD in children and adolescents worldwide (Polanczyk et al. 2007). Similarly, autistic symptoms in patients with ADHD are more frequent than in healthy controls (Mulligan et al. 2009). This evidence suggests a co-occurrence of two disorders and this hypothesis is supported by the presence of common risk factors and the increase of one disorder in the presence of the other (Rhee et al. 2008). In this framework, our results extend the knowledge about HERVs involvement in the pathogenesis of neurodevelopmental disorders. Indeed, in a previous study, for the first time, we have demonstrated that PBMCs from ASD patients show a higher expression of HERV-H with respect to sex- and age-matched controls (Balestrieri et al. 2012). The results described in the present study were all obtained from drug-naive patients. This is of particular relevance because when the samples studied are under drug treatment the question arises as to whether the HERVs overexpression in patients may be due to the effect of drug treatment rather than to the disease. Indeed, recent studies on patients with psychiatric disorders documented a relationship between drug treatment and HERVs expression in brain tissue. In particular, patients with schizophrenia showed a significantly higher HERV-W transcription associated with valproic acid treatment (Diem et al. 2012), indicating the intrinsic potential of HERVs to change, depending to environmental conditions, during a lifetime. Finally, our findings contribute to support the hypothesis that HERVs are involved in the pathogenesis of many complex diseases with multifactorial aetiology and genetic basis, including psychiatric disorders such as schizophrenia and bipolar disorder, as recently proposed by other investigators (Perron et al. 2012; Leboyer et al. 2013), in agreement with the old viral hypothesis formulated by Crow (1984). HERVs expression is subject to epigenetic

modifications (Gogvatze and Buzdin 2009) which seem to be involved also in the pathogenesis of neurodevelopmental disorders such as ADHD (Mill and Petronis 2008) and ASD (Nguyen et al. 2010). It is known that epigenetic processes can be induced following exposure to a wide range of external factors, and thus provide a mechanism by which the environment can cause long-term alterations in phenotype. The dynamic nature of epigenetic processes may also offer new information about several non-Mendelian features, such as the incomplete concordance rates in monozygotic twins (Fraga et al. 2005; Mill et al. 2006; Wang et al. 2009; Ollikainen and Craig 2011) and the asymmetric distribution of disease between males and females (Gilberg 1995). Indeed, DNA sequence is stable and strongly conserved, on the contrary epigenetic processes are influenced by environmental factors and potentially highly dynamic even within an individual. Therefore enviromental factors may shape the epigenome over the life-course, according to the rate of DNA-synthesis (Fraga et al. 2005). This is in agreement with the observations that exposure to immune challenges and other potential stressors, such as infections and the age period during which they occur, may increase the risk of schizophrenia in genetically susceptible individuals (Benros et al. 2012). On this basis, the different HERVs expression levels observed in ASD and ADHD patients and healthy controls, according to the different age groups analysed, could also be explained (personal data). One possible limitation of our study is the small number of subjects recruited, but our ADHD patients are all drug-free, without psychiatric comorbidities at the time of the first diagnostic assessment, and from this point of view, our findings seem to support the hypothesis that HERV-H overexpression could be represent a new possible parameter of susceptibility to ADHD.

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Statement of Interest

None to declare.

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