



NEWSLETTER



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BIBLIOGRAFIA ADHD SETTEMBRE 2013

Afr J Psychiatry (Johannesbg). 2013 Sep;16:356-63.

CLINICAL AND PSYCHO-SOCIAL PROFILE OF CHILD AND ADOLESCENT MENTAL HEALTH CARE USERS AND SERVICES AT AN URBAN CHILD MENTAL HEALTH CLINIC IN SOUTH AFRICA.

Raman N, Janse van Rensburg AB.

OBJECTIVE: National and international child and adolescent mental healthcare policy and action advocate that the health and well being of children should be increasingly given greater attention. The purpose of this study was to describe the demographic, socio economic and clinical profile of the users at the child and adolescent mental health clinic of the Rahima Moosa Mother and Child Hospital (RMMCH).

METHOD: A descriptive, retrospective clinical audit from users' clinical files was performed over a one-year period from January to December 2007. Descriptive statistical analyses of demographic and socio-economic variables were made and these variables were compared with the presenting clinical problems. Odds ratios were calculated for variables that showed a statistically significant association (p-value less than 0.05).

RESULTS: A total of 303 users attended this clinic. Statistical comparisons between demographic data and disorders revealed that being male increased the likelihood of presenting with ADHD and disruptive behaviour disorders; being female increased the likelihood of being sexually abused. Race showed a significant association with parent-child relationship difficulties. Regarding socio-economic variables, the identity of the caregiver of the child influenced the risk of disruptive behaviour disorders, sexual abuse, neglect and academic problems. Where the child was placed was a risk factor for disruptive behaviour disorders, sexual abuse, neglect and academic problems. Whether the mother of a user was alive or deceased, was found to be related to ADHD and disruptive behaviour and whether the father of a user was alive or deceased, was found to be related to sexual abuse and academic problems. The education level of the caregiver showed a significant association with sexual abuse, neglect and academic problems; the marital status of the parent (widowed mother) showed a significant association with bereavement. Household income was associated with sexual abuse, neglect and academic problems.

CONCLUSION: This study demonstrated the impact that socio-economic circumstances have on the prevalence of childhood disorders; hence the urgent need for government and social welfare departments to improve the socio-economic status of communities. There is a need to improve psychiatric services for the population served by this hospital, including more clinics in its catchment area, as well as child psychiatry training posts and extended social work services.

Allergy. 2013 Sep.

NONALLERGIC COMORBIDITIES OF ATOPIC ECZEMA: AN OVERVIEW OF SYSTEMATIC REVIEWS.

Deckert S, Kopkow C, Schmitt J.

The aims of this overview are to synthesize the current evidence of published systematic reviews (SRs) on nonallergic comorbidities of atopic eczema (AE). EMBASE and MEDLINE were searched for SRs published from inception to November 2012. SRs were selected independently based on predefined inclusion criteria. Methodological quality of SRs included was assessed by two independent reviewers using the Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) checklist. Nine SRs met all inclusion criteria. Six reviews addressing the association between AE and cancer suggest a decreased risk of glioma, meningioma, and acute lymphoblastic leukemia in patients with current or previous AE. One SR reported a consistent positive association of AE with attention-deficit hyperactivity disorder (ADHD). Diabetes mellitus type 1 and multiple sclerosis (MS) were not significantly related to AE in reviews based

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.

on cross-sectional and case-control studies. Patients with AE appear to be at decreased risk of brain tumors. The relationship of AE with Th1- and Th17-mediated (auto-)inflammatory conditions such as diabetes mellitus type 1 and MS should be clarified in prospective observational studies. Children with AE are at increased risk of ADHD. SRs on the risk of depression and Th17-mediated disorders such as inflammatory bowel disease of patients with AE are missing.

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Allergy Asthma Immunol Res. 2013 Sep;5:315-21.

ALLERGIC DISEASES IN PRESCHOOLERS ARE ASSOCIATED WITH PSYCHOLOGICAL AND BEHAVIOURAL PROBLEMS.

Chang HY, Seo JH, Kim HY, et al.

PURPOSE: The aim of the present study was to investigate the relationship between three major allergic diseases, asthma, allergic rhinitis (AR), and atopic dermatitis (AD), and psychological and behavioural problems in preschoolers based on a community survey.

METHODS: A cross-sectional survey was conducted using a modified International Study of Asthma and Allergies in Childhood questionnaire to determine the prevalence of symptoms and diagnosed allergic diseases, and a Korean version of the Child Behaviour Checklist to assess internalizing, externalizing, and sleep problems among 780 preschoolers. Five-hundred and seventy-five preschoolers with valid data were included in this study.

RESULTS: The prevalence of lifetime diagnosis and treatment in the past 12 months was 8.7% and 4.4% for asthma, 24.4% and 19.2% for AR, and 35.1% and 16.6% for AD, respectively. Scores for internalizing and sleep problems were significantly higher in those diagnosed with AR. Preschoolers who had been treated for AD in the past 12 months had higher attention problem and attention-deficit/hyperactivity disorder scores. Sleep problems were more severe in moderate to severe AD compared to control and mild AD groups, categorised according to SCORing index of AD. The severity of sleep problems correlated positively with the percentage of eosinophils in peripheral blood.

CONCLUSIONS: Psychological and behavioural problems differed among the three major allergic diseases, weaker association for asthma and stronger association for AR and AD. The results of this study may lead to the identification of potential underlying shared mechanisms common to allergic diseases and psychological and behavioural problems.

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Am J Speech Lang Pathol. 2013 Sep.

USE OF THE CHILDREN'S COMMUNICATION CHECKLIST-2 FOR CLASSIFICATION OF LANGUAGE IMPAIRMENT RISK IN YOUNG SCHOOL-AGE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Timler GR.

PURPOSE: Children with ADHD are at elevated risk for language impairment (LI). This study examined the feasibility of using the Children's Communication Checklist-2 (CCC-2; Bishop, 2006) to classify risk for LI in young children, ages 5 to 8 years, with ADHD.

METHOD: Parents of 32 children with ADHD and 12 typical peers completed the CCC-2. The Clinical Evaluation of Language Fundamentals-4 (CELF-4) and the Test of Narrative Language (TNL) were administered to diagnose LI. Language samples were collected to examine clinical markers of LI.

RESULTS: CCC-2 General Communication Composite scores ≤ 85 correctly classified ten participants with ADHD diagnosed with LI as defined by composite scores ≤ 85 on the CELF-4 or TNL. Five of these participants demonstrated one or more clinical markers of LI in language samples. Three additional participants, who received a GCC score ≤ 85 , yet scored above 85 on language tests, demonstrated CCC-2 profiles suggestive of pragmatic impairment. Sensitivity and specificity rates were 100% and 85.29% respectively. CCC-2 scores and most measures were significantly correlated.

CONCLUSION: The results support the feasibility of using the CCC-2 as a screener to identify children with ADHD who are at elevated risk for LI and need referral for comprehensive assessment.

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Am J Addict. 2013;22:460-65.

DOES EXPOSURE TO PARENTAL SUBSTANCE USE DISORDERS INCREASE SUBSTANCE USE DISORDER RISK IN OFFSPRING? A 5-YEAR FOLLOW-UP STUDY.

Yule AM, Wilens TE, Martelon MK, et al.

Background This study examined the impact of exposure to parental substance use disorders (SUD) (alcohol or drug abuse or dependence) on the development of SUD in offspring.

Methods The original sample was derived from pediatric and psychiatric ascertained females 6-17 years old with (N = 140) and without Attention Deficit Hyperactivity Disorder (ADHD; N = 122). At baseline, these groups had 143 and 131 biological siblings and 274 and 238 parents, respectively. All subjects and their family members were comprehensively and blindly assessed by structured psychiatric interviews for psychopathology and substance use. The female probands and their siblings were reassessed after a follow-up period of 5 years.

Results At follow-up the mean age of offspring was 17.9 (plus or minus) 4.20 years. Independently of ADHD, familial risk, and socioeconomic status, exposure to maternal drug use disorders, but not paternal drug use disorders, was significantly associated with the development of a drug use disorder in offspring (OR: 7.04; p = 0.03). There was a significant association between exposure to parental SUD during adolescence (relative to preschool or latency years) and SUD in offspring (OR: 3.61; p = 0.03).

Conclusions Exposure to maternal drug use disorders during adolescent years increased the risk for the development of a drug use disorder in a sample of females with and without ADHD and their siblings. Exposure to parental SUD during adolescence specifically increases the risk of SUD development in offspring.

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Atten Defic Hyperact Disord. 2013 Sep.

SELF-REGULATION STRATEGIES SUPPORT CHILDREN WITH ADHD TO OVERCOME SYMPTOM-RELATED BEHAVIOR IN THE CLASSROOM.

Guderjahn L, Gold A, Stadler G, et al.

Children with attention deficit hyperactivity disorder (ADHD) suffer from self-regulation deficits that cause inattention, impulsivity, and hyperactivity. Self-regulation interventions may address these deficits, but to date, only few empirical studies have examined their benefits for children with ADHD in everyday life. The present study investigated three classroom interventions to promote self-regulation and tested their benefit on self-regulatory competencies (assessed with an ADHD questionnaire) in children with ADHD. Students of a special education school for children with ADHD participated in the intervention study that included three sessions (Session 1: Goal Intention or Goal Intention + If-Then Plan; Session 2: Goal Intention + If-Then Plan; Session 3: Goal Intention + If-Then Plan + Self-Monitoring). Teacher-rated self-regulatory competencies were assessed both before and after the intervention sessions. Children with ADHD had better self-regulatory competencies after their first Goal Intention + If-Then Plan Session, but lasting intervention effects were found only when children started with a mere goal intention session.

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Autism. 2013 Sep.

PSYCHOTROPIC MEDICATION USE AMONG CHILDREN WITH AUTISM SPECTRUM DISORDERS WITHIN THE SIMONS SIMPLEX COLLECTION: ARE CORE FEATURES OF AUTISM SPECTRUM DISORDER RELATED?

Mire SS, Nowell KP, Kubiszyn T, et al.

Psychotropic medication use and its relationship to autism spectrum core features were examined in a well-characterized but nonstratified North American sample (N = 1605) of children/adolescents diagnosed with autism spectrum disorders utilizing the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised, from the multisite Simons Simplex Collection. Analyses included (a) prevalence of psychotropic use (overall, and by classes), (b) correlations between prevalence of use and autism spectrum core features, age, and cognitive functioning, and (c) logistic regression to identify whether these

factors were predictive of psychotropic use. Results indicated 41.7% ever used one or more classes of psychotropic medications, with attention deficit hyperactivity disorder medications used most. Small but significant correlations between psychotropic medication use and (a) social impairment ($p < .001$) and (b) repetitive behaviors ($p < .001$) were found. Overall, however, autism spectrum disorder core features are weakly related to medication use. Older children used more psychotropics ($p < .001$), and higher cognitive functioning was associated with less overall psychotropic use ($p < .001$). Logistic regression indicated that use of psychotropics was predicted by repetitive behaviors (both clinician-observed and parent-reported), age, and cognitive ability level. Limitations inherent to the Simons Simplex Collection sample, methodology, and the correlational analyses are discussed. Directions for future research include investigation of factors more influential than core symptoms on psychotropic treatment (e.g. parent perceptions, comorbid symptoms).

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Biol Psychiatry. 2013 Oct;74:560-62.

TOWARD SYSTEMS NEUROSCIENCE OF SHARED AND DISTINCT NEURAL EFFECTS OF MEDICATIONS USED TO TREAT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Castellanos FX, Meyer E.

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Biol Psychol. 2013 Sep.

REPRINT OF "NEUROFEEDBACK AND STANDARD PHARMACOLOGICAL INTERVENTION IN ADHD: A RANDOMIZED CONTROLLED TRIAL WITH SIX-MONTH FOLLOW-UP".

Meisel V, Servera M, Garcia-Banda G, et al.

The present study is a randomized controlled trial that aims to evaluate the efficacy of Neurofeedback compared to standard pharmacological intervention in the treatment of attention deficit/hyperactivity disorder (ADHD). The final sample consisted of 23 children with ADHD (11 boys and 12 girls, 7-14 years old). Participants carried out 40 theta/beta training sessions or received methylphenidate. Behavioral rating scales were completed by fathers, mothers, and teachers at pre-, post-treatment, two-, and six-month naturalistic follow-up. In both groups, similar significant reductions were reported in ADHD functional impairment by parents; and in primary ADHD symptoms by parents and teachers. However, significant academic performance improvements were only detected in the Neurofeedback group. Our findings provide new evidence for the efficacy of Neurofeedback, and contribute to enlarge the range of non-pharmacological ADHD intervention choices. To our knowledge, this is the first randomized controlled trial with a six-month follow-up that compares Neurofeedback and stimulant medication in ADHD.

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BMC Pediatr. 2013 Sep;13:147.

PREDICTION OF 7-YEAR PSYCHOPATHOLOGY FROM MOTHER-INFANT JOINT ATTENTION BEHAVIOURS: A NESTED CASE--CONTROL STUDY.

Allely CS, Johnson PC, Marwick H, et al.

BACKGROUND: To investigate whether later diagnosis of psychiatric disorder can be predicted from analysis of mother-infant joint attention (JA) behaviours in social-communicative interaction at 12 months.

METHOD: Using data from a large contemporary birth cohort, we examined 159 videos of a mother-infant interaction for joint attention behaviour when children were aged one year, sampled from within the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. Fifty-three of the videos involved infants who were later considered to have a psychiatric disorder at seven years and 106 were same aged controls. Psychopathologies included in the case group were disruptive behaviour disorders, oppositional-conduct disorder, attention-deficit/hyperactivity disorder, pervasive development disorder, anxiety and depressive disorders. Psychiatric diagnoses were obtained using the Development and Wellbeing Assessment when the children were seven years old.

RESULTS: None of the three JA behaviours (shared look rate, shared attention rate and shared attention intensity) showed a significant association with the primary outcome of case-control status. Only shared look rate predicted any of the exploratory sub-diagnosis outcomes and was found to be positively associated with later oppositional-conduct disorders (OR [95% CI]: 1.5 [1.0, 2.3]; $p = 0.041$).

CONCLUSIONS: JA behaviours did not, in general, predict later psychopathology. However, shared look was positively associated with later oppositional-conduct disorders. This suggests that some features of JA may be early markers of later psychopathology. Further investigation will be required to determine whether any JA behaviours can be used to screen for families in need of intervention.

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BMC Psychiatry. 2013 Sep;13:237.

LONG-ACTING METHYLPHENIDATE FORMULATIONS IN THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW OF HEAD-TO-HEAD STUDIES.

Coghill D, Banaschewski T, Zuddas A, et al.

BACKGROUND: The stimulant methylphenidate (MPH) has been a mainstay of treatment for attention-deficit/hyperactivity disorder (ADHD) for many years. Owing to the short half-life and the issues associated with multiple daily dosing of immediate-release MPH formulations, a new generation of long-acting MPH formulations has emerged. Direct head-to-head studies of these long-acting MPH formulations are important to facilitate an evaluation of their comparative pharmacokinetics and efficacy; however, to date, relatively few head-to-head studies have been performed. The objective of this systematic review was to compare the evidence available from head-to-head studies of long-acting MPH formulations and provide information that can guide treatment selection.

METHODS: A systematic literature search was conducted in MEDLINE and PsycINFO in March 2012 using the MeSH terms: attention deficit disorder with hyperactivity/drug therapy; methylphenidate/therapeutic use and All Fields: Concerta; Ritalin LA; OROS and ADHD; Medikinet; Equasym XL and ADHD; long-acting methylphenidate; Diffucaps and ADHD; SODAS and methylphenidate. No filters were applied and no language, publication date or publication status limitations were imposed. Articles were selected if the title indicated a comparison of two or more long-acting MPH preparations in human subjects of any age; non-systematic review articles and unpublished data were not included.

RESULTS: Of 15,295 references returned in the literature search and screened by title, 34 articles were identified for inclusion: nine articles from pharmacokinetic studies (nine studies); nine articles from laboratory school studies (six studies); two articles from randomized controlled trials (two studies); three articles from switching studies (two studies) and three articles from one observational study.

CONCLUSIONS: Emerging head-to-head studies provide important data on the comparative efficacy of the formulations available. At a group level, efficacy across the day generally follows the pharmacokinetic profile of the MPH formulation. No formulation is clearly superior to another; careful consideration of patient needs and subtle differences between formulations is required to optimize treatment. For patients achieving suboptimal symptom control, switching long-acting MPH formulations may be beneficial. When switching formulations, it is usually appropriate to titrate the immediate-release component of the formulation; a limitation of current studies is a focus on total daily dose rather than equivalent immediate-release components. Further studies are necessary to provide guidance in clinical practice, particularly in the treatment of adults and pre-school children and the impact of comorbidities and symptom severity on treatment response.

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BMC Psychiatry. 2013 Sep;13:233.

PREDICTIVE PROPERTIES OF THE A-TAC INVENTORY WHEN SCREENING FOR CHILDHOOD-ONSET NEURODEVELOPMENTAL PROBLEMS IN A POPULATION-BASED SAMPLE.

Larson T, Lundstrom S, Nilsson T, et al.

BACKGROUND: Identifying children with childhood-onset neurodevelopmental problems (NDPs, defined here as autism spectrum disorders [ASDs], attention-deficit/hyperactivity disorder [AD/HD], tic disorders

[TDs], learning disorders [LDs] and development coordination disorder), using easily administered screening instruments, is a prerequisite for epidemiological research. Such instruments are also clinically useful to prioritize children for comprehensive assessments, to screen risk groups, and to follow controls. Autism--Tics, ADHD, and other Co-morbidities inventory (A-TAC) was developed to meet these requirements; here the A-TAC's prospective and psychometric properties are examined, when used in a population-based, epidemiological setting.

METHODS: Since 2004, parents of all Swedish twins have been asked to take part in an ongoing, nationwide twin study (The Child and Adolescent Twin Study in Sweden). The study includes the A-TAC, carried out as a telephone interview with parents of twins aged 9 or 12. In the present study, screen-positive twins from three birth year cohorts (1993--1995) were invited to a comprehensive clinical follow-up (blinded for previous screening results) together with their co-twins and randomly selected, healthy controls at age 15 (Total N = 452).

RESULTS: Sensitivity and specificity of A-TAC scores for predicting later clinical diagnoses were good to excellent overall, with values of the area under the receiver operating characteristics curves ranging from 0.77 (AD/HD) to 0.91 (ASDs). Among children who were screen-positive for an ASD, 48% received a clinical diagnosis of ASDs. For AD/HD, the corresponding figure was also 48%, for LDs 16%, and for TDs 60%. Between 4% and 35% of screen-positive children did not receive any diagnosis at the clinical follow-up three years later. Among screen-negative controls, prevalence of ASDs, AD/HD, LDs, and TDs was 0%, 7%, 4%, and 2%, respectively.

CONCLUSIONS: The A--TAC appeared to be a valid instrument to assess NDPs in this population-based, longitudinal study. It has good-to-excellent psychometric properties, with an excellent ability to distinguish NDPs (mainly ASDs) from non-NDPs at least three years after the screening evaluations, although specific diagnoses did not correspond closely to actual clinical diagnoses.

BMC Psychiatry. 2013 Sep;13:219.

AN OBSERVATIONAL STUDY OF RESPONSE HETEROGENEITY IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER FOLLOWING TREATMENT SWITCH TO MODIFIED-RELEASE METHYLPHENIDATE.

Hautmann C, Rothenberger A, Dopfner M.

BACKGROUND: Methylphenidate (MPH) has been shown to be effective in the treatment of attention deficit hyperactivity disorder (ADHD) in children. The overall population of children and adolescents with ADHD may comprise distinct clusters of patients that differ in response to MPH. The aim of this analysis was to look for subgroups with different treatment trajectories and to identify their distinctive features.

METHODS: OBSEER was a prospective, observational study examining the effectiveness and safety of once-daily modified-release MPH over 3 months in patients (aged 6--17 years) with ADHD under routine care. Assessments were carried out at baseline (Visit 1), after 1--3 weeks (Visit 2) and 6--12 weeks (Visit 3) after first use of once-daily modified-release MPH. Change in ADHD symptoms, as rated by parents and teachers, was examined post hoc in patients of the intent-to-treat-population (N = 822), using growth-mixture modelling to detect response trajectory groups after switching medication. Age, MPH dose at Visit 1 before medication switch, prescribed once-daily modified-release MPH dose at Visits 1 and 2, conduct problems and emotional symptoms were considered predictors of response subgroups.

RESULTS: Assessing formal statistical criteria and usefulness of the models, a 4-class solution best fitted the data: after switching medication two response groups with severe symptoms at study start and subsequent substantial treatment effects, and two showing no or comparatively little treatment effect, one of which had severe and the other less severe symptoms at study start. Patient age, conduct problems and MPH dose at Visit 1 were predictors of inclusion in subgroups.

CONCLUSIONS: Older children and children with few conduct problems were more likely to be members of a patient cluster with fewer symptoms at study start. Children with a low MPH dose before medication switch had a higher chance of being in the patient cluster with a strong treatment response after switching medication. The current analyses should assist in identifying children likely to achieve a favourable treatment course with MPH and, additionally, those who are in need of alternative treatment options.

BMJ Open. 2013;3:e003507.

IN UTERO EXPOSURE TO ANTIDEPRESSANT DRUGS AND RISK OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: A NATIONWIDE DANISH COHORT STUDY.

Laugesen K, Olsen MS, Telen Andersen AB, et al.

OBJECTIVE: To investigate whether in utero exposure to antidepressants is associated with increased risk of attention deficit hyperactivity disorder (ADHD).

DESIGN: Cohort study.

SETTING: Denmark.

PARTICIPANTS: All Danish singletons born alive from 1996 to 2009 were included. Using national medical registries, we defined in utero exposure to antidepressants as redemption of an antidepressant prescription by the mother 30 days prior to or during pregnancy. We defined maternal former users of antidepressants as women, who had redeemed a prescription up to 30 days prior to pregnancy, and never users as women who had never redeemed a prescription.

MAIN OUTCOME MEASURES: ADHD was defined as redemption of a prescription for ADHD medication or an ADHD hospital diagnosis. Children were followed through 2010, and we used proportional-hazards regression to compute adjusted HRs comparing children exposed in utero and children born to former antidepressant users with children born to never users. To adjust for confounding from family-related factors, we conducted a within-mother between-pregnancy analysis comparing exposed children with unexposed siblings using conditional logistic regression.

RESULTS: We identified a cohort of 877 778 children, of whom 1.7% were exposed in utero. The overall median follow-up time was 8 years; selective serotonin reuptake inhibitors were the most commonly used class of antidepressant during pregnancy (78% of users). The adjusted HR comparing children exposed to any antidepressant in utero with children born to never users was 1.2 (95% CI 1.1 to 1.4), and 1.6 (95% CI 1.5 to 1.8) comparing children born to former users to children born to never users of antidepressants. In the within-mother between-pregnancy analysis (n=867), the adjusted OR was 0.7 (95% CI 0.4 to 1.4).

CONCLUSIONS: This study provides no evidence to support a causal association between in utero exposure to antidepressants and risk of ADHD.

Brain Dev. 2013 Sep.

NO ASSOCIATION BETWEEN CATECHOL-O-METHYLTRANSFERASE (COMT) GENOTYPE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN JAPANESE CHILDREN.

Yatsuga C, Toyohisa D, Fujisawa TX, et al.

Objective: This study ascertained the association between attention deficit/hyperactivity disorder (ADHD) in Japanese children and a polymorphism of catechol-O-methyltransferase (COMT), a dopamine-control gene. The secondary aim of the study was the evaluation of a putative association between methylphenidate (MPH) effect/adverse effects and the COMT genotype.

Methods: To ascertain the distribution of the Val158Met variant of COMT, 50 children meeting ADHD inclusion criteria were compared with 32 healthy children. Clinical improvement and the occurrence of adverse effects were measured before and 3 months after MPH administration in children with ADHD, and analyzed for genotype association. Wechsler Intelligence Scale for Children-Third Edition (WISC-III), age, MPH dose were included as co-variables.

Results: The occurrence of the COMT Val/Val genotype was significantly higher in children with ADHD ($\chi^2(1)=7.13$, $p<0.01$). However, there was no significant difference in the Val/Val genotype according to disorder, and WISC and ADHD rating scale scores, after correcting for the interaction between disorder and COMT genotype. Furthermore, no significant difference in MPH effect/adverse effects was observed in association with the COMT genotype in the ADHD group.

Conclusions: These results showed a lack of association between the COMT Val/Val genotype and ADHD in Japan.

Can Fam Physician. 2013 Sep;59:947-48.

CAFFEINATED ENERGY DRINKS IN CHILDREN.

Goldman RD.

Question A 14-year-old boy came to my office to discuss his frequent consumption of energy drinks to enhance his performance at school and while playing soccer. What is the recommended use of energy drinks in children and is there any harm in consuming them? Answer Energy drinks are beverages with a high concentration of caffeine and additional stimulants. They are sold in numerous places and are easily accessed by children, adolescents, and young adults. Many reports warn about potential adverse effects associated with their consumption, especially in combination with alcohol among adolescents, and in combination with stimulant medications among children treated for attention deficit hyperactivity disorder. Children and adolescents should avoid energy drinks, and health care providers should educate youth and their parents about the risks of caffeinated drinks.

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Child Neuropsychol. 2013 Sep.

INHIBITION AND WORKING MEMORY IN YOUNG PRESCHOOL CHILDREN WITH SYMPTOMS OF ADHD AND/OR OPPOSITIONAL-DEFIANT DISORDER.

Skogan AH, Zeiner P, Egeland J, et al.

Background: Early symptoms of attention deficit/hyperactivity disorder (ADHD) and oppositional-defiant disorder (ODD) are associated with deficits in cognitive self-regulatory processes or executive functions (EF)s. However, the hypothesis that neurocognitive deficits underlying the two disorders are already evident during early preschool years still has limited empirical support. The present study investigated associations between symptoms of ADHD and/or ODD and two core EFs, inhibition and working memory, in a large nonclinical sample of 3-year old children.

Method: Participants were 1045 children (554 boys, age 37-47 months), recruited from the population based Norwegian Mother and Child Cohort Study (MoBa). Relations between behavioral symptoms and measures of inhibition and working memory were studied both categorically and dimensionally.

Results: Children with co-occurring symptoms of ADHD and ODD performed at a significantly lower level than typically developing children in 4 out of 5 EF measures. Symptoms of ADHD, both alone and in combination with ODD, were associated with reduced performance on tests of inhibition in the group comparisons. Dimensional analyses showed that performance within both EF domains contributed to variance primarily in ADHD symptom load. The associations between test results and behavioral symptoms remained significant after gender and verbal skills had been controlled.

Conclusion: Young preschoolers show the same pattern of relations between EF and behavioral symptoms of ADHD and/or ODD as previously described in older children diagnosed with ADHD and/or ODD. Effect sizes were generally small, indicating that measures of EF have limited clinical utility at this stage in development.

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Child Psychiatry Hum Dev. 2013 Sep.

ADDITIVE EFFECTS OF PARENT ADHERENCE ON SOCIAL AND BEHAVIORAL OUTCOMES OF A COLLABORATIVE SCHOOL-HOME BEHAVIORAL INTERVENTION FOR ADHD.

Villodas MT, McBurnett K, Kaiser N, et al.

The present study evaluated the impact of the Collaborative Life Skills Program (CLS), a novel school-home psychosocial intervention, on social and behavioral impairments among children with attention and behavior problems. Fifty-seven ethnically/racially diverse children (70 % boys) with attention and/or behavior problems in the second through fifth grades participated in a pilot study. Ten school-based mental health professionals were trained and then implemented the intervention at their respective schools. Children significantly improved from pre- to post-treatment on parent, teacher, and report card ratings of children's social and behavioral functioning. Treatment improvements were consistent for children with and without co-occurring disruptive behavior problems. The impact of the intervention was enhanced when

parents used the intervention strategies more regularly, according to both clinicians' and parents' reports. Findings support the emphasis of CLS on coordinating intervention strategies across contexts to facilitate the generalization of treatment-related improvements in social and behavioral functioning.

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Clin Neurol Neurosurg. 2013 Sep.

CLASSIFICATION OF ADHD AND BMD PATIENTS USING VISUAL EVOKED POTENTIAL.

Nazhvani AD, Boostani R, Afrasiabi S, et al.

OBJECTIVES: Children with Bipolar Mood Disorder (BMD) and those with Attention Deficit Hyperactivity Disorder (ADHD) share many clinical signs and symptoms; therefore, achieving an accurate diagnosis is still a challenge, especially in the first interview session. The main focus of this paper is to quantitatively classify the ADHD and BMD patients using their Visual Evoke Potential (VEP) features elicited from their Electroencephalogram (EEG) signals.

METHODS AND MATERIALS: In this study, 36 subjects were participated including 12 healthy ones, 12 patients with ADHD and 12 ones with BMD. The age of ADHD patients was 16.92 \pm 6.29 and for the BMD ones was 17.85 \pm 3.68. Their scalp EEG signals in the presence of visual stimulus were recorded using 22 silver electrodes located according to the 10-20 international recording protocol. To extract their VEP, first a preprocessing step was executed to remove the power line and movement artifacts. Afterward, the wavelet denoising and synchronous averaging were applied to the preprocessed trials in order to elicit the P100 component. To obtain interpretable features from the evoked patterns, amplitude and latency were extracted and applied to the 1-Nearest Neighbor (1NN) classifier due to the locally scattered distribution of the VEP features.

RESULTS: The evaluation was performed according to leave-one(subject)-out method and the experimental results were led to 92.85% classification accuracy which is a fairly promising achievement to distinguish the BMD, ADHD, and healthy subjects from each other.

CONCLUSION: From the physiological point of view, this result point out to the existence of significant difference in the neural activities of their visual system in the ADHD, BMD, and healthy subjects in response to a periodic optical stimulus.

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Clin Neuropharmacol. 2013 Sep;36:141-45.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND COMORBID SUBSYNDROMAL DEPRESSION: WHAT IS THE IMPACT OF METHYLPHENIDATE ON MOOD?

Golubchik P, Kodesh A, Weizman A.

BACKGROUND: Youths with attention-deficit/hyperactivity disorder (ADHD) may develop demoralization or depressive or dysthymic symptoms related to chronic social, familial, and academic difficulties that are associated with their ADHD and are at higher risk for developing mood disorders. We assessed the effectiveness of methylphenidate (MPH) on both ADHD and mood symptoms in children and adolescents diagnosed with ADHD and coexistent subsyndromal depression (SSD).

METHODS: A group of ADHD patients with SSD (n=47), aged 8 to 18 years, received 12 weeks of MPH treatment. The severity of depressive and ADHD symptoms was assessed using the Child Depression Rating Scale (CDRS) and the Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS), respectively.

RESULTS: A highly significant decrease in both ADHD-RS and CDRS scores was obtained in the total group (N=47) after MPH treatment (P=0.0001 and P=0.0001, respectively). A significant positive correlation was found between the changes in the CDRS total scores and the ADHD-RS (r=0.34, N=47, P=0.018). However, no such correlation was found in a subgroup (N=8) of patients with "possible depression" (baseline CDRS score, 65-74; r=0.026, P=0.95).

CONCLUSIONS: Methylphenidate treatment is effective for both ADHD and SSD symptoms. It seems that ADHD symptoms are less responsive to MPH in patients with relatively high CDRS scores (possible depression) and that those patients may be candidates for selective serotonin reuptake inhibitor treatment

as a supplement for MPH. Further, larger, placebo-controlled, double-blind studies are needed to examine the impact of MPH or d-amphetamine on patients with ADHD/SSD and ADHD/major depressive disorder.

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Environ Res. 2013 Sep.

LEAD, MERCURY, AND CADMIUM EXPOSURE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.

Kim S, Arora M, Fernandez C, et al.

BACKGROUND: There is limited research examining the relationship between lead (Pb) exposure and medically diagnosed attention deficit hyperactivity disorder (ADHD) in children. The role of mercury (Hg) and cadmium (Cd) exposures in ADHD development is even less clear.

OBJECTIVES: To examine the relationship between Pb, Hg, and Cd and ADHD in children living inside and outside a Lead Investigation Area (LIA) of a former lead refinery in Omaha, NE.

METHODS: We carried out a case-control study with 71 currently medically diagnosed ADHD cases and 58 controls from a psychiatric clinic and a pediatric clinic inside and outside of the LIA. The participants were matched on age group (5-8, 9-12 years), sex, race (African American or Caucasians and others), and location (inside or outside LIA). We measured whole blood Pb, total Hg, and Cd using inductively coupled plasma mass spectrometry.

RESULTS: Inside the LIA, the 27 cases had blood Pb geometric mean (GM) 1.89microg/dL and the 41 controls had 1.51microg/dL. Outside the LIA, the 44 cases had blood Pb GM 1.02microg/dL while the 17 controls had 0.97microg/dL. After adjustment for matching variables and maternal smoking, socioeconomic status, and environmental tobacco exposure, each natural log unit blood Pb had an odds ratio of 2.52 with 95% confidence interval of 1.07-5.92. Stratification by the LIA indicated similar point estimate but wider CIs. No associations were observed for Hg or Cd.

CONCLUSIONS: Postnatal Pb exposure may be associated with higher risk of clinical ADHD, but not the postnatal exposure to Hg or Cd.

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Epilepsy Behav. 2013 Sep.

FETAL ANTIPILEPTIC DRUG EXPOSURE: ADAPTIVE AND EMOTIONAL/BEHAVIORAL FUNCTIONING AT AGE 6 YEARS.

Cohen MJ, Meador KJ, Browning N, et al.

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study is a prospective observational multicenter study in the USA and UK, which enrolled pregnant women with epilepsy on antiepileptic drug (AED) monotherapy from 1999 to 2004. The study aimed to determine if differential long-term neurodevelopmental effects exist across four commonly used AEDs (carbamazepine, lamotrigine, phenytoin, and valproate). In this report, we examine fetal AED exposure effects on adaptive and emotional/behavioral functioning at 6 years of age in 195 children (including three sets of twins) whose parent (in most cases, the mother) completed at least one of the rating scales. Adjusted mean scores for the four AED groups were in the low average to average range for parent ratings of adaptive functioning on the Adaptive Behavior Assessment System-Second Edition (ABAS-II) and for parent and teacher ratings of emotional/behavioral functioning on the Behavior Assessment System for Children (BASC). However, children whose mothers took valproate during pregnancy had significantly lower General Adaptive Composite scores than the lamotrigine and phenytoin groups. Further, a significant dose-related performance decline in parental ratings of adaptive functioning was seen for both valproate and phenytoin. Children whose mothers took valproate were also rated by their parents as exhibiting significantly more atypical behaviors and inattention than those in the lamotrigine and phenytoin groups. Based upon BASC parent and teacher ratings of attention span and hyperactivity, children of mothers who took valproate during their pregnancy were at a significantly greater risk for a diagnosis of ADHD. The increased likelihood of difficulty with adaptive functioning and ADHD with fetal valproate exposure should be communicated to women with epilepsy who require antiepileptic medication. Finally, additional research is needed to confirm these findings in larger prospective study samples, examine potential risks associated with other AEDs,

better define the risks to the neonate that are associated with AEDs for treatment of seizures, and understand the underlying mechanisms of adverse AED effects on the immature brain.

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Eur Psychiatry. 2013 Sep.

ASSOCIATION BETWEEN ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDHOOD AND SCHIZOPHRENIA LATER IN ADULTHOOD.

Dalsgaard S, Mortensen PB, Frydenberg M, et al.

PURPOSE: To estimate the risk of schizophrenia in adulthood among children and adolescents with ADHD compared to the background population.

SUBJECTS/MATERIALS AND METHODS: Two hundred and eight youths with ADHD (183 boys; 25 girls) were followed prospectively. Diagnoses of schizophrenia were obtained from The Danish Psychiatric Central Register. The relative risk (RR) of schizophrenia for cases with ADHD, compared to the normal population, was calculated as risk ratios. Hazard ratios (HR's) by Cox regression were calculated in the predictor analyses.

RESULTS: Mean age for ADHD cases at follow-up was 31.1 years. Schizophrenia diagnoses were given to 3.8% of these cases. Compared to the general population, RR of schizophrenia in cases with ADHD was 4.3 (95% CI 1.9-8.57).

DISCUSSION AND CONCLUSION: This prospective follow-up study found children with ADHD to be at higher risk of later schizophrenia than controls. If replicated, these results warrant increased focus on the possible emergence symptoms of schizophrenia or schizophreniform psychosis during clinical follow-up of patients with ADHD.

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Eur Rev Med Pharmacol Sci. 2013 Sep;17:2345-49.

SWITCHING FROM IMMEDIATE RELEASE TO SUSTAINED RELEASE METHYLPHENIDATE IN THE TREATMENT OF CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Gormez V, Avery B, Mann H.

BACKGROUND: Switching from Immediate Release Methylphenidate (MPH-IR) to a sustained release formulation in treatment of attention deficit/hyperactivity disorder (ADHD) is often required to provide better compliance and convenience. However; the switch has been reported to be not always successful and small doses of MPH-IR may be added to sustained release preparations when its effect wears off.

SUBJECTS AND METHODS: In this survey, clinical case notes of 77 subjects aged 6-18 years who had been switched from MPH-IR to Concerta XL were retrospectively analyzed to demonstrate the effectiveness of the switch. The impact of adding MPH-IR to Concerta XL on the outcome was evaluated.

RESULTS: Switch to Concerta XL alone was successful in 94% of cases and all 23 (100%) subjects who had MPH-IR added to Concerta XL showed good response to the switch. However; more than 43% of the subjects required additional doses of MPH-IR and 55% needed a larger than recommended equivalent doses of Concerta XL for a successful switch.

CONCLUSIONS: Higher than equivalent doses of Concerta XL or an additional dose of MPH-IR may be required for a successful switch from immediate to sustained release methylphenidate.

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Eur Child Adolesc Psychiatry. 2013;1-4.

SCREENING FOR SUBSTANCE USE DISORDERS IN NEURODEVELOPMENTAL DISORDERS: A CLINICAL ROUTINE?

Palmqvist M, Edman G, Bolte S.

Evidence suggests that substance use disorders (SUD) tend to be underdiagnosed in psychiatry. The objective of this study was to investigate whether drug and alcohol screening is a clinical routine in the assessment of two prominent neurodevelopmental disorders, namely ADHD and autism spectrum disorder (ASD). We surveyed drug and alcohol screening routines in 34 general child and adolescent (only practice

for adolescents, not children, was assessed) and 29 adult psychiatric outpatient departments in Stockholm County, Sweden. Structured telephone interviews mapping SUD screening procedures were conducted with department representatives in charge. Only a minority of child and adolescent departments regularly used SUD screening questionnaires (6 %) in ADHD and ASD assessment, while this was more common in adult psychiatry (55 %). Urine/blood-based toxicology tests were always used in 28 % and sometimes or in case of clinical suspicion in 38 % of the adult units. Such tests were used sometimes or in case of clinical suspicion in 15 % of the child psychiatric departments, but never routinely. Findings reveal that screening for SUD in ADHD and ASD is not an integral part of routine clinical assessments in psychiatry, although increasingly an integral part of many clinical guidelines. Thus, SUD might be underdiagnosed in neurodevelopmental disorders, which could be particularly true for child and adolescent psychiatry settings.

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Front Psychol. 2013;4:564.

GROUP RHYTHMIC SYNCHRONY AND ATTENTION IN CHILDREN.

Khalil AK, Minces V, McLoughlin G, et al.

Synchrony, or the coordinated processing of time, is an often-overlooked yet critical context for human interaction. This study tests the relationship between the ability to synchronize rhythmically in a group setting with the ability to attend in 102 elementary schoolchildren. Impairments in temporal processing have frequently been shown to exist in clinical populations with learning disorders, particularly those with Attention Deficit Hyperactivity Disorder (ADHD). Based on this evidence, we hypothesized that the ability to synchronize rhythmically in a group setting—an instance of the type of temporal processing necessary for successful interaction and learning—would be correlated with the ability to attend across the continuum of the population. A music class is an ideal setting for the study of interpersonal timing. In order to measure synchrony in this context, we constructed instruments that allowed the recording and measurement of individual rhythmic performance. The SWAN teacher questionnaire was used as a measurement of attentional behavior. We find that the ability to synchronize with others in a group music class can predict a child's attentional behavior.

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Indian J Pediatr. 2013 Oct;80:826-31.

A 5-year hospital prevalence of child and adolescent psychiatric disorders from central India.

Khairkar P, Pathak C, Lakhkar B, et al.

OBJECTIVE: To examine the 5-year hospital prevalence of child and adolescent mental disorders from Central India.

METHODS: Using systemic random sampling method, of the 4410 families screened, 4278 children (607 aged 0 to 3 y and 3671 between 4 to 16 y) attending outpatient services of department of pediatrics at the tertiary rural hospital from June 2006 through December 2010 were evaluated. Standardized appropriate psychometric tools were used for both groups. Diagnostic interviews were administered and DSM-IV diagnoses were determined by consensus between two psychiatrists. A comprehensive hospital registration system provided the denominator.

RESULTS: Of the 4410 families screened, 4278 (97 %) of the subjects completed interviews. The overall prevalence of psychiatric disorders was found to be 20.8 %. Most common psychiatric disorders in group A were mental retardation (5.6 %) followed by epilepsy (2 %) whereas in group B, depressive disorder (3.73 %) were followed by non-organic enuresis (2.18 %) and ADHD (1.7 %). Eighty one percent of the parents from group A and 83 % of parents from group B of the children affected with psychiatric disorders and neurobehavioral problems had reported that they have had never thought of taking psychiatric consultation for their children.

CONCLUSIONS: The results of the study have helped in bridging and supporting the propositions in child epidemiology in India and also have implications for clinical training and practice.

Indian J Psychiatry. 2013 Jul;55:S379-S384.

FEASIBILITY AND EFFICACY OF YOGA AS AN ADD-ON INTERVENTION IN ATTENTION DEFICIT-HYPERACTIVITY DISORDER: AN EXPLORATORY STUDY.

Hariprasad VR, Arasappa R, Varambally S, et al.

CONTEXT: Attention deficit-hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders. Stimulant medication is frequently used in management, with significant adverse effects. There is a growing interest in complementary treatments like yoga.

AIMS: To study the effects of yoga as a complementary therapy in children with moderate to severe ADHD.

SETTINGS AND DESIGN: The study was performed on children (consent was taken from parents) admitted in a child psychiatry unit using an open-label exploratory study.

MATERIALS AND METHODS: Children between 5 and 16 years of age diagnosed with ADHD and co-operative for yoga were included. Subjects with other serious psychiatric and medical illnesses were excluded. The participants were given yoga training daily during their in-patient stay. They were rated on Conners' abbreviated rating scale - (CARS), ADHD-rating scale-IV (A).

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Innov Clin Neurosci. 2013 Jul;10:13-14.

ADDERALL-INDUCED TRICHOTILLOMANIA: A CASE REPORT.

Narine C, Sarwar SR, Rais TB.

Adderall (dextroamphetamine/amphetamine) is a psychostimulant medication approved by the United States Food and Drug Administration for the treatment of attention deficit hyperactivity disorder. This medication is usually well tolerated with minimal side effects. We report a case of a 12-year-old girl who was prescribed Adderall by her primary care physician to treat her attention deficit hyperactivity disorder and who subsequently developed trichotillomania. A short time following the initiation of the medication, the patient's family members noticed the patient displaying unusual hair-pulling behavior. The patient was referred to a psychiatrist for an evaluation of trichotillomania. Following a thorough evaluation, the decision was made to discontinue the Adderall and switch the patient to guanfacine. The urge to pull her hair along with her anxiety dissipated following this change. Close follow-up was maintained for over a year with both the psychiatrist and the primary care physician, and during this time the patient did not display any unusual hair pulling behaviors. This case appears to display a very unusual side effect of Adderall.

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Int J Hyg Environ Health. 2013 Aug.

URINARY 3,5,6-TRICHLORO-2-PYRIDINOL (TCPY) IN PREGNANT WOMEN FROM MEXICO CITY: DISTRIBUTION, TEMPORAL VARIABILITY, AND RELATIONSHIP WITH CHILD ATTENTION AND HYPERACTIVITY.

Fortenberry GZ, Meeker JD, Sanchez BN, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is the most commonly diagnosed and studied cognitive and behavioral disorder in school-age children. The etiology of ADHD and ADHD-related behavior is unclear, but genetic and environmental factors, such as pesticides, have been hypothesized. The objective of this study was to investigate the relationship between in utero exposure to chlorpyrifos, chlorpyrifos-methyl, and/or 3,5,6-trichloro-2-pyridinol (TCPY) and ADHD in school-age Mexican children using TCPY as a biomarker of exposure. The temporal reliability of repeated maternal urinary TCPY concentrations across trimesters was also explored (N=21). To explore associations with ADHD-related outcomes in children, third trimester urinary TCPY concentrations in were measured in 187 mother-child pairs from a prospective birth cohort. Child neurodevelopment in children 6-11 years of age was assessed using Conners' Parental Rating Scales-Revised (CRS-R), Conners' Continuous Performance Test (CPT), and Behavior Assessment System for Children-2 (BASC-2). Multivariable linear regression models were used to test relationships for all children combined and also stratified by sex. Intraclass correlation coefficients (ICC) calculations were based on a random effects model. The ICC was 0.41 for uncorrected TCPY, and ranged from 0.29 to 0.32 for specific gravity-corrected TCPY. We did not observe any statistically significant associations between tertiles of maternal TCPY concentrations and ADHD-related outcomes in children. However, compared to

the lowest tertile we found suggestive evidence for increased ADHD index in the highest TCPY tertile in boys (beta=5.55 points; 95% CI (-0.19, 11.3); p=0.06) and increased attention problems for the middle tertile in girls (beta=5.81 points; 95% CI (-0.75, 12.4); p=0.08). Considering the continued widespread agricultural and possible residential use of chlorpyrifos and chlorpyrifos-methyl in Mexico and the educational implications of cognitive and behavior deficits, these relationships deserve further study.

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J Abnorm Psychol. 2013 Aug;122:854-67.

THE ASSOCIATION OF ADHD AND DEPRESSION: MEDIATION BY PEER PROBLEMS AND PARENT-CHILD DIFFICULTIES IN TWO COMPLEMENTARY SAMPLES.

Humphreys KL, Katz SJ, Lee SS, et al.

Children with attention-deficit/hyperactivity disorder (ADHD) are at increased risk for the development of depression, with evidence that peer and academic difficulties mediate predictions of later depression from ADHD. In the present study, we hypothesized that parent-child relationship difficulties may be an additional potential mediator of this association. Academic, peer, and parent-child functioning were tested as mediators of the association of attention problems and depression in two distinctly different yet complementary samples. Study 1 was a cross-sectional sample of 5- to 10-year-old children (N = 230) with and without ADHD. Study 2 was a prospective longitudinal sample of 472 youth, followed prospectively from birth to age 20 years, at risk for depression. Despite differences in age, measures, and designs, both studies implicated peer and parent-child problems as unique mediators of depressive symptoms, whereas academic difficulties did not uniquely mediate the ADHD-depression association. Furthermore, inattention symptoms, but not hyperactivity, predicted depressive symptoms via the disruption of interpersonal functioning. The inclusion of oppositional defiant disorder into models impacted results and supported its independent role in parent-child problems. Implications include support for interventions that target interpersonal competence, which may effectively reduce the risk of depression among children with ADHD.

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J Atten Disord. 2013 Sep.

META-ANALYSIS: PARENTAL INTERVENTIONS FOR PRESCHOOL ADHD.

Mulqueen JM, Bartley CA, Bloch MH.

Objective: Although psychostimulants are commonly utilized to treat preschoolers with ADHD, side effects and parental preferences limit their use in younger children. The current meta-analysis examines the efficacy of parent interventions for the treatment of ADHD in preschoolers.

Method: We searched PubMed and the Cochrane Library for randomized, controlled trials comparing behavioral interventions for preschool children with ADHD. Our primary outcome measure was mean improvement in an ADHD rating scale compared with control conditions.

Results: Eight trials were included in the final analysis, totaling 399 participants. There was a significant benefit of parental behavioral interventions compared with control conditions (standardized mean difference [SMD] = 0.61, 95% confidence interval = [0.40, 0.83], z = 5.6, p < .001).

Conclusion: The present meta-analysis provides preliminary evidence that parental interventions are an efficacious treatment for preschool ADHD. Future research is needed to compare the relative efficacy of parental interventions for ADHD with medication management and to determine if the combination of parental training and medication management is more effective than either condition alone.

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J Atten Disord. 2013 Sep.

MORNING AND EVENING EFFECTS OF GUANFACINE EXTENDED RELEASE ADJUNCTIVE TO PSYCHOSTIMULANTS IN PEDIATRIC ADHD: RESULTS FROM A PHASE III MULTICENTER TRIAL.

Wilens TE, McBurnett K, Turnbow J, et al.

Objective: To examine efficacy and safety of adjunctive guanfacine extended release (GXR) on morning and evening ADHD symptoms using the Conners' Global Index-Parent (CGI-P) and Before-School Functioning Questionnaire (BSFQ).

Method: Participants 6 to 17 years with ADHD (N=461) and suboptimal psychostimulant response were maintained on current psychostimulants and randomized to dose-optimized GXR (≤ 4 mg/d) in the morning (GXR AM) or evening (GXR PM), or placebo.

Results: CGI-P scores improved with GXR (morning assessment, GXR AM, placebo-adjusted least squares [LS] mean=-1.7, GXR PM=-2.6; evening assessment, GXR AM=-2.4, GXR PM=-3.0; all $p < .01$). Parent-rated BSFQ scores reflected improved morning functioning with GXR (GXR AM, placebo-adjusted LS mean=-5.1; GXR PM=-4.7; both $p < .01$). Most adverse events were mild or moderate.

Conclusion: Adjunctive GXR AM or GXR PM was associated with improvements in morning and evening ADHD symptoms in children and adolescents.

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J Atten Disord. 2013 Sep.

DIFFERENTIAL EFFECT OF COGNITIVE TRAINING ON EXECUTIVE FUNCTIONS AND READING ABILITIES IN CHILDREN WITH ADHD AND IN CHILDREN WITH ADHD COMORBID WITH READING DIFFICULTIES.

Horowitz-Kraus T.

The comorbidity of ADHD and reading difficulties (ADHD+RD) is believed to be a disability distinct from ADHD alone, with unique challenges faced by individuals suffering from one disability versus the other. We aimed to examine the differential effect of 8 weeks of cognitive training on reading abilities and on executive functions, through use of the Wisconsin task, in children with ADHD and in children with ADHD+RD. Greater impairments in reading and executive functions, especially in speed of processing, were found in the comorbid group at baseline. The comorbid group showed greater improvements in most measures after training as well. We propose that the cognitive training used in the present study affected not only the immediate abilities of executive functioning but also the secondary ability of reading, especially in the comorbid group, by improving in particular, speed of processing. We suggest that a differential approach should be taken when treating children with ADHD+RD versus treating ADHD children.

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J Atten Disord. 2013 Sep.

DAILY SYMPTOM PROFILES OF CHILDREN WITH ADHD TREATED WITH MODIFIED-RELEASE METHYLPHENIDATE: AN OBSERVATIONAL STUDY.

Hautmann C, Rothenberger A, Dopfner M.

Objective: The aim was to identify subgroups of patients with ADHD with different daily symptom profiles and to characterize their response to modified-release methylphenidate (MR MPH) treatment, using data from the observational trial OBSEER.

Method: OBSEER included patients aged 6 to 17 years receiving MR MPH under routine care. To detect subgroups, a latent class cluster analysis was applied. Sex, age, MR MPH dose, and emotional symptoms were considered predictors of response.

Results: The analysis included 637 patients (81.3% male), with a mean age (standard deviation) of 10.1 (2.5) years. A two-class solution best fit the data, identifying a high-severity group (49.8%) with pronounced symptom reduction, and a low-severity group (50.2%) with minor changes throughout the day. Younger age, male sex, and higher MPH doses were predictive of the high-severity class.

Conclusion: Children with ADHD treated with MR MPH are heterogeneous, and subgroups with differential treatment response can be identified.

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J Atten Disord. 2013 Sep.

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

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

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

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

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

Conclusion: Results suggest that CAI offers a novel therapeutic strategy that may enhance cognitive-behavioral interventions for children with ADHD.

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J Atten Disord. 2013 Sep.

NEUROCOGNITIVE AND BEHAVIORAL PREDICTORS OF MATH PERFORMANCE IN CHILDREN WITH AND WITHOUT ADHD.

Antonini TN, Kingery KM, Narad ME, et al.

Objective: This study examined neurocognitive and behavioral predictors of math performance in children with and without ADHD.

Method: Neurocognitive and behavioral variables were examined as predictors of (a) standardized mathematics achievement scores, (b) productivity on an analog math task, and (c) accuracy on an analog math task.

Results: Children with ADHD had lower achievement scores but did not significantly differ from controls on math productivity or accuracy. N-back accuracy and parent-rated attention predicted math achievement. N-back accuracy and observed attention predicted math productivity. Alerting scores on the attentional network task predicted math accuracy. Mediation analyses indicated that n-back accuracy significantly mediated the relationship between diagnostic group and math achievement.

Conclusion: Neurocognition, rather than behavior, may account for the deficits in math achievement exhibited by many children with ADHD.

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J Atten Disord. 2013 Oct;17:565-73.

CASE REPORTS OF SLEEP PHENOTYPES OF ADHD: FROM HYPOTHESIS TO CLINICAL PRACTICE.

Miano S, Donfrancesco R, Parisi P, et al.

Objective: Five sleep ADHD phenotypes have been hypothesized: (a) the hypo-arousal state of the "primary" form of ADHD, (b) the sleep phase advanced disorder, (c) sleep disordered breathing (SDB), (d) restless legs syndrome and/or periodic limb movements disorder (PLMD), and (e) epilepsy.

Method: Five case reports are presented; each child but one underwent video-polysomnography.

Results: The first case report is an example of ADHD and SDB, with improvement of hypersomnolence after resolution of sleep apnea. The second case shows the impact of delayed sleep onset latency in the pathogenesis of ADHD, and the efficacy of melatonin. The third case report describes the association with

PLMD, with amelioration after iron supplementation. The other two cases are examples of ADHD and epilepsy, with clinical improvement after antiepileptic treatment was started.

Conclusion: A diagnostic and therapeutic algorithm should be designed to find the best first-line treatment for ADHD and sleep problems/epilepsy.

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J Atten Disord. 2013 Sep.

ASSOCIATION BETWEEN INSECURE ATTACHMENT AND ADHD: ENVIRONMENTAL MEDIATING FACTORS.

Storebo OJ, Darling RP, Simonsen E.

Objective: Psychological theories have postulated an association between insecure attachment and ADHD. The objective of this study is to investigate possible association between insecure attachment and ADHD in children and adults.

Method: Review of literature was performed using the PsycINFO, Medline, and EMBASE databases.

Results: Twenty-nine studies were included in the review. Overall, the studies showed that parental attachment problems and environmental mediating factors were significantly associated with childhood ADHD. Adults with ADHD had a much higher incidence of insecure attachment styles than reported in the general population.

Conclusion: There seems to be a clear association between ADHD and insecure attachment. It is likely that early intervention in the form of parent training and pharmacological treatment may prevent development of attachment problems. But such studies have not been carried out. Furthermore, adults with ADHD might need treatment for their lack of attachment competences as well. More research on this topic is much needed.

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J Autism Dev Disord. 2013 Sep.

CARDIAC REACTIVITY AND STIMULANT USE IN ADOLESCENTS WITH AUTISM SPECTRUM DISORDERS WITH COMORBID ADHD VERSUS ADHD.

Bink M, Popma A, Bongers IL, et al.

A large number of youngsters with autism spectrum disorders (ASD) display comorbid attention deficit/hyperactivity disorder (ADHD) symptoms. However, previous studies are not conclusive whether psychophysiological correlates, like cardiac reactivity, are different for ASD with comorbid ADHD (ASD+) compared to ADHD. Therefore, the current study investigated (dis)similarities in cardiac reactivity and attention task performance. In a clinical sample, adolescents diagnosed with ASD+ (n = 20) versus ADHD (n = 36) and stimulant medication use (56 %) were compared during a baseline with eyes closed and task performance. Results for cardiac reactivity were similar for both diagnostic groups. Stimulant-medicated adolescents showed decreased adaptation of LF/HF ratio and faster reaction times than stimulant-free adolescents. The current study underlines the psychophysiological overlap of ADHD symptoms in adolescents with ASD+ and adolescents with ADHD.

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J Child Adolesc Psychopharmacol. 2013 Sep;23:440-47.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DRUGS AND GROWTH: AN ITALIAN PROSPECTIVE OBSERVATIONAL STUDY.

Germinario EA, Arcieri R, Bonati M, et al.

Abstract Objective: This study was conducted to assess the long-term effect of methylphenidate (MPH) or atomoxetine (ATX) on growth in attention-deficit/hyperactivity disorder (ADHD) drug-naïve children.

Design: The study was an observational, post-marketing, fourth phase study.

Methods: Data on height and weight were collected at baseline and every 6 months up to 24 months.

Results: Both ATX and MPH lead to decreased height gain (assessed by means of z-scores); the effect was significantly higher for ATX than for MPH. At any time, height z-score decrease in the ATX group was

higher than the corresponding decrease observed in the MPH group, but the difference was significantly relevant only during the first year of treatment. An increment of average weight was observed both in patients treated with MPH and in those treated with ATX. However, using Tanner's percentile, a subset of patients showed a degree of growth lower than expected. This negative effect was significantly higher for ATX than for MPH.

Conclusions: We conclude that ADHD drugs show a negative effect on linear growth in children in middle term. Such effect appears more evident for ATX than for MPH.

J Child Adolesc Psychopharmacol. 2013 Sep;23:432-39.

FIVE-FOLD INCREASE IN NATIONAL PREVALENCE RATES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MEDICATIONS FOR CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, AND OTHER PSYCHIATRIC DISORDERS: A DANISH REGISTER-BASED STUDY.

Dalsgaard S, Nielsen HS, Simonsen M.

Abstract Objective: The purpose of this study was to estimate the prevalence and time trends in prescriptions of methylphenidate, dexamphetamine, and atomoxetine in children and adolescents, within three diagnostic groups: 1) autism spectrum disorder (ASD), 2) attention-deficit/hyperactivity disorder (ADHD), and 3) other psychiatric disorders.

Methods: Data from six different national registers were used and merged to identify a cohort of all children and adolescents born in Denmark between 1990 and 2001 (n=852,711). Sociodemographic covariates on cohort members and their parents and lifetime prescriptions of methylphenidate, dexamphetamine, and atomoxetine were extracted from the registers. Prescriptions were also stratified by duration (<6 months. vs. ≥6 months).

Results: Sixteen percent of 9698 children and adolescents with ASD (n=1577), 61% of 11,553 children and adolescents with ADHD (n=7021) and 3% of 48,468 children and adolescents with other psychiatric disorders (n=1537) were treated with one or more ADHD medications. There was a significant increase in prescription rates of these medications for all three groups. From 2003 to 2010, youth 6-13 years of age with ASD, ADHD, and other psychiatric disorders had 4.7-fold (4.4-4.9), 6.3-fold (6.0-6.4), and 5.5-fold (5.0-5.9) increases, respectively, in prescription rates of ADHD medications.

Conclusion: This is the largest study to date assessing stimulant treatment in children and adolescents with ASD, and is the first prospective study quantifying the change over time in the prevalence of treatment with ADHD medications in a population-based national cohort of children and adolescents with ASD. The prevalence of stimulant treatment in youth with ASD of 16% is consistent with earlier studies. The past decade has witnessed a clear and progressive increase in the prescription rates of medications typically used to treat ADHD in children and adolescents in Denmark. This increase is not limited to only those with ADHD, but includes others with neuropsychiatric disorders, including ASD. The risks and benefits of this practice await further study.

J Child Psychol Psychiatry. 2013 Oct;54:1038-46.

BIOLOGICAL AND REARING MOTHER INFLUENCES ON CHILD ADHD SYMPTOMS: REVISITING THE DEVELOPMENTAL INTERFACE BETWEEN NATURE AND NURTURE.

Harold GT, Leve LD, Barrett D, et al.

BACKGROUND: Families of children with attention deficit hyperactivity disorder (ADHD) report more negative family relationships than families of children without ADHD. Questions remain as to the role of genetic factors underlying associations between family relationships and children's ADHD symptoms, and the role of children's ADHD symptoms as an evocative influence on the quality of relationships experienced within such families. Utilizing the attributes of two genetically sensitive research designs, the present study examined associations between biologically related and nonbiologically related maternal ADHD symptoms, parenting practices, child impulsivity/activation, and child ADHD symptoms. The combined attributes of the study designs permit assessment of associations while controlling for passive genotype-environment

correlation and directly examining evocative genotype-environment correlation (rGE); two relatively under examined confounds of past research in this area.

METHODS: A cross-sectional adoption-at-conception design (Cardiff IVF Study; C-IVF) and a longitudinal adoption-at-birth design (Early Growth and Development Study; EGDS) were used. The C-IVF sample included 160 mothers and children (age 5-8 years). The EGDS sample included 320 linked sets of adopted children (age 6 years), adoptive-, and biologically related mothers. Questionnaires were used to assess maternal ADHD symptoms, parenting practices, child impulsivity/activation, and child ADHD symptoms. A cross-rater approach was used across measures of maternal behavior (mother reports) and child ADHD symptoms (father reports).

RESULTS: Significant associations were revealed between rearing mother ADHD symptoms, hostile parenting behavior, and child ADHD symptoms in both samples. Because both samples consisted of genetically unrelated mothers and children, passive rGE was removed as a possible explanatory factor underlying these associations. Further, path analysis revealed evidence for evocative rGE processes in the longitudinal adoption-at-birth study (EGDS) from biologically related maternal ADHD symptoms to biologically unrelated maternal hostile parenting through early disrupted child behavior (impulsivity/activation), with maternal hostile parenting and disrupted child behavior associated with later child ADHD symptoms, controlling for concurrent adoptive mother ADHD symptoms.

CONCLUSIONS: Results highlight the importance of genetically influenced child ADHD-related temperamental attributes on genetically unrelated maternal hostility that in turn links to later child ADHD symptoms. Implications for intervention programs focusing on early family processes and the precursors of child ADHD symptoms are discussed.

J Clin Psychiatry. 2013 Aug;74:821-27.

A RANDOMIZED PLACEBO-CONTROLLED TRIAL OF ELECTROENCEPHALOGRAPHIC (EEG) NEUROFEEDBACK IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Van Dongen-Boomsma M, Vollebregt MA, Slaats-Willemse D, et al.

OBJECTIVE: A double-blind, randomized, placebo-controlled study was designed to assess the efficacy and safety of electroencephalographic (EEG) neurofeedback in children with attention-deficit/hyperactivity disorder (ADHD). The study started in August 2008 and ended in July 2012 and was conducted at Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, The Netherlands.

METHOD: Forty-one children (aged 8-15 years) with a DSM-IV-TR diagnosis of ADHD were randomly assigned to treatment with either EEG neurofeedback (n=22) or placebo neurofeedback (n=19) for 30 sessions, given as 2 sessions per week. The children were stratified by age, electrophysiologic state of arousal, and medication use. Everyone involved in the study, except the neurofeedback therapist and the principal investigator, was blinded to treatment assignment. The primary outcome was severity of ADHD symptoms on the ADHD Rating Scale IV, scored at baseline, during treatment, and at study end. Clinical improvement as measured by the Clinical Global Impressions-Improvement scale (CGI-I) was a secondary outcome.

RESULTS: While total ADHD symptoms improved over time in both groups ($F_{1,39}=26.56$, $P<.001$), there was no significant treatment effect, ie, group x time interaction ($F_{1,39}=0.36$, $P=.554$); the same was true for clinical improvement as measured by the CGI-I ($P=.092$). No clinically relevant side effects were observed. Among the children and their parents, guessing treatment assignment was not better than chance level ($P=.224$ for children, $P=.643$ for parents).

CONCLUSION: EEG neurofeedback was not superior to placebo neurofeedback in improving ADHD symptoms in children with ADHD.

TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT00723684.

J Clin Psychopharmacol. 2013 Sep.

A RANDOMIZED, DOUBLE-BLIND COMPARISON OF ATOMOXETINE AND PLACEBO ON RESPONSE INHIBITION AND INTERFERENCE CONTROL IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER AND COMORBID Attention-Deficit/Hyperactivity Disorder Symptoms.

Anon.

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J Dent Child (Chic). 2013;80:67-70.

DENTAL CARE FOR CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Sujlana A, Dang R.

Attention deficit hyperactivity disorder (ADHD) is one of the most common biobehavioral disorders of childhood. ADHD has displayed increasing prevalence worldwide. Often, ADHD is mistaken for other problems, thus it is important that pediatric dentists identify and manage these children appropriately. This manuscript discusses how dental clinicians should treat children with ADHD.

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J Dev Behav Pediatr. 2013 Sep;34:469-77.

THE RELATIONSHIP BETWEEN ADHD SYMPTOM DIMENSIONS, CLINICAL CORRELATES, AND FUNCTIONAL IMPAIRMENTS.

Garner AA, O'connor BC, Narad ME, et al.

OBJECTIVE: To better understand how heterogeneity in attention-deficit hyperactivity disorder (ADHD) symptoms relates to heterogeneity in functional impairment domains in children with ADHD after accounting for demographic variables and comorbidities, in particular oppositionality and internalizing symptoms.

METHODS: Parents and teachers (n=5663) rated child/adolescent impairments across impairment domains in the International Classification of Functioning, Disability and Health as well as symptoms of ADHD and comorbidities. Hierarchical regressions were conducted to assess the relationship between parent and teacher ratings of ADHD symptom domains and functional impairments after accounting for personal factors and comorbid disorders.

RESULTS: Symptoms of inattention were the strongest predictors of ratings of academic (math, writing, and so on) functioning, while hyperactivity/impulsivity symptoms were the strongest predictor of classroom disruption even after accounting for the presence of learning disorders and oppositional symptoms. Symptoms of ADHD accounted for minimal variance in interpersonal functioning or participation in organized activities after controlling oppositional symptoms.

CONCLUSION: The ADHD symptom domains demonstrate domain-specific relations with various ADHD-related functional impairments. In addition, the results highlight the role of oppositionality in interpersonal relationship difficulties and participation in organized activities.

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J Headache Pain. 2013 Sep;14:79.

HEADACHE AND COMORBIDITY IN CHILDREN AND ADOLESCENTS.

Bellini B, Arruda M, Cescut A, et al.

Headache is one of the most common neurological symptom reported in childhood and adolescence, leading to high levels of school absences and being associated with several comorbid conditions, particularly in neurological, psychiatric and cardiovascular systems. Neurological and psychiatric disorders, that are associated with migraine, are mainly depression, anxiety disorders, epilepsy and sleep disorders, ADHD and Tourette syndrome. It also has been shown an association with atopic disease and cardiovascular disease, especially ischemic stroke and patent foramen ovale (PFO).

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J Int Neuropsychol Soc. 2013 Oct;19:1016-20.

IMPAIRMENT IN FLEXIBLE REGULATION OF SPEED AND ACCURACY IN CHILDREN WITH ADHD.

Vallesi A, D'Agati E, Pasini A, et al.

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J Med Econ. 2013 Sep.

TREATMENT PERSISTENCE IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A RETROSPECTIVE ANALYSIS OF PATIENTS INITIATED ON LISDEXAMFETAMINE VS OTHER MEDICATIONS.

Setyawar J, Guerin A, Hodgkins P, et al.

Abstract Objective: To compare treatment persistence in attention-deficit/hyperactivity disorder (ADHD) of patients initiated on lisdexamfetamine (LDX) vs other ADHD medications.

Methods: A large US administrative claims database was used to select ADHD patients who initiated an ADHD medication (index treatment) during/after 2007. Patients were classified, based on age and previous treatment status, as treatment-naïve or previously treated children and adolescents (6-17 years) and treatment-naïve or previously treated adults (18 years and older). Furthermore, patients were classified into seven mutually exclusive treatment groups, based on their index treatment: LDX, atomoxetine (ATX), osmotic-release methylphenidate hydrochloride long-acting (OROS MPH), other methylphenidate/dexamethylphenidate short-acting (MPH SA) and long-acting (MPH LA), and amphetamine/dextroamphetamine short acting (AMPH SA) and long-acting (AMPH LA). Treatment persistence, analyzed through discontinuation (interruption of the index treatment for ≥ 30 consecutive days), was compared between treatment groups using multivariate Cox proportional hazards. Patients were followed until first treatment discontinuation or up to 12 months after the initiation of the index treatment, whichever occurred first.

Results: Among children and adolescents, LDX patients had a significantly lower discontinuation rate compared to other treatment groups (range hazard ratios [HRs]; 1.04-2.26; all $p < 0.05$), except when compared to treatment-naïve patients on ATX and OROS MPH, where no statistically significant differences were found and where LDX had a higher risk of discontinuation, respectively. Among adults, LDX patients had a significantly lower discontinuation rate compared to patients in other treatment groups (range HR; 1.14-1.86; all $p < 0.05$), except for the comparison with AMPH LA patients, where differences were not statistically significant.

Limitations: This study did not control for ADHD severity.

Conclusion: LDX-treated patients were associated with higher persistence compared to patients initiated on other ADHD medications, except for the comparisons with OROS MPH and ATX treated patients in treatment-naïve children and adolescents and AMPH LA-treated patients in adults.

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J Mot Behav. 2013 Sep.

SPONTANEOUSLY HYPERTENSIVE RATS: POSSIBLE ANIMAL MODEL OF SLEEP-RELATED MOVEMENT DISORDERS.

Esteves AM, Lopes C, Frussa-Filho R, et al.

ABSTRACT Clinical experience suggests that restless legs syndrome (RLS), periodic leg movement (PLM), and attention-deficit hyperactivity disorder (ADHD) may co-occur in both children and adults. The purpose of the present study was to provide an electrocorticography and electromyography evaluation of the spontaneously hypertensive rat (SHR) to investigate the potential of this rat strain as an animal model of RLS-PLM. Initial work focused on evaluating sleep patterns and limb movements during sleep in SHR, having normotensive Wistar rats (NWR) as control, followed by comparison of two treatments (pharmacological-dopaminergic agonist treatment and nonpharmacological-chronic physical exercise), known to be clinically beneficial for sleep-related movement disorders. The captured data strengthen the association between SHR and RLS-PLM, revealing a significant reduction on sleep efficiency and slow wave sleep and an increase on wakefulness and limb movements for the SHR group during the dark period, as compared to the NWR group, effects that have characteristics that are strikingly consistent with RLS-PLM. The pharmacological and nonpharmacological manipulations validated these results. The

present findings suggest that the SHR may be a useful putative animal model to study sleep-related movement disorders mechanisms.

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J Neuropsychiatry Clin Neurosci. 2013 Jul;25:222-28.

WHITE-MATTER CONNECTIVITY AND METHYLPHENIDATE-INDUCED CHANGES IN ATTENTIONAL PERFORMANCE ACCORDING TO ALPHA2A-ADRENERGIC RECEPTOR GENE POLYMORPHISMS IN KOREAN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Park S, Hong SB, Kim JW, et al.

The authors examined the association between the Mspl C/G and Dral C/T genotypes of the alpha2A-adrenergic receptor gene and white-matter connectivity and attentional performance before and after medication in 53 children with attention-deficit hyperactivity disorder. Subjects who carried the T allele at the Dral polymorphism showed fewer changes in the mean commission error scores after 8 weeks of medication and decreased fractional anisotropy (FA) values in the right middle frontal cortex than subjects without the T allele. Subjects with the C allele at the Mspl polymorphism showed decreased FA values in the right postcentral gyrus than subjects without.

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Mult Scler. 2013 Sep.

PSYCHIATRIC DIAGNOSES AND COGNITIVE IMPAIRMENT IN PEDIATRIC MULTIPLE SCLEROSIS.

Weisbrot D, Charvet L, Serafin D, et al.

BACKGROUND: Pediatric multiple sclerosis (MS) represents approximately 5% of the MS population; information regarding clinical features is slowly accumulating. Cognitive and psychiatric impairments frequently occur, but remain poorly understood.

OBJECTIVES: To describe psychiatric diagnoses among children with MS referred for psychiatric assessment and their relation to cognitive impairment.

METHODS: Forty-five pediatric MS patients (aged 8 to 17 years) were referred for outpatient psychiatric evaluation including a psychiatric interview (K-SADS), a clinician-based global assessment of functioning (Children's Global Assessment Scale, CGAS), a neurologic examination including the Expanded Disability Status Scale (EDSS), and a neuropsychological test battery.

RESULTS: The most common categories of psychiatric diagnoses were anxiety disorders (n=15), attention deficit hyperactivity disorder (ADHD, n=12), and mood disorders (n=11). Cognitive impairment was classified in 20/25 (80%) of patients meeting criteria for a psychiatric disorder versus 11/20 (55%) of those without psychiatric disorder (p=0.08). Those diagnosed with anxiety or mood disorder had the highest frequency of cognitive impairment, with a significantly higher rate when compared with those with psychiatric diagnoses in other categories (p=0.05).

CONCLUSIONS: A variety of psychiatric diagnoses can occur in children with pediatric MS. Many of these children also had cognitive impairment, particularly those in the mood and anxiety groups.

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Nat Rev Urol. 2013 Oct.

URINARY INCONTINENCE IN CHILDREN WITH SPECIAL NEEDS.

von GA.

Nocturnal enuresis, daytime urinary incontinence, lower urinary tract symptoms and faecal incontinence are more common in children with special needs than in typically developing children. Children with intellectual disability, which can be attributed to a range of causes, are particularly affected. Indeed, the epidemiological and clinical studies conducted to date show clear associations that children with special needs have higher rates of urinary (and faecal) incontinence than children without development, physical or cognitive impairments. For example, low intelligence quotient (IQ)-associated physical disability and conditions such as Fragile X and Rett syndromes increase the risk for incontinence, which can persist into

adulthood if left untreated. Although the association of attention deficit hyperactivity disorder and incontinence has been shown in many studies, further research is needed on other specific disorders, such as autism. As many children are not receiving adequate care, specific multimodal treatments based on rigorous assessment of the incontinence, underlying condition and associated comorbid disorders should be actively offered.

Neuropsychiatr Dis Treat. 2013;9:1301-09.

PREDICTING ACUTE SIDE EFFECTS OF STIMULANT MEDICATION IN PEDIATRIC ATTENTION DEFICIT/HYPERACTIVITY DISORDER: DATA FROM QUANTITATIVE ELECTROENCEPHALOGRAPHY, EVENT-RELATED POTENTIALS, AND A CONTINUOUS-PERFORMANCE TEST.

Ogrim G, Hestad KA, Brunner JF, et al.

BACKGROUND: The aim of this study was to search for predictors of acute side effects of stimulant medication in pediatric attention deficit/hyperactivity disorder (ADHD), emphasizing variables from quantitative electroencephalography (QEEG), event-related potentials (ERPs), and behavior data from a visual continuous-performance test (VCPT).

METHODS: Seventy medication-naïve ADHD patients aged 7-16 years were tested with QEEG, including a go/no-go task condition (VCPT) from which behavior data and ERPs were extracted, followed by a systematic trial on stimulant medication lasting at least 4 weeks. Based on data from rating scales and interviews, two psychologists who were blind to the QEEG/ERP test results independently rated the patients as having no or small side effects (n=37) or troublesome side effects (n=33). We determined if the side effects were related to sex, age, IQ, ADHD subtype, comorbidities, clinical outcome, and variables in QEEG, ERPs, and VCPT.

RESULTS: There was a moderate negative correlation between clinical outcome and side effects. Three variables were significantly associated with side effects in a multivariate logistic regression analysis. In the ERP independent component - contingent negative variation - which reflected action preparation and time evaluation, patients with high amplitudes (close to normal values) experienced more side effects than patients with lower amplitudes. A faster-than-normal reaction time in VCPT was associated with side effects, as was a high amplitude in an early ERP component (early visual independent component), reported to be influenced by attention, perceptual sensitivity, and anxiety.

CONCLUSION: The group with troublesome side effects had normal action-preparation electrical brain activity, a faster-than-normal reaction time, and an increased level of anxiety (measured by ERP) compared with the no side-effects group.

Neuropsychology. 2013 Sep.

NEUROPSYCHOLOGICAL DEFICITS ASSOCIATED WITH HEAVY PRENATAL ALCOHOL EXPOSURE ARE NOT EXACERBATED BY ADHD.

Glass L, Ware AL, Crocker N, et al.

Objective: Neuropsychological functioning of individuals with attention-deficit/hyperactivity disorder (ADHD) or heavy prenatal alcohol exposure has been well documented independently. This study examined the interaction between both factors on cognitive performance in children.

Method: As part of a multisite study, 344 children (8-16 y, M=12.28, SD=2.52) completed a comprehensive neuropsychological battery. Four subject groups were tested: children with histories of heavy prenatal alcohol exposure (AE) and ADHD (AE+, n=90), alcohol-exposed without ADHD, (AE-, n=38), nonexposed with ADHD (ADHD, n=80), and nonexposed without ADHD (CON, n = 136).

Results: Separate 2(AE) x 2(ADHD) MANCOVAs revealed significant main and interactive effects of ADHD and AE on overall WISC-IV, D-KEFS, and CANTAB performance. Individual ANOVAs revealed significant interactions on 2 WISC-IV indices [Verbal Comprehension (VCI), Perceptual Reasoning (PRI)], and four D-KEFS and CANTAB subtests [Design Fluency, Verbal Fluency, Trail Making, Spatial Working Memory]. Follow-up analyses demonstrated no difference between AE+ and AE- groups on these

measures. The combined AE+/- group demonstrated more severe impairment than the ADHD group on VCI and PRI, but there were no other differences between clinical groups.

Conclusions: These results support a combined AE+/- group for neuropsychological research and indicate that, in some cases, the neuropsychological effects seen in ADHD are altered by prenatal alcohol exposure. The effects of alcohol exposure on verbal comprehension and perceptual reasoning were greater than those related to having ADHD without alcohol exposure, although both conditions independently resulted in cognitive impairment compared to controls. Clinically, these findings demonstrate task-dependent patterns of impairment across clinical disorders.

Neuropsychology. 2013 Sep.

ESTIMATING THE PASSAGE OF MINUTES: DEVIANT OSCILLATORY FRONTAL ACTIVITY IN MEDICATED AND UNMEDICATED ADHD.

Wilson TW, Heinrichs-Graham E, White ML, et al.

Objective: Attention-deficit/hyperactivity disorder (ADHD) is a common and extensively treated psychiatric disorder in children, which often persists into adulthood. The core diagnostic symptoms include inappropriate levels of hyperactivity, impulsivity, and/or pervasive inattention. Another crucial aspect of the disorder involves aberrations in temporal perception, which have been well documented in behavioral studies and, recently, have been the focus of neuroimaging studies. These functional magnetic resonance imaging studies have shown reduced activation in anterior cingulate and prefrontal cortices in ADHD using a time-interval discrimination task, whereby participants distinguish intervals differing by only hundreds of milliseconds.

Method: We used magnetoencephalography (MEG) to evaluate the cortical network serving temporal perception during a continuous, long-duration (in minutes) time estimation experiment. Briefly, medicated and unmedicated persons with ADHD, and a control group responded each time they estimated 60 s had elapsed for an undisclosed amount of time in two separate MEG sessions. All MEG data were transformed into regional source activity, and subjected to spectral analyses to derive amplitude estimates of gamma-band activity.

Results: Compared to controls, unmedicated patients were less accurate time estimators and had weaker gamma activity in the anterior cingulate, supplementary motor area, and left prefrontal cortex. After medication, these patients exhibited small but significant increases in gamma across these same neural regions and significant improvements in time estimation accuracy, which correlated with the gamma activity increases.

Conclusion: We found deficient gamma activity in brain areas known to be crucial for timing functions, which may underlie the day-to-day abnormalities in time perception that are common in ADHD.

Neuropsychopharmacology. 2013 Sep.

CEREBELLAR MORPHOLOGY AND THE EFFECTS OF STIMULANT MEDICATIONS IN YOUTHS WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Ivanov I, Murrough JW, Bansal R, et al.

Background: The cerebellum is emerging as a key anatomical structure underlying normal attentional and cognitive control mechanisms. Dysregulation within cerebellar circuits may contribute to the core symptoms of Attention Deficit/Hyperactivity Disorder (ADHD). In the present study we aimed to characterize surface morphological features of the cerebellum in ADHD and healthy comparison youths. Further, we studied the association of cerebellar morphology with the severity of ADHD symptoms and the effects of stimulant treatment.

Methods: We examined 46 youths with ADHD and 59 comparison youths 8-18 years of age in a cross-sectional, case-control study using magnetic resonance imaging. Measures of cerebellar surface morphology were the primary outcome.

Results: Relative to comparison participants, youths with ADHD exhibited smaller regional volumes corresponding to the lateral surface of the left anterior and the right posterior cerebellar hemispheres. Stimulant medication was associated with larger regional volumes over the left cerebellar surface, whereas more severe ADHD symptoms were associated with smaller regional volumes in the vermis.

Discussion: We used optimized measures of morphology to detect alterations in cerebellar anatomy specific to ADHD, dimensions of symptomology, and stimulant treatment. Duration of treatment correlated positively with volumes of specific cerebellar subregions, supporting a model whereby compensatory morphological changes support the effects of stimulant treatment.

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Pediatr Neurol. 2013 Sep.

CHILDREN'S SLEEP DISTURBANCE SCALE IN DIFFERENTIATING NEUROLOGICAL DISORDERS.

Cohen R, Halevi A, Shuper A.

BACKGROUND: We use the Sleep Disturbance Scale for Children (SDSC) routinely as a tool for evaluating children's sleep quality in our pediatric neurology clinic. We analyzed at its ability to detect sleep disturbances distinctive to selected neurological disorders.

PATIENTS: One-hundred and eighty-six children (age range 2-18 years) who were evaluated by the SDSC questionnaire were divided into three groups according to their principal diagnosis: epilepsy, attention deficit hyperactivity disorder, or others. Their responses were analyzed.

RESULTS: The average frequency of abnormal total sleep score was 26.9%. The most frequent sleep disorders were excessive somnolence (25.3%), initiating and maintaining sleep (24.7%), and arousal/nightmares (23.1%). There were no significant group differences for total scores or sleep disorder-specific scores; although a sleep-wake transition disorder was more frequent among children with epilepsy (31%). A literature search revealed that the frequency of abnormal total scores in several neurological disorders (e.g., epilepsy, cerebral palsy) ranges between 20% and 30%.

CONCLUSIONS: The mechanism underlying sleep disturbances in many neurological disorders may be unrelated to that of the primary disease but rather originate from nonspecific or environmental factors (e.g., familial/social customs and habits, temperament, psychological parameters). Although the SDSC is noninformative for studying the effect of a specific neurological disorder on sleep, we still recommend its implementation for screening for sleep disturbances in children with neurological abnormalities.

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Percept Mot Skills. 2013 Apr;116:564-80.

POSTUROGRAPHY CHARACTERISTICS OF OBESE CHILDREN WITH AND WITHOUT ASSOCIATED DISORDERS.

Steinberg N, Nemet D, Kohen-Raz R, et al.

A group of 59 obese children ages 6-12 years were interviewed for current medical diagnoses (e.g., Attention Deficit Hyperactivity Disorder- ADHD, and clumsiness) and later were examined posturographically for balance and stability. General stability of all the obese children deviated significantly from norms. 32.2% of the obese children had a pattern of balance that could indicate orthopedic problems. Obese children with ADHD or perceived clumsiness had significantly worse balance and postural performance compared to other obese children. Balance and posture among obese children without suspicion of problems were similar to non-obese controls. In conclusion, obese children with associated disorders (such as ADHD and perceived clumsiness) manifested disturbance in balance control. Thus, physical activity interventions for these children should include safety measures to decrease the chances of falling and subsequent injury.

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PLoS ONE. 2013;8:e74909.

RISKY BEHAVIOR IN GAMBLING TASKS IN INDIVIDUALS WITH A.

Groen Y, Gaastra GF, Lewis-Evans B, et al.

OBJECTIVE: The aim of this review was to gain insight into the relationship between Attention deficit hyperactivity disorder (ADHD) and risky performance in gambling tasks and to identify any potential alternate explanatory factors.

METHODS: PsycINFO, PubMed, and Web of Knowledge were searched for relevant literature comparing individuals with ADHD to normal controls (NCs) in relation to their risky performance on a gambling task. In total, fourteen studies in children/adolescents and eleven studies in adults were included in the review.

RESULTS: Half of the studies looking at children/adolescents with ADHD found evidence that they run more risks on gambling tasks when compared to NCs. Only a minority of the studies on adults with ADHD reported aberrant risky behavior. The effect sizes ranged from small to large for both age groups and the outcome pattern did not differ between studies that applied an implicit or explicit gambling task. Two studies demonstrated that comorbid oppositional defiant disorder (ODD) and conduct disorder (CD) increased risky behavior in ADHD. Limited and/or inconsistent evidence was found that comorbid internalizing disorders (IDs), ADHD subtype, methylphenidate use, and different forms of reward influenced the outcomes.

CONCLUSION: The evidence for increased risky performance of individuals with ADHD on gambling tasks is mixed, but is stronger for children/adolescents with ADHD than for adults with ADHD, which may point to developmental changes in reward and/or penalty sensitivity or a publication bias for positive findings in children/adolescents. The literature suggests that comorbid ODD/CD is a risk factor in ADHD for increased risky behavior. Comorbid IDs, ADHD subtype, methylphenidate use, and the form of reward received may affect risky performance in gambling tasks; however, these factors need further examination. Finally, the implications of the findings for ADHD models and the ecological validity of gambling tasks are discussed.

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Postgrad Med. 2013;125:154-61.

INATTENTION SYMPTOMS PREDICT LEVEL OF DEPRESSION IN EARLY CHILDHOOD.

Rajendran K, O'Neill S, Halperin JM.

Objective: To investigate the potential bidirectional relationships between severity of inattention and depression across early childhood.

Methods: Children (N=216) from the New York, N Y, metropolitan area were recruited when they were aged 3 to 4 years (T1) and studied again at age 6 (T2) and 7 (T3) years. Child inattention symptoms were measured using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime, along with both parent and teacher reports on the Behavior Assessment System for Children, Second Edition (BASC-2). Severity of child depression was assessed at each time point using parent and teacher reports on the BASC-2. After examining correlations between child inattention and depression, structural equation modeling was used to investigate whether child inattention was longitudinally related to child depression, and whether child depression symptoms were associated with later child inattention.

Results: Severity of child inattention at T1 and T2 was longitudinally associated with increased severity of child depression at T2 and T3, respectively. Early child depression was not longitudinally associated with later child inattention.

Conclusion: Child inattention is a risk factor for increased levels of child depression. Pediatricians and clinicians who assess children's inattention symptoms also need to investigate symptoms of depression. This study makes a case for treating children's inattention symptoms at preschool and early childhood, before emotional problems become more severe.

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Prax Kinderpsychol Kinderpsychiatr. 2013;62:473-90.

DIAGNOSTIC OF ADHD IN CHILDHOOD AND ADOLESCENCE WITH THE K-SADS-PL.

Schmidt S, Banaschewski T, Garbe E, et al.

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most prevalent psychiatric disorders in childhood and adolescence, often accompanied by comorbid disorders. A high standard of diagnostic assessment combined with a demand for valid diagnostic instruments is necessary. The K-SADS-PL is an established semi-structured interview, focusing on the categorical assessment of psychiatric disorders. The aim of the following study was to examine specific characteristics of ADHD symptomatology including functional and behavioral assessment. Therefore correlations between the result in a diagnostic interview (K-SADS-PL) and different ADHD-specific instruments were performed. Groups were formed (exposed vs. unexposed), based on the diagnostic finding in the K-SADS-PL. Group-specific test score differences were calculated and compared by multivariate analyses of covariance. Children with ADHD showed a significantly higher impact of conduct and emotional problems than the unexposed group. Health related quality of life was more impaired in children and families suffering from ADHD which refers to the relevance of family-oriented psychotherapy.

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Psychodyn Psychiatry. 2013;41:419-35.

IS INCREASED SEXUAL BEHAVIOR A SYMPTOM OF BIPOLAR DISORDER IN CHILDREN AND ADOLESCENTS?

Adelson S, Bell R, Graff A, et al.

Abstract While there is consensus that bipolar disorder exists in children and adolescents, its diagnostic criteria are debated. Excessive sexual behavior has been reported in youth who may have juvenile bipolar disorder (JBD), and has been termed "hypersexuality." Although there is no universal definition of this term, this observation has led to a hypothesis that increased sexual behavior characterizes the bipolar syndrome in children and adolescents, and differentiates it from attention deficit hyperactivity disorder. Although this hypothesis is plausible, evidence for it is incomplete, because testing it definitively would require both establishing a standard definition of hypersexuality in children and adolescents, and also reaching consensus about the other nonsexual criteria for pediatric bipolar disorder. In addition, studies to test it would need to control factors other than JBD that are known to increase sexual behavior in children and adolescents. These include sexual abuse and related posttraumatic stress disorder, excessive exposure to sexual stimuli, psychiatric illness in general, and social variables such as family chaos and social stress. Some of these factors might increase sexual behavior in youth with bipolar disorder through psychodynamic mechanisms rather than as a result of the illness itself. Therefore, further research is needed to determine whether increased sexual behavior can serve as a diagnostically valuable criterion for bipolar disorder in children and adolescents, and whether it differentiates the disorder from other conditions known to be associated with increased sexual behavior in youth.

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Psychodyn Psychiatry. 2013;41:437-66.

A NEW LOOK AT BORDERLINE PERSONALITY DISORDER AND RELATED DISORDERS: HYPER-REACTIVITY IN THE LIMBIC SYSTEM AND LOWER CENTERS.

Stone MH.

Abstract Borderline Personality Disorder (BPD) has been often described recently as a condition characterized by emotional dysregulation. Several other conditions share this attribute; namely, Bipolar Disorder (BD), Attention-Deficit/Hyperactivity Disorder (ADHD), Intermittent Explosive Disorder (IED), and Major Depressive Disorder (MDD). The dysregulation is not always in the same direction: BPD, BD, ADHD, and IED, for example, show over-reactivity or "hyperactivity" of emotional responses, whereas patients with MDD show emotional sluggishness and underactivity. At the clinical/descriptive level the "over-reactive" conditions appear separate and distinct. BPD constitutes a large domain within the psychopathological arena, appearing to contain within it a variety of etiologically diverse subtypes. Among the latter is a type of BPD linked closely with Bipolar Disorder; family studies of either condition show an overrepresentation of

both: BPD patients with bipolar relatives; Bipolar patients with BPD relatives. A significant percentage of children with ADHD go on to develop either BPD or BD as they approach adulthood. If one shifts the spotlight to neurophysiology, as captured by MRI studies, however, it emerges that an important subtype of BPD, and also BD, ADHD, and IED-share common features of abnormalities and peculiarities in the limbic system and in the cortex, especially the prefrontal cortex. Deeper subcortical regions such as the periaqueductal gray may also be implicated in strong emotional reactions. The diversity of clinical "over-reactive" conditions appear to harken back to a kind of unity at the brain-change level. There are therapeutic implications here, such as the advisability of mood stabilizers in many cases of BPD, not just for Bipolar Disorder.

Psychol Addict Behav. 2013 Sep;27:832-40.

STIMULANT MEDICATION USE IN COLLEGE STUDENTS: COMPARISON OF APPROPRIATE USERS, MISUSERS, AND NONUSERS.

Hartung CM, Canu WH, Cleveland CS, et al.

While stimulant medication is commonly prescribed to treat Attention-Deficit/Hyperactivity Disorder in children and adolescents (Merikangas, He, Rapoport, Vitiello, & Olfson, 2013; Zuvekas & Vitiello, 2012) and is considered an empirically supported intervention for those groups (Barkley, Murphy, & Fischer, 2008; Pelham & Fabiano, 2008; Safren et al., 2005) surprisingly little is known about the efficacy of stimulants in the slightly older emerging adult population. A focus has emerged, however, on illicit stimulant use among undergraduates, with studies suggesting such behavior is not uncommon (e.g., Arria et al., 2013). Unfortunately, details are lacking regarding outcomes and personal characteristics associated with different patterns of stimulant misuse. The current study compares the characteristics of four groups of college students, including those with stimulant prescriptions who use them appropriately (i.e., appropriate users), those who misuse their prescription stimulants (i.e., medical misusers), those who obtain and use stimulants without a prescription (i.e., nonmedical misusers), and those who do not use stimulant medications at all (i.e., nonusers). Undergraduates (N=1,153) from the Southeastern, Midwest, and Rocky Mountain regions completed online measures evaluating patterns of use, associated motives, side effects, ADHD symptomatology, and other substance use. Both types of misusers (i.e., students who abused their prescriptions and those who obtained stimulants illegally) reported concerning patterns of other and combined substance use, as well as higher prevalence of debilitating side effects such as insomnia and restlessness. Research and practical implications are discussed.

Psychol Med. 2013 Sep;1-13.

NEUROPSYCHOLOGICAL FUNCTIONS AMONG ADOLESCENTS WITH PERSISTENT, SUBSYNDROMAL AND REMITTED ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Lin YJ, Chen WJ, Gau SS.

BACKGROUND: Previous studies have reported mixed results on neuropsychological deficits in attention deficit hyperactivity disorder (ADHD) and only a few studies have focused on adolescents. There is also a debate about whether the executive function (EF) impairments in ADHD are primary deficits or have some contribution from the underlying non-EF processes. The aim of this study was to investigate the impairments in EF and neuropsychological function with relatively low executive demand (low-EF) in adolescents with childhood diagnosis of ADHD as a function of current ADHD status.

METHOD: Psychiatric diagnostic interviews and computerized neuropsychological tests classified into EF and low-EF tasks were completed by 435 adolescents with a childhood diagnosis of ADHD (300 adolescents classified as persistent ADHD, 109 as subsyndromal ADHD and 26 as remitted ADHD based on the current diagnosis) and 263 typically developing (TD) adolescents.

RESULTS: There were significant EF (spatial working memory, spatial planning and verbal working memory) and low-EF (signal detectability, spatial span and visual recognition memory) impairments in persistent and subsyndromal ADHD. The impairments in EF were independent of low-EF despite significant

moderate correlations between any two of these tasks. Adolescents with remitted ADHD showed no deficit in either EF or low-EF.

CONCLUSIONS: This study suggests that adolescents with persistent and subsyndromal ADHD have EF and low-EF impairments that might contribute to ADHD independently.

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Psychol Med. 2013 Sep;1-11.

PSYCHIATRIC DISORDERS IN 22q11.2 DELETION SYNDROME ARE PREVALENT BUT UNDERTREATED.

Tang SX, Yi JJ, Calkins ME, et al.

BACKGROUND: Chromosome 22q11.2 deletion syndrome (22q11DS) is a common genetic disorder with high rates of psychosis and other psychopathologies, but few studies discuss treatment. Our aim was to characterize the prevalence and treatment of major psychiatric illnesses in a well-characterized sample of individuals with 22q11DS.

METHOD: This was a cross-sectional study of 112 individuals aged 8 to 45 years with a confirmed diagnosis of 22q11DS. Each participant was administered a modified Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) and the Structured Interview for Prodromal Syndromes (SIPS). Phenotypes assessed were threshold and subthreshold psychosis, depression, mania, generalized and separation anxiety, obsessions/compulsions, inattention/hyperactivity and substance use. Histories of mental health care and current psychotropic treatment were obtained.

RESULTS: Psychopathology was common, with 79% of individuals meeting diagnostic criteria for a disorder at the time of assessment. Diagnoses of psychosis were made in 11% of cases, attenuated positive symptom syndrome (APS) in 21%, and 47% experienced significant subthreshold symptoms. Peak occurrence of psychosis risk was during adolescence (62% of those aged 12-17 years). Criteria for a mood disorder were met by 14%, for anxiety disorder 34% and for attention deficit hyperactivity disorder (ADHD) 31%. Mental health care had been received by 63% of individuals in their lifetime, but only 40% continued therapy and 39% used psychotropics. Antipsychotics were used by 42% of participants with psychosis and none of the participants with APS. Half of those at risk for psychosis were receiving no mental health care.

CONCLUSIONS: Psychopathology is common in 22q11DS but is not adequately treated or clinically followed. Particular attention should be paid to subthreshold psychotic symptoms, especially in adolescents.

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Psychol Res Behav Manag. 2013;6:87-99.

THE LONG-TERM OUTCOMES OF INTERVENTIONS FOR THE MANAGEMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS.

Parker J, Wales G, Chalhoub N, et al.

PURPOSE: To systematically identify and review the currently available evidence on the long-term outcomes of recommended attention-deficit hyperactivity disorder (ADHD) interventions following randomized controlled trials with children and young people.

METHOD: A systematic search was conducted to identify trials >1 year in length using the following databases: CINAHL.

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Psychophysiology. 2013 Aug.

THE EFFECTS OF PERFORMANCE-BASED REWARDS ON NEUROPHYSIOLOGICAL CORRELATES OF STIMULUS, ERROR, AND FEEDBACK PROCESSING IN CHILDREN WITH ADHD.

Rosch KS, Hawk LW, Jr.

Rewards have been shown to improve behavior and cognitive processes implicated in attention-deficit hyperactivity disorder (ADHD), but the information-processing mechanisms by which these improvements occur remain unclear. We examined the effect of performance-based rewards on ERPs related to

processing of the primary task stimuli, errors, and feedback in children with ADHD and typically developing controls. Participants completed a flanker task containing blocks with and without performance-based rewards. Children with ADHD showed reduced amplitude of ERPs associated with processing of the flanker stimuli (P3) and errors (ERN, Pe), but did not differ in feedback-processing (FRN). Rewards enhanced flanker-related P3 amplitude similarly across groups and error-related Pe amplitude differentially for children with ADHD. These findings suggest that rewards may improve cognitive deficits in children with ADHD through enhanced processing of relevant stimuli and increased error evaluation.

Psychotherapy (Chic). 2013 Sep.

THE USE OF EMPATHY AND TRANSFERENCE AS INTERVENTIONS IN PSYCHOTHERAPY WITH ATTENTION DEFICIT HYPERACTIVE DISORDER LATENCY-AGED BOYS.

Conway F.

Psychodynamic-oriented therapies are uniquely positioned to address the internal experiences of a child whose external presentation is consistent with an Attention Deficit Hyperactivity Disorder (ADHD) diagnosis, an area of treatment intervention that is conspicuously absent from common ADHD treatment modalities. This article presents two psychodynamic psychotherapy treatment interventions that demonstrate (1) the importance of empathy in the therapeutic relationship and (2) the use of transference in psychotherapy with ADHD children. Through the use of case examples, the use of empathy is demonstrated in developing the therapeutic alliance, facilitating the development of the child's reflective capacity on affective states, and organizing the child's affective experiences. The benefits of transference interventions with ADHD children are reviewed, and case examples are provided to demonstrate how the therapist worked with the idealized and mirroring transference. Interventions are presented in the context of Object Relations and Self-Psychology Theories.

Rehabil Psychol. 2013 Sep.

CLINICAL UTILITY OF THE BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION-SELF-REPORT (BRIEF-SR) IN ADOLESCENTS WITH TRAUMATIC BRAIN INJURY.

Byerley AK, Donders J.

Objective: To evaluate the factor structure and correlates of the Behavior Rating Inventory of Executive Function-Self-Report (BRIEF-SR) in 118 adolescents with traumatic brain injury (TBI).

Method: Cross-sectional study. Maximum-likelihood exploratory, as well as confirmatory, factor analysis. External correlates of factor scores were evaluated.

Results: Two latent constructs were identified, with notable variation in scale loading pattern compared with standardization sample findings of the BRIEF-SR. These factors covaried inversely with severity of TBI; more severe injuries were associated with lower self-ratings of executive dysfunction, indicating a possible lack of deficit awareness in those with relatively severe injuries. Premorbid ADHD affected both factors, resulting in higher self-ratings of executive dysfunction, suggesting preserved awareness of preexisting difficulties in those with uncomplicated mild injuries. In addition, males reported less executive dysfunction than females.

Conclusions/Implications: Findings suggest that the BRIEF-SR measures somewhat different latent constructs after TBI than in typically developing adolescents, and that BRIEF-SR scores need to be considered in concert with objective measures of injury severity and premorbid demographic and historical variables.

Res Dev Disabil. 2013 Sep;34:4142-53.

MOTOR SKILLS IN CZECH CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THEIR NEUROTYPICAL COUNTERPARTS.

Scharoun SM, Bryden PJ, Otípková Z, et al.

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioural disorder. Characterized by recurring problems with impulsiveness and inattention in combination with hyperactivity, motor impairments have also been well documented in the literature. The aim of this study was to compare the fine and gross motor skills of male and female children with ADHD and their neurotypical counterparts within seven skill assessments. This included three fine motor tasks: (1) spiral tracing, (2) dot filling, (3) tweezers and beads; and four gross motor tasks: (1) twistbox, (2) foot tapping, (3) small plate finger tapping, and (4) large plate finger tapping. It was hypothesized that children with ADHD would display poorer motor skills in comparison to neurotypical controls in both fine and gross motor assessments. However, statistically significant differences between the groups only emerged in four of the seven tasks (spiral tracing, dot filling, tweezers and beads and foot tapping). In line with previous findings, the complexity underlying upper limb tasks solidified the divide in performance between children with ADHD and their neurotypical counterparts. In light of similar research, impairments in lower limb motor skill were also observed. Future research is required to further delineate trends in motor difficulties in ADHD, while further investigating the underlying mechanisms of impairment.

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Res Dev Disabil. 2013 Sep;34:3709-19.

THE EX-GAUSSIAN DISTRIBUTION OF REACTION TIMES IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hwang Gu SL, Gau SS, Tzang SW, et al.

We investigated the three parameters (μ , σ , τ) of ex-Gaussian distribution of RT derived from the Conners' continuous performance test (CCPT) and examined the moderating effects of the energetic factors (the inter-stimulus intervals (ISIs) and Blocks) among these three parameters, especially τ , an index describing the positive skew of RT distribution. We assessed 195 adolescents with DSM-IV ADHD, and 90 typically developing (TD) adolescents, aged 10-16. Participants and their parents received psychiatric interviews to confirm the diagnosis of ADHD and other psychiatric disorders. Participants also received intelligence (WISC-III) and CCPT assessments. We found that participants with ADHD had a smaller μ , and larger τ . As the ISI/Block increased, the magnitude of group difference in τ increased. Among the three ex-Gaussian parameters, τ was positively associated with omission errors, and μ was negatively associated with commission errors. The moderating effects of ISIs and Blocks on τ parameters suggested that the ex-Gaussian parameters could offer more information about the attention state in vigilance task, especially in ADHD.

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Res Dev Disabil. 2013 Sep;34:3936-45.

THE EFFECT OF DIFFERENT STIMULUS ATTRIBUTES ON THE ATTENTIONAL PERFORMANCE OF CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND DYSLLEXIA.

Wang LC, Tsai HJ, Yang HM.

While teachers have traditionally used the interesting objects to increase student attention in the classroom, evidence supporting the effectiveness of this method is lacking. The present study investigated the influence of different stimulus attributes for typical developing students and for students with attention deficit/hyperactivity disorder (ADHD) and dyslexia. Thirty children with ADHD, 30 children with dyslexia, and 30 typical developing students were tested using a measuring tool that was constructed by the authors to assess their sustained attention and selective attention on the geometric-figure assessment and the interesting-figure assessment. The geometric-figure assessment included a square, circle, trapezium, and triangle; and the interesting-figure assessment included a house, cat, hand, and tree. While the typical developing group showed better selective attention on the geometric-figure assessment, there was no

difference between the dyslexic group and the ADHD group with respect to selective attention. Furthermore, the typical developing and dyslexic groups did not differ in the geometric-figure assessment in sustained attention and were both better in this area than the ADHD group. In the interesting-figure assessment, the typical developing and dyslexic groups performed similarly in sustained attention, but selective attention of the dyslexic group improved more than the ADHD group, similar to the typical developing group. Both selective attention of the dyslexic group and sustained attention of the ADHD group showed positive significant differences in the interesting-figure assessment, but sustained attention of the dyslexic group and selective attention of the ADHD group showed little difference in the interesting-figure assessment. Surprisingly, the typical developing group did not show any significant difference in the interesting-figure assessment, possibly because they had previously demonstrated a ceiling effect in the geometric-figure assessment.

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Res Dev Disabil. 2013 Sep;34:4203-09.

ADHD SYMPTOM PREVALENCE AND RISK FACTORS IN A SAMPLE OF TODDLERS WITH ASD OR WHO ARE AT RISK FOR DEVELOPMENTAL DELAY.

Turygin N, Matson JL, Tureck K.

Individuals with attention deficit/hyperactivity disorder (ADHD) experience difficulties with inattention, hyperactivity, and impulsivity which significantly interfere with their daily functioning. Symptoms of the disorder occur in children, but the developmental trajectory of ADHD symptoms is not known. The present study examines the prevalence of ADHD symptomology in a sample of 2956 children who were determined to be at risk for developmental delay. Prevalence rates for ADHD in the overall sample was 4.50%, and prevalence rates by gender, race, and presence of autism spectrum disorder (ASD) were comparable. The prevalence was not significantly different in children with an ASD diagnosis. No significant effects of gender or ASD diagnosis were observed. ADHD should be considered as a diagnosis among young children who present to clinics for children at risk for developmental delay, and future researchers should further study its developmental trajectory, beginning at an early age.

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Scand J Caring Sci. 2013 Sep.

PUBLIC HEALTH NURSES' CONCEPTIONS OF THEIR ROLE RELATED TO FAMILIES WITH A CHILD HAVING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Moen OL, Hedelin B, Hall-Lord ML.

Attention-deficit/hyperactivity disorder is one of the most common behavioural disorders diagnosed in children. Children who have this disorder have difficulties regarding regulation of their emotions, maintaining attention and impulse control. Parents may need guidance in creating structure and predictable boundaries. One of the personnel who meet these families is the public health nurse. The aim of this study was to explore the public health nurses role in relation to these families. A qualitative explorative design with a phenomenographic approach was used. Interviews were performed with 19 nurses, six in group and one individual. In the data analyses, three descriptive categories emerged: 'supporting the family-unit', which describes the nurses supervising the parents and the child in everyday challenges; 'understanding the child', which describes how the public health nurses use professional competence and choose the time and arena to observe the child and; 'collaborating multidisciplinary', which describes how the public health nurses define their own role and conceive their collaboration with other professionals. The public health nurse (PHN)'s support for the parents and the entire family is important, and the PHN is the first encounter and trustful follower throughout the course of diagnosis and care.

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Suppl Clin Neurophysiol. 2013;62:275-87.

RESTING STATE BRAIN OSCILLATIONS AND SYMPTOM PROFILES IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Barry RJ, Clarke AR.

Our perspective on resting-state electroencephalogram (EEG) is that it provides a window into the substrate of cognitive and perceptual processing, reflecting the dynamic potential of the brain's current functional state. In an extended research program into the electrophysiology of attention deficit/hyperactivity disorder (AD/HD), we have examined resting-state EEG power and coherence, and event-related potentials (ERPs), in children, adolescents, and adults with the disorder. We sought initially to identify consistent AD/HD anomalies in these measures, relative to normal control subjects, and then to understand how these differences related to existing models of AD/HD. An emergent strand in this program has been to clarify the EEG correlates of "arousal" and to understand the role of arousal dysfunction as a core anomaly in AD/HD. To date, findings in this strand serve to rule out a commonly held dictum in the AD/HD field: that elevated theta/beta ratio is an indicator of hypo-arousal. In turn, this requires further work to elucidate the ratio's functional significance in the disorder. Our brain dynamics studies relating prestimulus EEG amplitude and phase states to ERP outcomes are expected to help in this regard, but we are still at a relatively early stage, currently examining these relationships in control children, in order to better understand normal aspects of brain dynamics before turning to children with AD/HD. This range of studies provides a framework for our recent work relating resting-state EEG anomalies, in individuals with AD/HD, to their symptom profile. This has had promising results, indicating links between increased inattention scores and reduced resting EEG gamma power. With resting-state EEG coherence, reduced left lateralized coherences across several bands have correlated negatively with inattention scores, while reduced frontal interhemispheric coherence has been correlated negatively with hyperactivity/impulsivity scores. Such linkages appear to provide encouraging leads for future EEG research in AD/HD.

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Suppl Clin Neurophysiol. 2013;62:289-301.

EVENT-RELATED OSCILLATIONS REFLECT FUNCTIONAL ASYMMETRY IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Yordanova J, Kolev V, Rothenberger A.

Previous studies have found that event-related theta and gamma oscillations elicited in an auditory selective attention task are deviant in children with attention deficit/hyperactivity disorder (ADHD). It has been suggested that these deviations are associated with deficient motor inhibition in ADHD, which may lead to increased excitability of not only the motor generation networks but also the networks involved in sensory and cognitive processing of the stimulus requiring motor response. Within this suggestion, the present study used the same experimental database to compare the motor cortical activation of healthy controls and children with ADHD during the performance of the auditory selective attention task. Electroencephalography mu (8-12 Hz) activity at C3 and C4 electrodes was used as a measure of motor cortical activation. Mu power was analyzed for four stimulus conditions of the task (attended target, unattended target, attended nontarget, and unattended nontarget). It was found that motor cortical activation as reflected by mu power suppression was not overall greater in ADHD than healthy children. However, stimuli that possessed only partial target features and did not require motor responding (unattended target and attended nontarget) produced a significant reduction of mu activity in ADHD patients. These results suggest that motor cortical excitability is not generally increased in ADHD children. Rather, the co-existence of conflict features in complex stimuli induces task-irrelevant motor activation in these children. The deficient inhibition of motor cortical networks contralateral to the response may therefore be responsible for the functional asymmetry in stimulus processing in ADHD.

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Turk Psikiyatri Derg. 2013;24:158-67.

SOCIODEMOGRAPHIC/CLINICAL CHARACTERISTICS AND RISK FACTORS ASSOCIATED WITH CHRONIC TIC DISORDERS.
Hesapcioglu ST, Tural MK, Kandil S.

OBJECTIVE: This study aimed to investigate comorbidity, and sociodemographic and clinical characteristics in children and adolescents with Tourette's syndrome (TS) and chronic motor or vocal tic disorder (CMVTD), and to determine the predictors of tic disorders.

MATERIALS AND METHODS: In all, 57 children and adolescents with TS and CMVTD were compared with a control group. Data were obtained using the Yale Global Tic Severity Scale (YGTSS), Turgay DSM-IV-Based Disruptive Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S), Children's Depression Inventory (CDI), Screen for Child Anxiety-Related Disorders (SCARED), Maudsley Obsessive-Compulsive Inventory (MOCI), and Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL).

RESULTS: Mean age of the patients was 10.5 +/- 2.4 years. In all, 56 (98.2%) of the patients had simple motor tics, 50 (87.7%) had complex motor tics, and 43 (75.4%) had vocal tics. Self-injurious behavior was observed in 24 (42.1%) patients. In total, 46 (80.7%) of the patients had ≥ 1 comorbid disorder. Among the observed comorbid disorders, attention deficit-hyperactivity disorder (ADHD) was the most common (observed in 40.4% of the patients), followed by obsessive-compulsive disorder (OCD) (19.3%). A higher-level of maternal education and absence of ADHD were associated with a reduction in the risk of a tic disorder. A family history of psychiatric disorder increased the risk of a tic disorder 5.61-fold, and nail biting increased the risk of a tic disorder 8.2-fold. Every 1-unit increase in CDI score increased the risk of a tic disorder by 12%.

CONCLUSION: Chronic tic disorders (CTDs) are often accompanied by other psychiatric disorders. Both child- and family-related factors are associated with the risk of developing a tic disorder. Determination of both the protective and risk factors would be beneficial for improving the mental health of the general public.

Zhongguo Dang Dai Er Ke Za Zhi. 2013 Sep;15:723-27.

STUDY ON ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN BASED ON RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING.

Yang RX, Ding KJ, Liu RX, et al.

OBJECTIVE: To compare resting-state functional magnetic resonance imaging (fMRI) findings of children with attention-deficit hyperactivity disorder (ADHD) and normal children, and to investigate the possible mechanism of brain dysfunction in children with ADHD.

METHODS: Resting-state fMRI was performed on 18 children who met the DSM-IV diagnostic criteria for ADHD (ADHD group) and 18 normal children (control group) matched for age, sex, IQ, degree of education and handedness. The two groups were compared in terms of amplitude of low frequency fluctuation (ALFF) and regional homogeneity (ReHo).

RESULTS: Compared with the control group, the ADHD group had decreased ALFF in the bilateral posterior lobes of the cerebellum and the left side of the pons, increased ALFF in the right precentral gyrus, decreased ReHo in the left medial frontal gyrus, right superior frontal gyrus, and left precuneus, and increased ReHo in the left anterior lobe of the cerebellum, left caudate nucleus, right parahippocampal gyrus, left precentral gyrus, and right middle frontal gyrus.

CONCLUSIONS: In resting state, children with ADHD have decreased brain activity in some regions, including the cerebellum and frontal cortex, compared with normal children, which supports the hypothesis of dysfunctional fronto-cerebellar circuits in ADHD.

Zhongguo Dang Dai Er Ke Za Zhi. 2013 Sep;15:728-32.

COMORBIDITIES AND FUNCTIONAL IMPAIRMENTS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Xiao ZH, Wang QH, Luo TT, et al.

OBJECTIVE: To assess comorbidities and functional impairments in children with attention deficit hyperactivity disorder (ADHD), and to investigate their relationship with the core symptoms (attention deficit and hyperactivity) of ADHD.

METHODS: A total of 319 children with suspected ADHD were included in the study. The Vanderbilt ADHD Parent Rating Scale (VADPRS) was completed by their parents. Diagnosis and classification were performed based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Comorbidities and functional impairments were evaluated according to the VADPRS. Children with various types of ADHD were compared in terms of comorbidities and functional impairments, and their relationship with the core symptoms of ADHD was analyzed.

RESULTS: Of the 319 children, 196 were diagnosed with ADHD, including 84 cases of predominantly inattentive type (ADHD-I), 35 cases of predominantly hyperactive-impulsive type (ADHD-HI) and 77 cases of combined type (ADHD-C); 123 did not meet the diagnostic criteria for ADHD. At least one other psychiatric disorder (oppositional defiant disorder, conduct disorder or emotional disorder) was seen in 63.8% (125/196) of the children with ADHD, versus 37.4 % (46/123) of the children without ADHD ($P<0.05$). The incidence of oppositional defiant disorder and conduct disorder in the ADHD-C subgroup was significantly higher than in the ADHD-I subgroup ($P<0.05$). The sums of oppositional defiant disorder, conduct disorder and emotional disorder symptoms were weakly correlated with the sums of hyperactive-impulsive and inattentive symptoms ($P<0.01$). Up to 89.8% of children with ADHD and 74.8% of children without ADHD showed functional impairments ($P<0.05$). The ADHD-C subgroup had a significantly higher overall incidence of functional impairments than the ADHD-I and ADHD-HI subgroups ($P<0.05$). The sum of inattentive symptoms was weakly correlated with the scores of learning ability, sibling relationship and participation in organized activities ($P<0.01$), and the sum of hyperactive-impulsive symptoms was weakly correlated with the score of sibling relationship ($P<0.01$).

CONCLUSIONS: The incidence of comorbidities and functional impairments among children with ADHD is high, especially in those with ADHD-C. The severity of core symptoms in children with ADHD can influence the occurrence of comorbidities and functional impairments. The incidence of psychiatric disorders and functional impairments is also high in children with suspected ADHD who do not meet the diagnostic criteria for ADHD, so attention also needs to be paid to interventions among these children.

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Zhongguo Dang Dai Er Ke Za Zhi. 2013 Sep;15:733-36.

CLINICAL FEATURES AND COMORBIDITIES OF ASPERGER SYNDROME IN CHILDREN.

Fu XY, Xie XT, Mei Z, et al.

OBJECTIVE: To investigate and summarize the clinical features and comorbidities of Asperger syndrome (AS) in children and to provide a theoretical basis for improving the understanding and diagnosis of AS.

METHODS: Inquiry of medical history, physical examination, behavioral observation, psychiatric examination, questionnaire survey, and the Wechsler Intelligence Scale were used to summarize and analyse the clinical data of 95 children with AS, including chief complaint, symptoms, perinatal and familial conditions, family genetic history, and common comorbidities.

RESULTS: AS was more common in male children, with hyperactivity, inattention, and social withdrawal as frequent chief complaints. The main clinical manifestations included poor communication skills (95%), restricted interest (82%), repetitive and stereotyped patterns of behavior (77%), semantic comprehension deficit (74%), and indiscipline (68%). Verbal IQ was higher than performance IQ in most patients. The comorbidities of AS included attention deficit hyperactivity disorder (ADHD) (39%), emotional disorder (18%), and schizophrenia (2%); emotional disorder was more common in patients aged 13-16 years, while ADHD was more common in patients aged 7-16 years. Among these patients, 61% had fathers with introverted personality, 43% had mothers with introverted personality, and 19% had a family history of mental illness.

CONCLUSIONS: AS has specific clinical manifestations. It is essential to know more about the clinical features and comorbidities of AS, which is helpful for early identification and diagnosis of AS.

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Zhonghua Yi Xue Za Zhi. 2013 May;93:1555-58.

MATHEMATICAL COGNITIVE FUNCTION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A BEHAVIOR AND EVENT-RELATED POTENTIAL STUDY.

Wang DD, Dong X, Ren YL, et al.

OBJECTIVE: To explore the mathematics cognitive function of children with attention deficit hyperactivity disorder and explore neural mechanisms with event-related potential(ERP) and behaviors.

METHODS: Behavior data and ERP elicited by performing mental calculation tasks were recorded in 27 children with ADHD and 29 normal controls from July to October 2012 at Third Affiliated Hospital of Soochow University. The differences of behaviors and N2 component of ERP were compared and analyzed.

RESULTS: The reaction time of the children with ADHD were longer than the control group in addition, subtraction and multiplication ((949 +/- 144) vs (829 +/- 166) ms, (981 +/- 129) vs (856 +/- 170) ms, (944 +/- 136) vs (825 +/- 172) ms, all $P < 0.05$). While the correct rate were less than normal control in all three arithmetic operations (0.80% (0.72%, 0.88%) vs 0.90% (0.85%, 0.96%), 0.78% (0.64%, 0.85%) vs 0.90% (0.84%, 0.93%), 0.86% (0.74%, 0.92%) vs 0.93% (0.90%, 0.98%), all $P < 0.05$). N2 component could be elicited by all subjects in forehead. The amplitude of N2 of children with ADHD were significantly lower than control group in all three arithmetic operations at left frontal (F3: (-3.5 +/- 5.2) vs (-6.7 +/- 3.5) microV, (-3.8 +/- 4.0) vs (-7.4 +/- 4.5) microV, -5.8 (-7.6, 1.6) vs -6.4 (-10.3, -4.9) microV, all $P < 0.05$) and Fz ((-4.3 +/- 6.4) vs (-7.4 +/- 4.2) microV, (-5.0 +/- 5.4) vs (-7.9 +/- 4.6) microV, -5.2 (-9.7, -0.6) vs -7.9 (-10.5, -5.1) microV, all $P < 0.05$), the latency of ADHD group were prolouger than controls in subtraction operations at right and left frontal ((328 +/- 36) vs (307 +/- 27) ms, 325 (307, 354) vs 309 (280, 330) ms) and frontal electrodes ((331 +/- 35) vs (311 +/- 30) ms, all $P < 0.05$). In addition and multiplication operations, there was no significant difference in latency (all $P > 0.05$).

CONCLUSIONS: The children with ADHD have weak capacities of inhibition irrelevant information and paying attention to control. Their deficits in mental arithmetics may be due to the difficulties of selecting the best strategy during cognitive tasks.

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Michela Di Trani*, Francesca Di Roma, Maria Cristina Scatena and Renato Donfrancesco

Severity of symptomatology and subtypes in ADHD children with comorbid oppositional defiant and conduct disorders

Abstract

Background: The relationship between attention-deficit/hyperactivity disorder (ADHD), oppositional defiant and conduct disorders (ODD/CD) requires further studies.

Methods: The aim was to examine the relationship among ADHD severity [assessed by ADHD Rating Scale-Parent Version (PV)], ADHD subtypes, and the comorbidity with ODD/CD in 217 Italian ADHD children.

Results: A total of 35.02% of the participants displayed ADHD with ODD, 14.29% ADHD with CD, and 50.69% no ODD/CD comorbid diagnosis. The Hyperactivity Score of the ADHD Rating Scale-PV was a significant predictor of ODD; age and the Hyperactivity Score were significant predictors of CD. The combined subtype was significantly higher in CD children.

Conclusions: Data, which confirm the only recent article on the topic, help to clarify the relationship between ADHD and externalizing disorders.

Keywords: attention-deficit/hyperactivity disorder (ADHD); comorbidity; externalizing disorders.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is associated with a significant functional impairment characterized by inattention, impulsivity, and motor restlessness. ADHD is often complicated by oppositional defiant disorder (ODD), a disorder characterized by hostility and defiance, and Conduct Disorder (CD), which is marked by a pattern of repetitive behavior wherein the rights of others or social norms are violated [1, 2]. Although findings from

epidemiological studies have consistently demonstrated that ADHD, ODD, and CD frequently co-occur [2, 3], little is known about the nature of this comorbidity.

As regards the relationship between ODD and CD, several studies have suggested that ODD increases the risk of CD, although the majority of patients with ODD do not go on to develop CD [4–9]. Moreover, other studies have shown that ODD is the primary precursor of CD and that these disorders may share the same underlying pathology [10, 11]; by contrast, other studies consider these two diseases as separate disorders [12, 13]. Indeed, the similarities between ODD and CD have given rise to a debate on whether they are truly separate entities or merely different manifestations of the same pathology [7].

The etiology of these comorbid disorders is influenced by both genetic and environmental factors [14, 15]. The risk factors associated with ODD and CD include poverty, lack of parental monitoring, community violence, and poor and disadvantaged neighborhoods [16]. Paternal psychopathology and the quality of the mother-child relationship may represent a risk specifically for comorbid CD [17].

With regard to specific aspects of the relationship between ADHD and ODD/CD, ADHD comorbidity with CD may be associated with an increased symptom severity of disruptive behavior disorders and learning problems [18]. Indeed, a study conducted on 200 boys with ADHD revealed greater ADHD symptom severity (using the ADHD Rating Scale-Parent Version (PV)) in boys with either ADHD plus ODD or ADHD plus CD than in those with ADHD alone [3]. Moreover, the relationships in the families of ADHD plus ODD/CD children were found to be more conflictual and less organized than those of children with ADHD alone [19]. The co-occurrence of CD or ODD with ADHD also is associated to other psychiatric comorbidities, such as depression, bipolar disorder, and anxiety [6].

With regard to ADHD subtypes, studies have shown that ODD is usually associated with the combined ADHD subtype [3, 8] and hyperactivity subtype [20]. Moreover, hyperactivity/impulsivity behaviors appear to foster the development of ODD behaviors [21, 22], whereas the inattention factor is not predictive of ODD symptoms over

time. This hypothesis is based on the observation of hyperactivity/impulsivity behaviors in children who are more difficult to parent, which increases the likelihood of difficult parent-child interactions and, consequently, the development of ODD behaviors [23]. By contrast, ODD behaviors are not considered to foster the development of hyperactivity/impulsivity behaviors over time [24].

The main aim of our study was to examine the relationship among ADHD severity, ADHD subtypes, and the presence or absence of an oppositional/conduct comorbid disorder in a sample of 217 Italian children with ADHD. In particular, the sample comprised, for the first time, all Italian children and is composed of all drug-free children.

We hypothesized that (a) ADHD children with comorbid ODD or CD display more severe symptoms than ADHD children without comorbid disorders and (b) ADHD children with comorbid ODD or CD are more frequently diagnosed with the combined and hyperactive ADHD subtypes.

Methods

Participants

All 6- to 14-year-old children at their first diagnosis of ADHD consecutively studied in the Outpatient Service of "ASL Roma A" between January 2009 and September 2010 were enrolled in the present study. All were drug free. The age range selected for the purposes of this study was considered to include the most representative years of "classic" childhood ADHD.

The sample comprised 217 Caucasian children (191 boys and 26 girls; mean age, 8.60 years; SD, 2.43 years). The entire sample was subdivided into 102 children with the ADHD-combined subtype, 26 with the ADHD-primarily hyperactive subtype, and 89 with the ADHD-primarily inattentive subtype.

As regards the comorbid diagnosis, 76 children displayed an oppositional defiant comorbid disorder (ADHD with ODD group; 35.02% of the sample), whereas 31 displayed a conduct comorbid disorder (ADHD with CD group; 14.29% of the sample).

As regards intellectual functioning, total intellectual quotient (IQ), verbal IQ (V-IQ), and performance IQ (P-IQ) [assessed by Wechsler Intelligence Scale for Children, Third Edition (WISC-III)] all fell within the normal range (total IQ: mean, 100.08; SD, 14.31; V-IQ: mean, 103.40; SD, 14.62; P-IQ mean, 95.87; SD, 14.29).

All the subjects fell within a middle to upper middle socioeconomic level, with a mean score of 71.01 (SD, 15.15) on the Hollingshead Scale [25].

Assessments

Psychiatric and psychometric evaluation

Psychiatric diagnoses, including ADHD and psychiatric comorbidity, with particular attention on ODD and CD, were established according

to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria [26] and confirmed by semi-structured interview Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version [27], which was conducted by an experienced child psychiatrist (R.D.). Moreover, parents of all the children were asked to fill out the ADHD Rating Scale-PV, adapted to the Italian population [28], which is designed to explore the severity of ADHD symptomatology. WISC-III (Italian version) [29] was used to estimate the children's IQ.

Medical assessment

A medical history was collected, and neurological and physical examinations, including an electroencephalogram, were performed in all the ADHD participants to exclude comorbid medical and neurological conditions.

Informed consent

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents of all participants, and written assent was obtained from all the children.

Procedure

The following exclusion criteria were adopted: (1) intellectual deficiency (full-scale IQ <70 on the WISC-III, Italian version [29], according to DSM-IV-TR criteria [26]); (2) any neurological diseases. The adoption of these two criteria was designed to reduce neurobiological heterogeneity that may affect childhood behavior.

All the ADHD children enrolled in the study were stimulant naive at the first diagnosis. In Italy, stimulant treatment can only be prescribed after a thorough diagnostic procedure confirms the diagnosis of ADHD. Upon confirmation of the diagnosis, children with ADHD are included in a "national surveillance register" [30], after which treatment can commence. As this procedure discourages family and doctors from using drugs, children are rarely treated with stimulants before a formal diagnosis of ADHD has been made.

Statistical analysis

Differences in sociodemographic characteristics (age, gender, and socioeconomic level) were evaluated in all three groups (ADHD with ODD, ADHD with CD, ADHD without ODD/CD) using χ^2 analysis on categorical variables and one-way ANOVAs on continuous variables.

To assess intergroup differences in the IQ levels and ADHD symptom severity, one-way ANOVAs were also performed on the ADHD Rating Scale-PV scores and total, V-IQ, and P-IQ scores. Subsequently, Bonferroni's post hoc test was performed to assess any specific differences between groups.

In addition, χ^2 analysis was computed to test group differences in subtype distributions (combined, hyperactive, and inattentive) in the three groups.

Lastly, logistic regressions were used to confirm the former results about the demographic variables and to verify the predictive role of severity and ADHD subtypes on the presence/absence of an ODD or CD comorbid diagnosis, which were codified as dummy variables. In particular, in different sets of analyses, the presence/absence of an ODD and presence/absence of CD comorbid diagnosis were included as dependent variables, and two models were run: the first included age, gender, IQ, socioeconomic level, and ADHD Rating Scale-PV scores (Total, Hyperactive, and Inattentive scores) as independent variables, whereas the second model included age, gender, IQ, socioeconomic level, and ADHD subtypes (combined, hyperactive, and inattentive subtypes) as independent variables.

Results

In our sample, 107 (49.31%) of the participants displayed a comorbid externalizing disorder. In particular, children with ADHD and ODD are 76 (35.02% of the sample), whereas children with ADHD and CD are 31 (14.29%).

As Table 1 shows, no differences in gender distribution or socioeconomic level were observed between ADHD patients with ODD, those with CD, and those without ODD/CD. By contrast, significant differences emerged among the three groups in age, with the post hoc analysis revealing that children with CD were older than either children with ODD ($p < 0.01$) or those without ODD/CD ($p < 0.01$).

Although no differences were found among the three ADHD groups in IQ levels (p always > 0.1), differences emerged in the severity level of the disorder. Indeed, regarding the ADHD Rating Scale-PV, ADHD children

without ODD/CD had lower scores in the Total, Hyperactivity, and Inattentive Scales than either ADHD children with ODD (p always < 0.01) or those with CD (p always < 0.01) (see Table 2).

As regards the ADHD subtype distribution, 37 (48.7%) of the ADHD subjects with ODD presented the combined subtype, 10 (13.2%) the hyperactive-impulsive subtype, and 29 (38.1%) the inattentive subtype. Twenty-five (80.6%) of the ADHD children with CD presented the combined subtype, 2 (6.5%) the hyperactive-impulsive subtype, and 4 (12.9%) the inattentive subtype. Forty (36.4%) of the ADHD children without ODD/CD presented the combined subtype, 14 (12.7%) the hyperactive-impulsive subtype, and 56 (50.9%) the inattentive subtype.

The number of cases of combined subtype was significantly higher among ADHD children with comorbid CD than among children without ODD/CD ($\chi^2 = 19.33$, $p < 0.01$) or those with ODD ($\chi^2 = 9.23$, $p < 0.01$). Moreover, the number of inattentive subtype cases was significantly lower among ADHD children with CD than among children without ODD/CD ($\chi^2 = 14.29$, $p < 0.01$) or those with comorbid ODD ($\chi^2 = 6.58$, $p < 0.005$).

Lastly, logistic regression analysis showed that only the Hyperactivity Score of the ADHD Rating Scale-PV was a significant predictor of the presence of comorbid ODD in ADHD children ($B = 0.17$, $p < 0.01$), whereas age ($B = 0.03$, $p < 0.01$) and the Hyperactivity Score of the ADHD Rating Scale ($B = 0.14$, $p < 0.05$) were significant predictors of the presence of comorbid CD.

Table 1 Demographic data.

	ADHD with ODD (n=76)	ADHD with CD (n=31)	ADHD without ODD/CD (n=110)	χ^2/F	p-Value
Boys	71	28	92	4.26	NS
Age, mean (SD)	8.77 (2.71)	10.54 (2.35)	8.45 (2.30)	9.11	0.00
Socioeconomic status, mean (SD)	71.97 (13.23)	66.81 (20.38)	71.53 (14.63)	1.42	NS

Table 2 Comparison of ADHD children with ODD, ADHD with ODD plus CD, and ADHD without ODD/CD at the cognitive level and according to ADHD symptomatology.

	ADHD with ODD (n=76)	ADHD with CD (n=31)	ADHD without ODD/CD (n=110)	F/χ^2	p-Value
IQ, mean (SD)					
Total IQ	105.20 (31.33)	100.16 (11.38)	98.64 (13.98)	1.34	NS
IQ-P	97.71 (15.40)	96.68 (12.47)	94.36 (13.92)	1.29	NS
IQ-V	105.71 (16.19)	103.42 (13.99)	101.80 (13.53)	1.62	NS
ADHD-RS, mean (SD)					
Total Score	39.61 (7.21)	40.84 (7.98)	33.90 (8.53)	15.80	0.00
Hyperactivity scale	20.28 (4.31)	20.23 (4.76)	16.21 (5.33)	18.38	0.00
Inattentive scale	19.39 (4.77)	20.61 (3.85)	17.61 (4.98)	6.18	0.00

Discussion

The aim of our study was to examine the relationship among ADHD severity, ADHD subtypes, and the presence or absence of ODD/CD as comorbid disorders. No study was performed in the past about this concern in a European country, as Italy, so the objective of the article was also to verify the literature data on this topic in an Italian sample.

We first investigated whether there are any differences among ADHD patients with ODD, ADHD with CD, and ADHD without any externalizing comorbidity in gender, age, socioeconomic level, and IQ. Subsequently, we compared the symptom severity level and subtype distribution in the three groups.

No significant differences were found when the gender, socioeconomic level, and IQ of the different ADHD groups were compared. Regarding gender and socioeconomic state, this is not expected, and the reason might be that the female group (26 patients) or low socioeconomic class was underrepresented. As expected, significant differences were found in age, with ADHD children with CD being older than either ADHD children with ODD or those without ODD/CD.

Moreover, our results showed that also in a European country, specifically in Italy, ODD and CD are frequent in ADHD population. Indeed, 35.02% of our ADHD sample had comorbid ODD, whereas 14.29% had CD, which is consistent with previously published findings in other countries [1, 3].

Our work instead yields novel results regarding the relationship between ADHD subtypes and comorbid CD. Although several previous studies have found a higher frequency of the combined ADHD subtype in ODD children [3, 8], in our study, the combined ADHD subtype was significantly more frequent in children with CD than in those without comorbidity or those with ODD. This could be a specific feature of Italian ADHD population.

Another finding of our study is the association that emerged between the severity of ADHD, as assessed by means of the ADHD Rating Scale-PV, and comorbid CD: ADHD children with ODD and ADHD children with CD displayed higher scores in both the Hyperactive and Inattentive Scales. This finding may, however, reflect the greater strictness of these children's parents, who

might describe children with oppositional and CD as being more hyperactive and inattentive than they actually are. Future studies based on an objective measurement tool, such as an actometer, are warranted to clarify this issue.

Lastly, also in our Italian ADHD population, the severity of the Hyperactivity Score in the ADHD Rating Scale-PV emerged as a strong predictor of the presence of comorbid ODD and comorbid CD in ADHD children, which is in keeping with the results of previous studies performed in other countries [21, 22, 24].

In conclusion, our findings, which support those reported in previous studies, highlight the greater prevalence of ODD/CD in children with ADHD and suggest that ADHD increases the risk of developing externalizing disorders [3]. Our results also confirm the findings of a recent study [1] that ADHD with ODD comorbidity is found in 60% of children with ADHD and ADHD with CD is found in 15%. The results of our study also point to the importance, for both clinical and empirical interests, of screening children that present ODD/CD for ADHD symptoms.

One of the strengths of this study is that patients are stimulant naïve at the first diagnosis; one limitation, however, is the lack of an objective evaluation of the severity of the symptoms, which means that the results may represent a perceived severity of the disorder as opposed to the real presence of major disruptive behavior. Moreover, another limitation of the ADHD subtype analysis is the small subtype sample size; future studies are warranted to confirm and shed further light on the relationship between combined ADHD subtype and comorbid CD. Lastly, our sample may be not representative of the Italian general population because the recruitment was done in only one center and only in the clinical population.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

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EDITORIAL

Gym for the Attention-Deficit/Hyperactivity Disorder Brain? Still a Long Run Ahead....

Samuele Cortese, M.D., Ph.D.

Currently, the mainstay of treatment for attention-deficit/hyperactivity disorder (ADHD), at least in North America, is pharmacologic, with psychostimulants usually the first line and nonpsychostimulant agents as secondary options.¹ When considering the effect size on ADHD core symptoms in short-term trials, psychostimulants are the most effective drugs in psychiatry. However, psychostimulants and nonpsychostimulant medications present some limitations: clinical normalization does not occur in all treated patients; available agents are symptomatic over the short term and not curative; adverse events, such as sleep disturbances and appetite decrease, are common during treatment, although generally temporary and/or easily manageable; long-term effectiveness and safety of psychotropic treatments cannot be definitively established; and some parents, patients, and even clinicians have reservations about long-term use of medication for a behavioral condition. Non-pharmacologic options, such as behavioral interventions, diet regimens, cognitive training, and neurofeedback, are also available, although the empirical evidence for their efficacy, at least for ADHD core symptoms, remains uncertain.² Therefore, there is a need for additional non-pharmacologic approaches that can target underlying specific pathophysiologic mechanisms, thus providing long-term curative action. In addition, ADHD is increasingly conceived as a syndrome resulting from a complex interplay of risk and protective factors, genetic and environmental; as such, promoting protective factors early in the child's development may contribute to decrease the symptoms and associated impairments.

Rommel *et al.*³ nicely build on these unmet needs to discuss the role of physical exercise as a possible approach grounded on the pathophysiology of ADHD to contribute to the treatment/prevention of the disorder or the impairment

associated with it. The authors first surveyed the literature on the brain and cognitive effects of physical exercise (in animal models and humans), which provided a background for the hypothesis of physical exercise as a putative management strategy for ADHD. With regard to brain effects, the authors focused in particular on the exercise-induced increase of brain-derived neurotrophic factor, although the role of brain-derived neurotrophic factor in the pathophysiology of ADHD remains unclear. Other possible brain effects of physical exercise involve increased neurogenesis, synaptic plasticity, spine density, angiogenesis, and extracellular dopamine and norepinephrine. Clearly, these are general mechanisms that likely affect several cognitive and behavioral processes cutting across different psychiatric disorders, rather than being specific to ADHD. With regard to the cognitive effects of exercise in children, meta-analytic evidence has shown a significant effect, although the moderate effect size (~ 0.3 overall) calls for further clarification of the actual clinical impact that physical exercise might have (values ≤ 0.2 , 0.5 , and ≥ 0.8 define, respectively, small, moderate, and large effect sizes).

After providing this background, the authors reviewed the studies that specifically assessed the effects of physical exercise on ADHD and/or ADHD-related impairments. By a comprehensive search in the most common electronic databases, they were able to locate only a relatively small number of studies ($n = 16$) conducted in humans or in animal models (rats) of ADHD.

Retrieved studies in rats ($n = 4$) were heterogeneous in assessed outcomes (hyperactivity, attention orienting, and spatial learning memory). Nonetheless, they suggest that physical exercise might improve cognition and behavior in animal models of ADHD. Preliminary evidence from these studies also has indicated that physical exercise might be as effective as ADHD

medications on ADHD-related cognitive impairment. However, animal models often use cognitive measurements that barely overlap with the cognitive paradigms in human research. Therefore, the extent to which these preliminary results from animal models can be applied to humans requires further elucidation.

The reviewed studies in humans ($n = 12$), taken together, indicated that physical exercise may decrease at least some of the behavioral, emotional, and neuropsychological impairments in children with ADHD. However, this preliminary conclusion should be taken very cautiously given the heterogeneity of the studies in duration of physical exercise (from acute bouts to several weeks training), assessed outcomes (executive functions, behavioral ratings, or academic performance), and, perhaps more importantly, study design: only 2 studies were randomized controlled trials, the others being nonrandomized case-control trials, within-group comparisons, or correlational studies. The effect sizes also varied across studies, depending on the specific assessed outcome, but in general were small to moderate. The underlying neurobiological changes induced by physical exercise were investigated in only 3 studies, with contrasting results in relation to the effects on catecholamine levels.

Therefore, additional methodologic sound research, based on a rigorous randomized controlled design, will be needed to answer several questions. First, is and to what extent is physical exercise an effective treatment/preventive approach in children with ADHD? In particular, given the heterogeneous and, in general, small effect sizes detected thus far, it will be pivotal to determine whether physical exercise could be an effective approach per se or should be better considered complementary to other existing interventions. The latter would seem more likely, considering the difficulties of implementing regular physical activity in children with ADHD, or at least in some of them: "(S)he started practicing sport but (s)he stopped it since (s)he could not stay focused during the activity" is a sentence that practitioners dealing with children with ADHD are very familiar with. Second, which type, duration, and frequency of physical exercise are most effective on cognitive and behavioral functions? To this regard, it will be important to differentiate the acute and long-term effects of exercise and to understand the exact amount of required exercise, given evidence of a curvilinear relation between intensity of physical exercise

and cognitive effects (i.e., moderate aerobic exercise has been found to be more effective than intense activity⁴). Third, which ADHD-related characteristics can be improved with exercise? In line with the current trends in intervention research in ADHD,⁵ it will be interesting to assess if physical exercise can affect not only ADHD core symptoms, but also more general indicators of quality of life. Fourth, which subgroup of patients can better benefit from physical exercise, in relation to their genetic, neurocognitive, and behavioral profiles?

Only once such a body of methodologic sound research is available will it be possible to apply the deep level of scrutiny that has been recently used by the European ADHD Guidelines Group (EAGG) to assess the effectiveness of nonpharmacologic interventions for ADHD.² One of the main findings by the EAGG is that the extent to which a nonpharmacologic intervention for ADHD is effective depends on the blinding status of the rater, with unblinded raters providing generally better estimates, likely because of expectation effects. Therefore, it will be critical to include blinded ratings in future research assessing physical exercise in ADHD.

Positive results from future well-designed studies may provide empirical support to the recommendation of physical exercise as a management strategy for children with ADHD. Although all children may benefit from physical exercise, it may be especially worthy to recommend it for children with ADHD; this is particularly relevant in light of preliminary evidence pointing to an increased risk of obesity in children with ADHD.⁶ Also, the adoption of physical exercise as a treatment/preventive strategy for behavioral and cognitive dysfunctions may have major public health implications, in consideration of the current decrease, at least in the United States, of opportunities for physical activities during the school day given budgetary constraints.

Rommel *et al.*³ should be praised for pointing to a possible novel management approach in ADHD, focusing on protective, rather than risk, factors within a neurodevelopmental perspective. However, their review suggests that there is still a long run ahead to understand if, to which extent, and how physical exercise can be an effective treatment/preventive strategy for ADHD. Such research could turn out to be a very fruitful exercise for the field, and, ultimately, relevant impact for our patients. &

CORTESE

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Case Reports of Sleep Phenotypes of ADHD: From Hypothesis to Clinical Practice

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Abstract

Objective: Five sleep ADHD phenotypes have been hypothesized: (a) the hypo-arousal state of the “primary” form of ADHD, (b) the sleep phase advanced disorder, (c) sleep disordered breathing (SDB), (d) restless legs syndrome and/or periodic limb movements disorder (PLMD), and (e) epilepsy. **Method:** Five case reports are presented; each child but one underwent video-polysomnography. **Results:** The first case report is an example of ADHD and SDB, with improvement of hypersomnolence after resolution of sleep apnea. The second case shows the impact of delayed sleep onset latency in the pathogenesis of ADHD, and the efficacy of melatonin. The third case report describes the association with PLMD, with amelioration after iron supplementation. The other two cases are examples of ADHD and epilepsy, with clinical improvement after antiepileptic treatment was started. **Conclusion:** A diagnostic and therapeutic algorithm should be designed to find the best first-line treatment for ADHD and sleep problems/epilepsy. (*J. of Att. Dis.* 2013; 17(7) 565-573)

Keywords

sleep disorders, children, treatment

Introduction

Although a wide range of sleep disorders, ranging from insomnia to hypersomnia, have been reported to affect more than half of the individuals with ADHD, the association between sleep and ADHD has yet to be fully understood. One reason for the limited knowledge available on this association is the heterogeneity of the sleep studies that have been conducted to date, which differ considerably with regard to the methods adopted (questionnaire, actigraphic, and polysomnographic studies), the subjects' age (ranging from childhood to adulthood), the diagnosis (ADHD with and without comorbidities), and the type of sleep disorders investigated (Miano, Parisi, & Villa, 2012). Despite these limitations, it has clearly been demonstrated that there is a strong association between sleep disorders and ADHD, which in turn has a significant impact on the subjects' quality of life since sleep problems persist into adulthood (Yoon, Jain, & Shapiro, 2013). Moreover, there is a growing interest in gaining a better characterization and understanding of the various sleep disorders (Miano et al., 2012). One simple explanation for the close relationship between sleep and ADHD is that sleep loss has similar daytime cognitive and behavioral costs, affecting various aspects of performance and reducing attention and vigilance, decision-making abilities, and memory functions (Nobili et al., 2012). In other words, the more severe and chronic the sleep disorder is, the more severe the daytime

cognitive and behavioral consequences are, as has been demonstrated in several experimental human and animal studies on sleep deprivation (Hanlon, Faraguna, Vyazovskiy, Tononi, & Cirelli, 2009; Landsness et al., 2009; Landsness et al., 2011).

We recently proposed five sleep ADHD phenotypes (Miano et al., 2012): (a) a sleep phenotype characterized mainly by a hypo-arousal state, resembling narcolepsy, which may be considered a “primary” form of ADHD; (b) one associated with delayed sleep onset latency; (c) one associated with sleep disordered breathing (SDB); (d) one associated with restless legs syndrome (RLS) and/or periodic limb movements disorder (PLMD); and (e) the last one associated with epilepsy/or electroencephalographic (EEG) interictal discharges. All the sleep phenotypes, except for the primary form of ADHD and those related to focal benign epilepsy or focal EEG discharges, are associated with an increased level of arousal during sleep, which induces sleep loss. Moreover, sleep deprivation is obviously also present in individuals with sleep phase advanced syndrome because

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the total sleep time at their disposal to attend to normal daily activities, which usually start in the early morning, is reduced.

A dysfunction of one of the three main sleep regulatory processes may be hypothesized in each sleep ADHD phenotype: an alteration of the circadian process that couples the timing for sleep and wakefulness with the light–dark cycle is implicated in the sleep phenotype of insomnia with delayed sleep onset; an alteration of the homeostatic process, which modulates sleep intensity, may be implicated in all the sleep phenotypes associated with sleep deprivation (obstructive sleep apnea [OSA] syndrome, RLS and or PLMD, epilepsy); and last, an alteration of the ultradian process, which regulates the intra-sleep non-REM–REM (random eye movement) alternation, might be implicated in the “primary” form of ADHD (Borbély & Achermann, 1999).

The clinical and therapeutic implications of this theoretical distinction will be described and discussed hereafter through the presentation of case reports that illustrate the clinical subdivision in sleep phenotypes. Each child but one described in the following sections underwent a polysomnography (PSG) in our sleep center, which is an accredited sleep laboratory specifically designed for pediatric studies. Since the descriptions do not include any children with ADHD without sleep problems, who probably belong to the “primary ADHD” phenotype, the case reports do not aim to accurately portray the distribution of sleep problems in ADHD.

The Sleep Phenotype of Obstructive Sleep Apnea: Case Report 1

An obese Caucasian boy was referred to the Sleep Paediatric Centre of the Sant'Andrea Hospital, “La Sapienza” University of Rome, at the age of 15.8 years, because he snored loudly and had experienced several episodes of OSA associated with daytime sleepiness. The parents reported that the sleep respiratory problems had started in the child's first years of life.

The boy was born at term, after an uneventful pregnancy and normal delivery. At the age of 2 years he underwent an adenoidectomy for adenoid hypertrophy, though with no significant improvement in his sleep respiratory problems.

He was hyperactive during daytime since the first years of his life. Five years ago, he was evaluated in a Clinic for Developmental Neurology and Psychiatry and diagnosed with ADHD-combined subtype and dyspraxia, according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association [APA], 1994). He was placed on therapy with methylphenidate and fluoxetine, which led to an improvement in the attention deficit and hyperactivity disorder.

At the first physical examination, his height was normal for his age (172 cm, 42nd centile), but he was found to be overweight (109.2 kg, 121st centile), with a BMI of 35.9 kg/m²

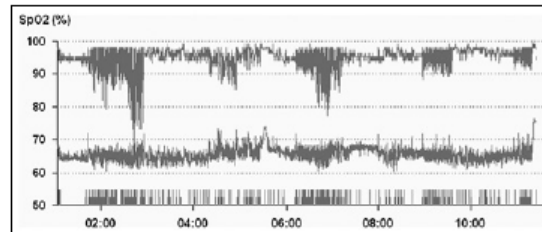


Figure 1. Overnight pulse oximetry (SpO₂%) recording showing five clusters of oxygen desaturation (Case Report 1).

Note. LOC = left oculogram; ROC = right oculogram; ECG = electrocardiogram; SaO₂ = overnight oxygen saturation; R/L-LEG = right/left leg (Case Report 1).

(120th centile); he also had macroglossia, a right unilateral crossbite, and Grade 2 tonsillar hypertrophy, according to a standardized scale (Friedman, Ibrahim, & Joseph, 2004). Nocturnal pulse oximetry revealed a mean oxygen saturation of 94.7% and a total of 215 desaturations, including 51 events with oxygen saturation <88%, with a McGill score of 4 (Nixon et al., 2004; see Figure 1).

To define the severity of OSA more accurately, 2 months later he underwent a standard overnight video-polysomnography (PSG). The variables recorded included a scalp EEG, electrocardiogram, electro-oculogram, chin electromyogram, nasal pressure, oral airflow, respiratory effort, chest and abdominal movement, oxygen saturation, and bilateral tibialis anterior electromyogram. Sleep staging and sleep respiratory events were scored according to the standard criteria of the American Academy of Sleep Medicine (Iber, Ancoli-Israel, Chesson, & Quan, 2007). PSG confirmed a severe form of OSA, with an apnea/hypopnea index (AHI) of 97.6 (n/h) and an overnight oxygen saturation of 93.4% (see Figure 2).

The otorhinolaryngologic evaluation revealed a basal right deviation of the nasal septum, uvulopalatal prolapse, and hypertrophy of the basal tongue. A second PSG was performed the following day to titrate continuous positive airway pressure (C-PAP). The child was then discharged on nasal C-PAP therapy at 6 cm H₂O, combined with topical nasal corticosteroid therapy.

At the 3-month follow-up following the start of C-PAP, a third PSG showed a reduction in AHI to 8 n/h and a slight increase in overnight saturation (94.0%), associated with an improvement in the child's sleep problems and daytime sleepiness.

The Sleep Phenotype of ADHD and Delayed Sleep Phase Syndrome: Case Report 2

An 11.7-year-old Caucasian boy was referred to the Sleep Paediatric Centre of the Sant'Andrea Hospital owing to delayed sleep onset (after 11:00 p.m.), restless sleep, daytime irritability and sleepiness, and co-sleeping since

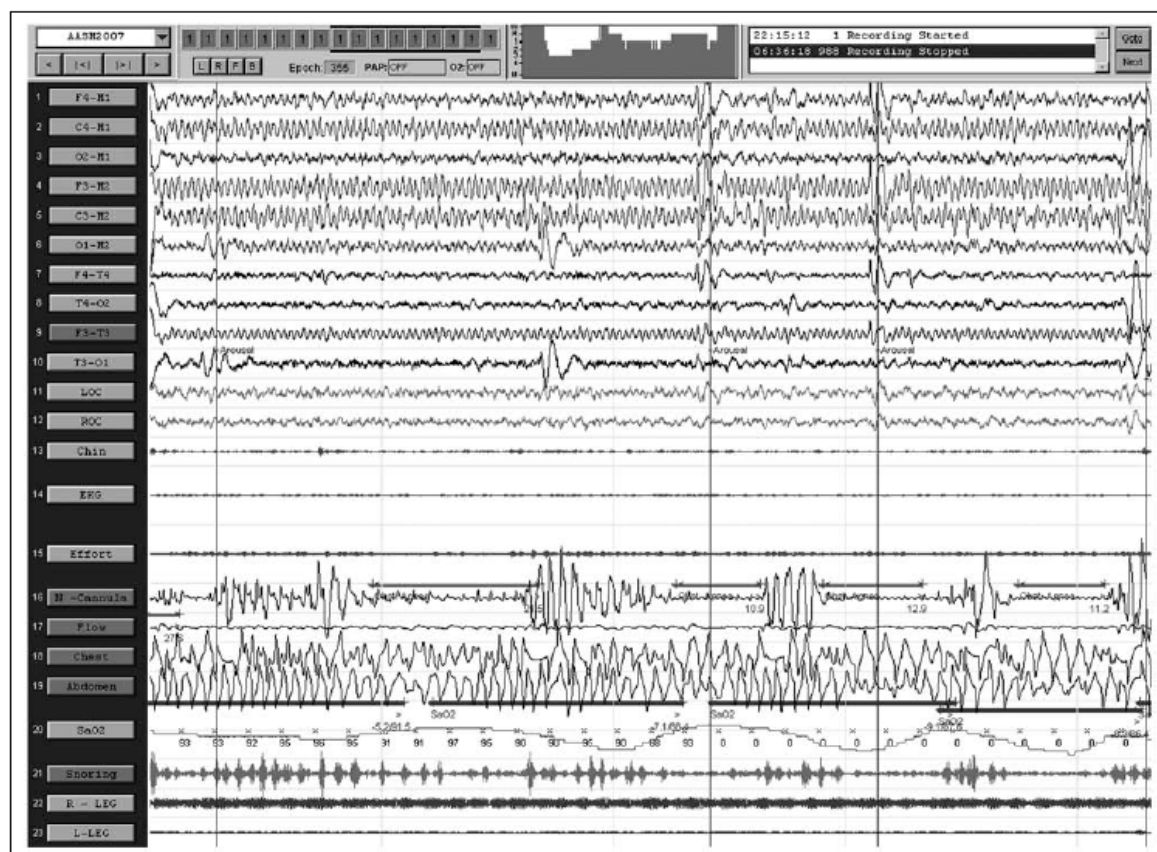


Figure 2. Two-min epoch of polysomnography showing a sequence of obstructive sleep apnea associated with significant oxygen desaturation.

Note. LOC = left oculogram; ROC = right oculogram; ECG = electrocardiogram; SaO₂ = overnight oxygen saturation; R/L-LEG = right/left leg (Case Report 1).

starting school. Some months before, he had been evaluated in a Clinic for Developmental Neurology and Psychiatry owing to a suspected learning disability, where he was diagnosed with attention disorder and dyslexia, according to the *DSM-IV* (APA, 1994). The boy was born at term, after an uneventful pregnancy and normal delivery.

At our clinical examination, he was found to have inferior turbinate hypertrophy, normotrophic tonsils, deep bite, and a normal height of 151 cm (57° centile) and weight of 43 kg (63° centile), with a BMI of 18.9 m/kg (62° centile).

He underwent a PSG (see Case Report 1 for details), which only revealed an altered sleep quality, with a reduced sleep efficiency (70.16%).

Treatment with melatonin (1-mg fast-release, 4-mg controlled-release) was prescribed. Three months of therapy led to a complete resolution of the insomnia as well as a significant improvement in school performance and ADHD symptoms, as reported by the teachers and parents.

The Sleep Phenotype of ADHD and RLS: Case Report 3

A 6.2-year-old boy was referred to our Sleep Disorder Centre for a maintaining sleep disorder with restless sleep, awakenings during sleep, nocturnal leg movements and daytime irritability. The onset of the sleep disorder occurred at the age of 2 years. He was hyperactive and inattentive until preschool age, at school and at home.

The boy was born at term, after an uneventful pregnancy and normal delivery. He also had respiratory allergic symptoms (rhinitis, nasal itching, conjunctivitis, chronic nasal obstruction) and dermatitis, as demonstrated by a positive skin prick test to *Dermatophagoides pteronyssinus* and *D. farinae*, and a positive blood test to albumen.

At the clinical examination we conducted, he displayed a Grade 2 tonsillar hypertrophy according to a standardized scale (Friedman et al., 2004), open bite, high-arched palate,

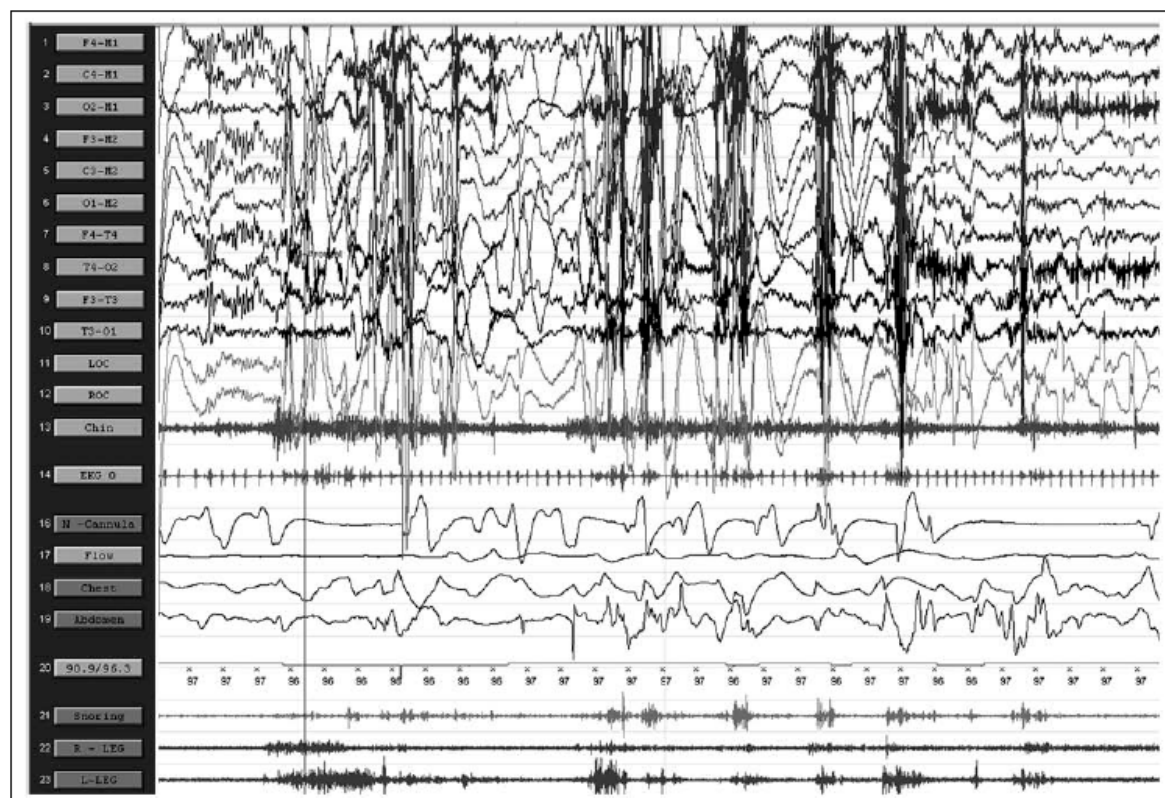


Figure 3. Thirty-second epoch of polysomnography showing a sequence of periodic limb movement, associated with cortical arousal and movement artifact.

Note. LOC = left oculogram; ROC = right oculogram; EEG = electrocardiogram; SaO₂ = overnight oxygen saturation; R/L-LEG = right/left leg (Case Report 3).

and inferior turbinate hypertrophy; his weight was 27 kg (97th centile), his height was 126.5 cm (97th centile), and he had a BMI of 16.9 kg/m² (82nd centile).

An overnight PSG was performed in our Sleep Centre for suspected PLMD (see Case Report 1 for details of the sleep recording). The recording only revealed a sleep quality alteration, with a sleep efficiency of 80.7%, a total wake time after sleep onset of 57.5 min, associated with a PLM's index of 6.6 and numerous limb movements that did not fall within periodic sequences (see Figure 3).

A blood test performed at the same time revealed an increase in the patient's Antistreptolysin-O-titer (971 UI/ml, normal blood values = 0-200 UI/ml) and a decrease in his ferritin level (17 ng/ml, normal blood values = 11-336 ng/ml), while the serum iron, total iron-binding capacity (TIBC), and complete blood count (CBC) were normal; thyroid function and celiac antibodies were within the normal range.

An oral iron supplementation was therefore prescribed (50 mg/die) to improve the subject's quality of sleep. After 3 months of iron supplementation, his sleep problems

resolved completely and his school performance improved, as reported by his teachers and parents.

The Sleep Phenotype of ADHD and Epilepsy: Case Report 4

An 11.5-year-old Caucasian girl was referred to our Sleep Disorder Centre for delayed sleep onset (sleep onset at midnight), restless sleep, and several awakenings during sleep since the age of 10.5 years, following a car accident.

When referred to a Clinic for Developmental Neurology and Psychiatry at 11 years of age on account of difficulties at school, she was diagnosed with dysgraphia associated with the ADHD-combined subtype and tic disorders, according to the *DSM-IV* (APA, 1994). The subject also suffered from recurrent abdominal pain. She was born at term, after an uneventful pregnancy and normal delivery. Her mother suffers from celiac disease and Hashimoto's thyroiditis. The girl's blood and genetic tests were negative for celiac disease, and her iron levels were normal.

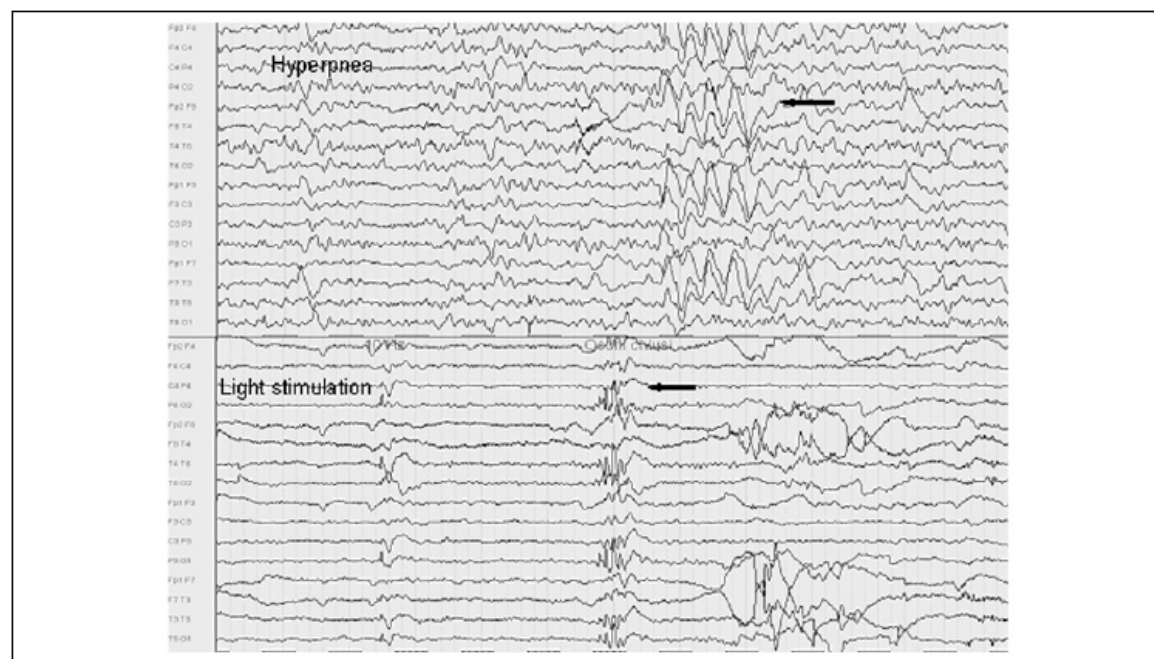


Figure 4. Ten-second epoch of standard EEG showing the occurrence of frontotemporal slow wave activity with superimposed spike during hyperpnea, and photoparoxysmal activity represented by poly-spikes over the parietal-occipital regions.

A standard EEG recording performed after 2 weeks revealed ictal activity during hyperpnoea consisting of diffuse spike and waves, prevalently over the posterior regions, lasting less than 1 s, and a photoparoxysmal response with occurrence of diffuse spikes and poly-spikes, prevalently over the posterior regions, associated with autonomic sensations (see Figure 4). Interictal epileptiform discharges were represented by slow activity and sharp waves over the parietal and occipital regions.

The blood test revealed a high FT3 level (4.56 pg/ml, normal value 2.6-4.5 pg/ml), though with a normal thyroid antibody value, a high Antistreptolysin-O-titer (1,115 UI/ml, normal blood values: 0-200 UI/ml), and a low ferritin level (17 ng/ml, normal blood values = 11-336 ng/ml), whereas transferrin saturation, total iron-binding capacity (TIBC), and complete blood count (CBC) were normal. An allergic blood test revealed an allergy to albumen, wheat, and milk.

She was put on a therapy with lamotrigine (75 mg/die), and received a definitive diagnosis of partial epilepsy (probably a benign form of occipital epilepsy). One month later, at the outpatient follow-up visit, when she said she was "happy," there was a significant improvement in her school performance and attention capacity, a significant reduction in her abdominal pain and sleep problems, while her tic disorder was unchanged. This neurobehavioral improvement

was confirmed by her parents. We recommended that she start a milk- and albumen-free diet.

The Sleep Phenotype of ADHD and Epilepsy: Case Report 5

An 11.4-year-old Caucasian boy was referred to the Sleep Paediatric Centre of the Sant'Andrea Hospital for a maintaining sleep disorder, with restless sleep and sleep hyperkinesia. He had previously suffered from SDB such as snoring and apneas, which had improved following an adenotonsillectomy performed when he was 8 years old. Five months before coming to our attention, he was examined in a Clinic for Developmental Neurology and Psychiatry on account of a suspected learning disability, where he was diagnosed with ADHD-inattentive subtype disorder associated with dyslexia, dyscalculia, and dysgraphia, according to the *DSM-IV* (APA, 1994).

The boy was born at term, after a high-risk pregnancy with threatened miscarriage and caesarean delivery; his psycho-motor development, which was slightly delayed, returned to normal within the first 2 years of his life.

At the age of 13 months, following a head trauma, he suffered an episode characterized by stiffness, gaze deviation, cyanosis, drooling, and hypotonia during prolonged crying. The cerebral magnetic resonance imaging and

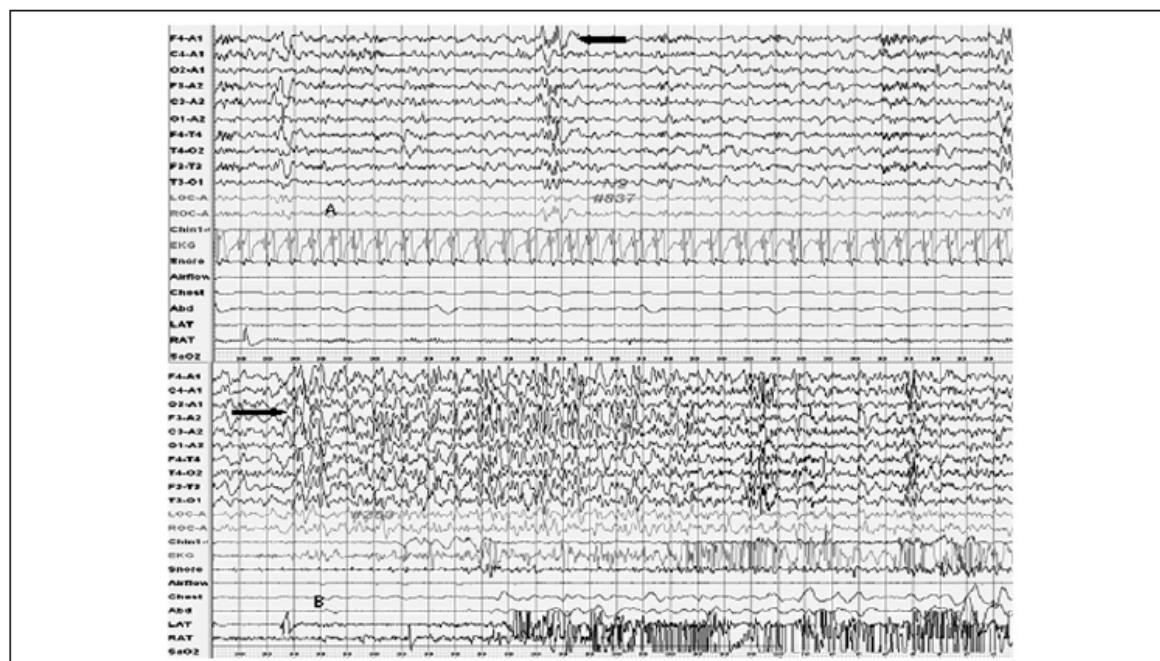


Figure 5. Thirty-second epoch of polysomnography showing interictal epileptiform discharges over the frontal regions, Panel A (theta sharp waves), and ictal discharges (Panel B), prevalently represented by rhythmic diffuse theta activity and movement artifact. Note. LOC = left oculogram; ROC = right oculogram; EKG = electrocardiogram; SaO₂ = overnight oxygen saturation, R/L-LEG = right/left leg (Case Report 5).

computed tomography performed after this episode were negative. After suffering a similar episode a year later, he was diagnosed with breath holding spells.

When we conducted the clinical examination, he was found to have inferior turbinate hypertrophy; his height was 142 cm (95th centile), his weight was 36.4 kg (91st centile), while his BMI was 18.1 kg/m² (78th centile).

An overnight PSG, performed in our Sleep Centre on account of suspected PLMs (see Case Report 1 for details of the sleep recording), revealed epileptiform discharges composed of slow and sharp waves over the anterior regions, 10 nocturnal seizures characterized by rhythmic diffuse theta activity and movement artifact at the EEG, and a sudden awakening from a supine position, with a head and trunk flexion, eyes open, looking around, rotation of head to right (minimal motor events) at the video-recording. In one longer episode (a minor event, lasting about 10 s), he assumed a dystonic and stiff posture, which prevalently affected the extremities and was markedly asymmetric (see Figure 5). According to international criteria (Derry, Harvey, Walker, Duncan, & Berkovic, 2009; Oldani, Zucconi, Ferrini-Strambi, Bizzozero, & Smirne, 1996), he received a definitive diagnosis of nocturnal frontal lobe epilepsy and was discharged with antiepileptic therapy, that is, carbamazepine 300 mg/day, to be administered at bedtime.

After 6 months of therapy, he underwent a second PSG, which showed that his sleep quality had improved when compared with the first PSG: The number of awakenings dropped from 15 to 2, wake after sleep onset dropped from 140 min to 103 min, total sleep time increased from 413 min to 532.8 min, while sleep efficiency rose from 78.28% to 96.64%. The boy's parents also referred a significant improvement in his scholastic performance, inattentive disorder, and nocturnal symptoms.

Discussion

The first case report is a clear example of the ADHD sleep phenotype associated with OSA. Although it may appear obvious that sleep respiratory disorders need to be ruled out (along with other medical conditions) before a diagnosis of ADHD is made, this does not always occur in clinical practice, as the case of this boy, who even had craniofacial abnormalities, demonstrates. We cannot prove that early treatment for OSA would have improved the ADHD symptoms and cognitive dysfunction, but we do believe that the methylphenidate and fluoxetine treatment he received was neither sufficient nor appropriate, and that it should have been associated with multidisciplinary treatment for OSA (adenotonsillectomy, orthodontic therapy, and/or C-PAP therapy).

The second case report is a clear example of the significant impact of sleep phase advanced disorder in the pathogenesis of ADHD, since the child's parents and teacher reported a significant improvement in cognitive performance after treatment. Bearing in mind that the onset of sleep phase advanced disorder typically occurs in adolescence, we may presume that the circadian disorder in children with ADHD starts early. It has been demonstrated over the last decade that children with ADHD and delayed sleep onset also have a delayed nocturnal pattern of melatonin secretion, and that it can be effectively treated with melatonin (Van der Heijden, Smits, Van Someren, & Gunning, 2005; Van der Heijden, Smits, Van Someren, Ridderinkhof, & Gunning, 2007). The result obtained in our case report is surprising because an improvement was observed in the night-time and daytime disturbances, whereas studies in the literature only report the resolution of the sleep disorders (Van der Heijden et al., 2007). This discrepancy may be due to the lack of evidence-based guidelines about the dosage and timing of intake, as well as the scarce knowledge available regarding pharmaceutical preparations for children (Holvoet & Gabriëls, 2013). It is noteworthy, however, that abnormalities in the circadian secretion of melatonin, as well as lower mean concentrations, have also been found in children with autism (Kulman et al., 2000; Tordjman, Anderson, Pichard, Charbuy, & Touitou, 2005). This has changed views on sleep disorders in autism, which are now attributed to circadian sleep rhythm changes rather than to insomnia. Moreover, many studies, including randomized trials, have demonstrated the efficacy and safety of treatment with melatonin for sleep problems in autistic children (for a complete review of the literature, see Miano & Ferri, 2010). One interesting hypothesis in this regard is that the neurobehavioral manifestations of melatonin secretion abnormalities may differ depending on the timing of the onset of the circadian abnormalities, that is, during the initial years of life in children with autism, whereas at pre-school age and/or school age in children with ADHD and sleep delayed insomnia.

The third case report is an example of ADHD associated with PLMD. PLMs in sleep are brief leg or arm jerks during sleep, associated with negative cardiac and blood pressure consequences, and increased cortical arousals during sleep. Children with PLMs and low-iron stores, as defined by low-serum ferritin levels, may benefit from iron therapy. Several studies have highlighted the potential benefit of raising serum ferritin above 50 ng/ml (Konofal, Lecendreux, Arnulf, & Mouroen, 2004; Simakajornboon et al., 2003). There is a growing body of evidence suggesting that there is a similar association (PLMD and low-serum ferritin levels) in children with ADHD (Cortese, Angriman, Lecendreux, & Konofal, 2012). This case report is emblematic because the boy only reported sleep hyperkinesia, without evident leg discomfort, which suggests that the clinician should systematically screen for and effectively treat RLS/PLMD,

even before stimulant treatment is started, in view of the increased cardiovascular risk associated with this sleep disorder (Angriman, Bruni, & Cortese, 2013).

Case Reports 4 and 5 are examples of epilepsy associated with ADHD. The diagnosis of epilepsy was not easy in either case because the reported symptoms were very unspecific (abdominal pain, sleep disorders). A standard EEG during wakefulness was sufficient in the first case, whereas in the second case, a video-PSG was required to make a definitive diagnosis of nocturnal frontal lobe epilepsy. Although the girl in the latter case did not undergo a PSG, as she reported a maintaining sleep disorder, we may argue that epileptiform discharges have a direct impact on sleep continuity (Parisi et al., 2010). It has recently been demonstrated that a prolonged sleep EEG recording raises the possibility of detecting epileptiform discharges in children with ADHD (Millichap, Millichap, & Stack, 2011), while a video-PSG study demonstrated a high percentage (53.1%) of epileptiform discharges in children with ADHD, with nocturnal seizures being recorded in three patients: two with atypical interictal rolandic spikes and one with left frontal slow abnormalities (Silvestri et al., 2009).

Although the significant increase in Antistreptolysin-O-titer found in two cases, one of which was also associated with a tic disorder, deserves discussion, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections are a huge research topic that is beyond the scope of this paper.

The aforementioned sleep phenotypes of ADHD represent some clinical examples of different treatment choices for “non-primary” forms of ADHD. In these cases, treatment should focus on the underlying sleep disorders (sleep onset insomnia, RLS, and/or PLMs during sleep, OSA syndrome) as well as on comorbidities (i.e., epilepsy). It is noteworthy that the majority of the referred sleep disorders are unspecific and related to disorders of initiating and maintaining sleep, with the exception of the snoring and witnessed apnea reported in Case Report 1. We recommend a diagnostic and therapeutic algorithm designed to find the best first-line treatment for children with ADHD and sleep problems (see Figure 6).

Last, all these case reports displayed clinical signs and symptoms of sleep loss. It has been hypothesized that cognitive impairment and performance deficits induced by sleep deprivation are caused by the occurrence of cortical and sub-cortical local “islands of sleep” in behaviorally fully awake subjects (Nobili et al., 2012). It may be hypothesized that the same phenomenon, with the occurrence of local “islands of sleep,” even occurs in “primary” ADHD as a result of an alteration in the ultradian process. The schematic subdivision of sleep disorders in individuals with ADHD according to a dysfunction of the three main sleep process (circadian, homeostatic, and ultradian process) may help future research to avoid generalizations (e.g., employing genetic, neuroimaging, and biochemical studies on iron metabolism ferritin levels only in children with ADHD and RLS and PLMs, or using genetic,

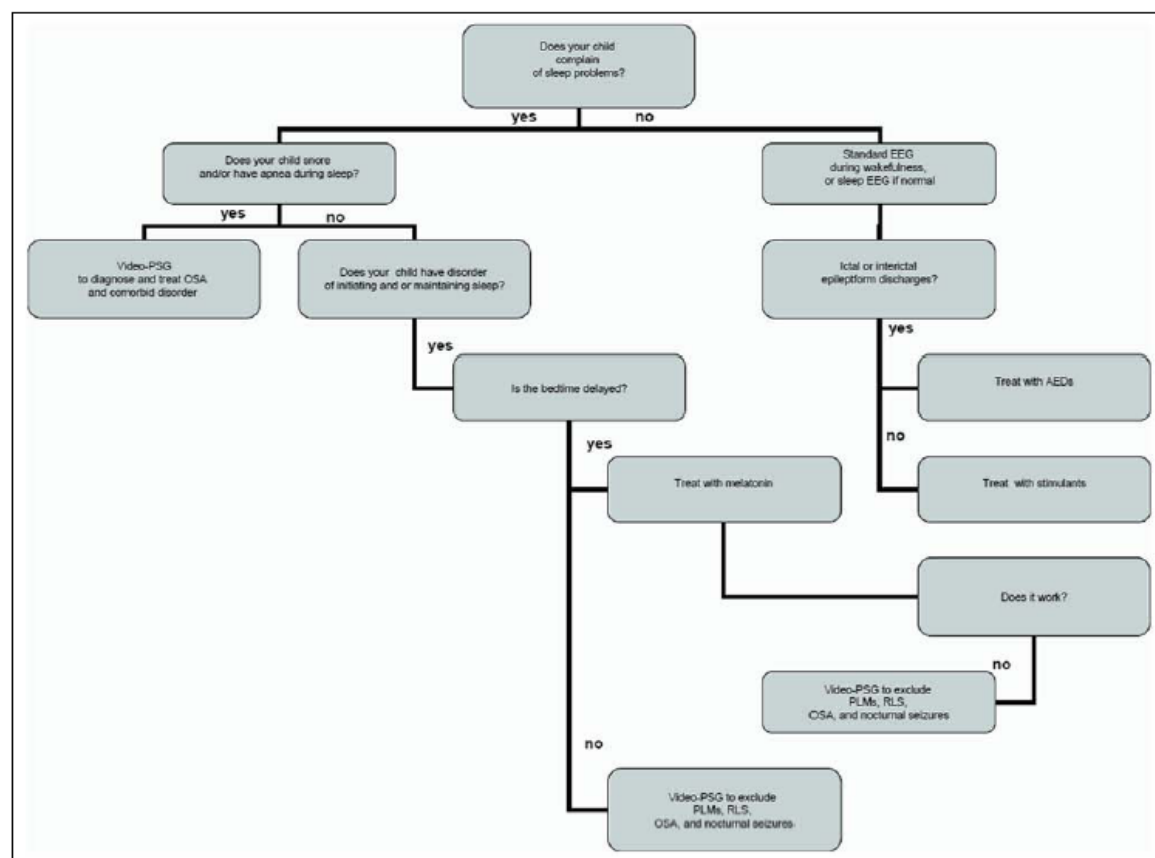


Figure 6. Diagnostic and therapeutic algorithm of sleep problems in children with ADHD.

Note. PSG = polysomnography; OSA = obstructive sleep apnea syndrome; RLS = restless legs syndrome; PLMD = periodic limb movement disorder; AED = antiepileptic drugs.

neuroimaging, biochemical studies on melatonin only in children with delayed sleep onset).

Authors' Note

Silvia Miano conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Alessandra Tabarrini supervised data collection. Ottavio Vitelli reviewed and revised the manuscript. Anna Rita Mazzotta carried out the initial analyses. Jole Ravasco carried out the initial analyses. Renato Donfrancesco coordinated and supervised data collection, and approved the final manuscript as submitted. Pasquale Parisi critically reviewed and revised the manuscript, and approved the final manuscript as submitted. Maria Pia Villa critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Biographies

Silvia Miano is a developmental neurologist and psychiatrist, and sleep medicine expert, with a PhD in paediatric science, who is involved in studies about the correlation between sleep, cognition, paediatric neurobehavioral problems, and epilepsy.

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Attention-Deficit/Hyperactivity Disorder Drugs and Growth: An Italian Prospective Observational Study

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Abstract

Objective: This study was conducted to assess the long-term effect of methylphenidate (MPH) or atomoxetine (ATX) on growth in attention-deficit/hyperactivity disorder (ADHD) drug-naïve children.

Design: The study was an observational, post-marketing, fourth phase study.

Methods: Data on height and weight were collected at baseline and every 6 months up to 24 months.

Results: Both ATX and MPH lead to decreased height gain (assessed by means of z-scores); the effect was significantly higher for ATX than for MPH. At any time, height z-score decrease in the ATX group was higher than the corresponding decrease observed in the MPH group, but the difference was significantly relevant only during the first year of treatment. An increment of average weight was observed both in patients treated with MPH and in those treated with ATX. However, using Tanner's percentile, a subset of patients showed a degree of growth lower than expected. This negative effect was significantly higher for ATX than for MPH.

Conclusions: We conclude that ADHD drugs show a negative effect on linear growth in children in middle term. Such effect appears more evident for ATX than for MPH.

Introduction

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is one of the most common behavioral disorders in children and adolescents (Skounti et al. 2007). Pharmacological treatment may reduce ADHD symptom severity (MTA Cooperative Group 1999; Biederman and Faraone 2005). Methylphenidate (MPH) and other psychostimulants are recommended as first-choice drugs for ADHD (Schachter et al. 2001). Atomoxetine (ATX), a selective norepinephrine reuptake inhibitor, is considered as a second choice (Cheng et al. 2007). Adverse events may occur both with psychostimulants and ATX. Available evidence suggests that children and adolescents are at higher risk than adults for adverse events during treatment with psychotropic drugs (Greenhill et al. 2003).

According to a systematic review (Faraone et al. 2008), ~38% of included studies showed a growth slowdown in children treated with ADHD drugs. The effect, although attenuated, persisted over time for 4 years (Mattes and Gittelman 1983). However, discontinuation of treatment with stimulants showed a compensatory

growth spurt (Mattes and Gittelman 1983; Klein et al. 1988; Klein and Mannuzza 1988).

As for ATX, meta-analytic evidence shows a slight weight decrease (~1 kg) in the short term (2–3 months) (Cheng et al. 2007). Two additional meta-analyses assessed reported the effect of long-term use of ATX on height and weight. The first showed a decrease in weight (average 2.5 kg) and in height (average 2.7 cm) after 2 years of treatment with ATX in 6–7-year-old children in relation to baseline percentiles (Kratochvil et al. 2006). The second meta-analysis reported a less evident effect on weight and height, 0.87 kg and 0.44 cm, respectively (Spencer et al. 2005).

The Italian ADHD National Registry was activated in April 2007. It is managed by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) and supervised by a national panel of experts with the aim of implementing an active pharmacovigilance, and to assess the risk/benefit ratio of ADHD drugs (Panei et al. 2004). According to Italian regulation, children can receive pharmacological treatment for ADHD only after registration with the ADHD National Registry. Care providers choose the treatment based on their own experience, and on current clinical practice.

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Italian law requires close monitoring of drugs for 2 years after registration, in order to assess safety in current clinical practice. An observational post-marketing study of pharmacovigilance is mandatory for every new drug approved for ADHD.

The objective of this study was to assess the effect on growth during 2 years of treatment with MPH or ATX in ADHD children and adolescents enrolled in the Italian ADHD National Registry.

Patients and Methods

Subjects

This observational prospective study included 1758 children and adolescents (6–18 years of age) with ADHD, who were consecutively recruited from 87 centers accredited for the management of ADHD in Italy between June 2007 and June 2010. All subjects treated with ADHD drugs were included in this study and were drug naïve.

Participants were either referred by their child neuropsychiatrists or self-referred to a reference center for a suspicion of ADHD.

ADHD was diagnosed according to American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) (American Psychiatric Association 1994) criteria for ADHD based on clinical history and confirmed by a structured interview. Accordingly, to be diagnosed with ADHD, subjects had to present with a significant functional impairment and symptoms had to: 1) Be present, at least in part, before the age of 7 years, 2) persist for at least 6 months, and 3) be present in more than one setting (e.g., at home, and/or at school, and/or in another setting). All subjects were screened for other mental disorders, and participants with an autism spectrum disorder were excluded, as per DSM-IV criteria. Subjects with follow-up or compliance problems were also excluded.

All subjects who accepted the pharmacological treatment signed an informed consent explaining the aim of the study and the tests to be performed in order to evaluate the primary parameters (i.e., effect on height growth).

The study was approved by the Ethical Committee of the Istituto Superiore di Sanità.

Treatments

Two study groups were defined according to the pharmacological treatment, and the choice of treatment was based on current clinical practice by child neuropsychiatrists.

Group A. This group consisted of subjects treated with MPH plus behavioral treatment. The drug compound was methylphenidate chlorhydrate 10 mg tablet (Ritalin[®], Novartis Pharma, Italia). MPH was administered orally (0.3–0.6 mg/kg/dose/day).

A methylphenidate test dose of 0.3 mg/kg was administered first. The dosage could be increased up to 0.6 mg/kg/dose depending upon the subject's clinical response and tolerability. The total dose could be administered in two or three doses/day. The duration of the renewable prescription was 1 month.

Group B. This group consisted of subjects treated with ATX plus behavioral treatment. Atomoxetine chlorhydrate (5 mg, 10 mg, 18 mg, 25 mg, 40 mg, or 60 mg tablets; Strattera[®], Lilly) was used. Route of administration was oral, with the following schedule: Beginning with 0.5 mg/kg/day once a day, at least for 7 days, then increase the dose up to 1.2 mg/kg/day, related to the subject's clinical response and tolerability. Duration of the renewable prescription was 1 month.

Data collection and management

All relevant information was collected by standard procedures. The clinical assessment was performed monthly, and included measurement of height in centimeters, and of weight in kilograms. Height and weight measurements were collected in according Tanner's standard procedure (Tanner et al. 1966). Each measure of weight and height was also computed in percentiles.

Clinical monitoring of the register included regular checking via the Internet. All clinical data, relative to recruitment and follow-up of each enrolled child, were entered in an electronic Case Report Form (eCRF), that was located in a restricted area (https://www.farmacovigilanza.iss.it/cgi-bin/adhd/index_gen) of the web site www.iss.it/adhd. Centers, child psychiatrist services, and pediatricians could access this restricted area through user i.d. and password.

The database of the register was based at Istituto Superiore di Sanità, Rome, which was responsible for its protection and management. The data management was designed by an infrastructure named "Advanced Multicenter Research developed by Consorzio Inter-Universitario per il Calcolo Automatico dell'Italia nord-orientale." This program application allowed the checking of any informative flow, the data input, the monitoring of information, and the analysis of results.

Determination of sample size

The required sample size was estimated with respect to the 1 year variation in height z-score (the primary outcome of the study), based on the paired Student's *t* test (comparison of the mean value between baseline and 12 months within the treatment group), two tailed (we were interested in demonstrating differences in height z-score variation in whatever direction).

From previous studies, the standard deviation of the 1 year variation in height z-score in the overall group of subjects, apart from sex and age, was estimated at 0.4.

Moreover, we considered as clinically relevant a z-score difference from baseline to 12 months height z-score variation ≥ 0.1 (corresponding to a Cohen's $d=0.25$, i.e., a small-to-medium effect size according to Cohen, 1988). Finally, considering a type I error probability $\alpha=0.05$ and a power $1-\beta=0.80$, the minimal sample size required for the study was 133 subjects in each treatment group.

This sample size also allowed for detection of a difference between MPH and ATX groups in the height z-score 1 year variation ≥ 0.15 (corresponding to a Cohen's $d=0.375$, i.e., a small-to-medium effect size according to Cohen, 1988), based on a two tailed Student's *t* test for independent samples, with a type I error probability $\alpha=0.05$ and a power $1-\beta=0.85$.

Statistical analysis

Categorical variables (i.e., sex, treatment, and height and weight percentile changes) are shown as absolute and percent frequencies, whereas quantitative variables (age, height, weight) are summarized as means \pm standard deviations.

In order to maximize the number of subjects included in the statistical analyses, data were separately analyzed according to three reference periods: From enrollment (time 0) to 6 months, from 0 to 12 months, and from 0 to 24 months of follow-up. With respect to treatment, subjects were divided into four groups according to drug(s) received during the reference period under examination: MPH-treated (MPH group), ATX-treated (ATX group), both drugs-treated (MIXED group), and those not treated with either

MPH or ATX, but receiving other psychotropic drugs. The last two groups were excluded from the analysis (Fig. 1).

For any reference period, only subjects with data at baseline and at the end of the period were included in the statistical analyses.

To assess the difference between observed and expected changes in height and weight during each reference periods, heights and weights were categorized in percentile classes (from 0 to 3rd, from >3rd to 10th, from >10th to 25th, from >25th to 50th, from >50th to 75th, from >75th to 90th, from >90th to 97th, and >97th percentile) based on Tanner's age- and sex-specific data. Subsequently, each subject was classified as passing to a lower percentile (percentile decreased), remaining in the same percentile (percentile unchanged), or passing to a higher percentile (percentile increased) from baseline to the end of the reference period. The frequency of subjects shifting to a lower percentile class was compared with that of those moving to a higher class using the binomial test. Moreover, the distribution of subjects according to the percentile variation from baseline to the end of the period was compared between the two treatment groups, using the χ^2 test.

To take into account the effect of sex and age, height was also transformed in z-score, according to the formula

$$\text{height } z\text{-score} = (\text{height}_i - \text{height mean}) / \text{height standard deviations}$$

where height_i = height of the subject at the time of assessment, height mean = mean of sex- and age-specific height, height standard

deviation = standard deviation of sex- and age-specific height, using sex- and age-specific height means and standard deviations taken from Tanner's tables on cross-sectional-type standards for height attained (Tanner et al. 1966).

Because of asymmetry in the variable distribution, weight could not be transformed in z-scores, and, therefore, was analyzed and presented as raw data.

Comparisons within the MPH or ATX groups with respect to height and weight data were performed by paired Student's *t* test to compare measurements taken at baseline and at the end of the specific reference period within each treatment group. The differences between the MPH and ATX groups for height and weight changes, occurring during the period, were tested using Student's *t* test for independent samples. Nonparametric tests (Wilcoxon and Mann-Whitney *U* tests for paired data and independent samples, respectively) were also performed on weight data to validate results of parametric tests. As the results were concordant, only parametric tests were reported.

Results

Through June 30 2010, 1758 children and adolescents with ADHD were recruited from the Italian ADHD National Registry. Of these, 1558 (88.6%) were males. Analyzing age classes, subjects <11 years were the most represented (991 subjects) and accounted for ~57% of the entire population.

Stratified by type of treatment, 840 (47.8%) subjects were treated with MPH and 918 (52.2%) were treated with ATX.

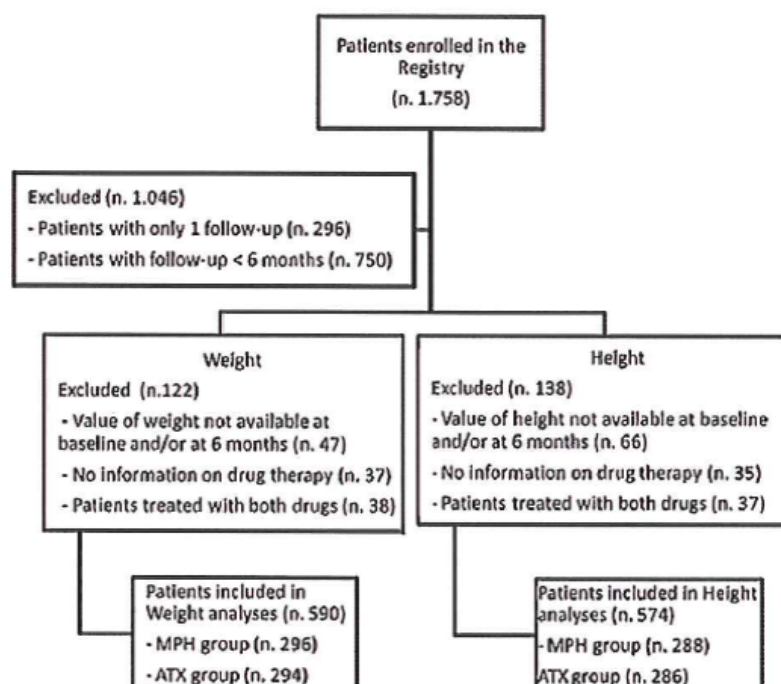


FIG. 1. Flow chart of patients at 6 months of follow-up. The figure reports the number of patients included in weight and height analysis, stratified for each group of treatment (methylphenidate group, atomoxetine group). The reasons for which the patients were excluded from analysis were also reported.

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MPH was prescribed at average daily dose equal to 0.48 mg/kg ($SD \pm 0.22$) and with total average daily dose of 18.8 mg ($SD \pm 10.7$). ATX was prescribed at average daily dose of 38.7 mg ($SD \pm 20.5$).

Subjects in the MPH or ATX groups in relation to the three different periods (0 vs. 6 months, 0 vs. 12 months, 0 vs. 24 months) were compared with respect to age at baseline and sex distribution. No significant differences were found between MPH and ATX groups, except for sex when comparing the two groups of treatment in relation to the period 0 versus 24 months, when a lower proportion of females was observed in the ATX group (46 males and 9 females in the MPH group vs. 34 males and only 1 female in the ATX group, $p = 0.047$).

During the study, monitoring of height and weight was recommended monthly. The mean number of height measures per subject was 6.11, ranging from 1 to 33, whereas the mean number of weight measures per subject was 6.14, ranging from 1 to 33.

For primary analysis, we used follow-up data at 6, 12, and 24 months. One thousand and sixty-four (60.5%) subjects dropped out of the study. Reasons for dropping out are reported in Figure 1.

Weight evaluation

Five hundred and ninety subjects were included in the analysis (Table 1). The comparison for age, sex, subtype of ADHD and comorbidity showed no significant differences between the subjects included in the analysis and those excluded, except for the depression. Two hundred and ninety-six out of 590 (50.2%) were treated with MPH and 294 (49.8%) were treated with Atomoxetine.

Percentile variations are shown in Table 2. As can be seen, in all reference periods, the proportion of subjects shifting to a lower percentile class was larger than that of those moving to a higher percentile class. The difference between these two groups has always been significant, except for MPH subjects in the reference period 0–24 months. The difference was stronger in ATX- than in MPH-treated

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF SUBJECTS STRATIFIED BY GROUPS INCLUDED AND NOT INCLUDED IN THE WEIGHT ANALYSIS

Variables	Included in the analysis 590 subjects	Not included in the analysis 1168 subjects
Gender, n (%)		
Male	514 (87.1)	1044 (89.4)
Female	76 (12.9)	124 (10.6)
Age class, n (%)		
<11 years	341 (57.8)	662 (56.8)
11–<15 years	207 (35.1)	406 (34.9)
≥15 years	42 (7.1)	97 (8.3)
Type of ADHD, n (%)		
ADHD – I	33 (5.6)	61 (5.2)
ADHD – H	26 (4.4)	60 (5.1)
ADHD – C	531 (90.0)	1028 (88.0)
Presence of comorbidity		
Oppositional defiant disorder	247 (41.9)	463 (39.6)
Conduct disorder	32 (5.4)	79 (6.8)
Depression	32 (5.4)	82 (7.0)
Anxiety	73 (12.4)	190 (16.3)
Learning disorder	269 (45.6)	479 (41.0)

ADHD, attention-deficit/hyperactivity disorder; ADHD-I, Subtype Inattentive ADHD; ADHD-H, Subtype Hyperactive ADHD; ADHD-C, Subtype Combined ADHD.

TABLE 2. PERCENTILE CHANGES OF PATIENTS' WEIGHT AT DIFFERENT REFERENCE PERIODS STRATIFIED BY TYPE OF DRUGS

	From 0 to 6 months (n 296 MPH; n 294 ATX) Percentile			From 0 to 12 months (n 184 MPH; n 159 ATX) Percentile			From 0 to 24 months (n 55 MPH; n 28 ATX) Percentile		
	decreased	unchanged	increased	decreased	unchanged	increased	decreased	unchanged	increased
Methylphenidate (MPH)	83 (28.1%) Binomial $\chi^2 = 7.43$	178 (60.1%) test $df = 2$	35 (11.8%) $p < 0.001$	58 (31.5%) Binomial $\chi^2 = 7.48$	92 (50.0%) test $df = 2$	34 (18.5%) $p = 0.018$	23 (41.8%) Binomial $\chi^2 = 1.94$	17 (30.9%) test $df = 2$	15 (27.3%) $p = 0.267$
Atomoxetine (ATX)	112 (38.1%) Binomial $\chi^2 = 7.43$	158 (53.7%) test $df = 2$	24 (8.2%) $p < 0.001$	73 (45.9%) Binomial $\chi^2 = 7.48$	63 (39.6%) test $df = 2$	23 (14.5%) $p < 0.001$	15 (53.6%) Binomial $\chi^2 = 1.94$	9 (32.1%) test $df = 2$	4 (14.3%) $p = 0.010$
MPH vs ATX			$p = 0.024$			$p = 0.024$			$p = 0.580$

The binomial test refers to the comparison between frequencies of percentile decreased and increased subjects, based on the null hypothesis of equal distribution between the two categories. The χ^2 test refers to the comparison between the distributions of MPH- and ATX-treated subjects in the percentile change categories. df , degrees of freedom.

TABLE 3. WEIGHT OF PATIENTS STRATIFIED BY TYPE OF DRUGS AT DIFFERENT TIMES FROM ENROLMENT

	MPH n	Mean \pm SD (kg)	ATX n	Mean \pm SD (kg)	MPH vs ATX <i>t</i> test ^a
0 months	296	38.70 \pm 13.40	294	41.03 \pm 15.84	
6 months		39.91 \pm 13.75		41.41 \pm 15.76	
0 vs 6 mo. <i>t</i> test ^b		<i>t</i> ₂₉₅ = 7.85 <i>p</i> < 0.001		<i>t</i> ₂₉₃ = 2.17 <i>p</i> < 0.031	<i>t</i> ₅₈₈ = 3.53 <i>p</i> < 0.001
0 months	184	38.38 \pm 13.26	159	40.55 \pm 13.93	
12 months		41.58 \pm 13.72		42.58 \pm 14.42	
0 vs 12 mo. <i>t</i> test ^b		<i>t</i> ₁₈₃ = 11.98 <i>p</i> < 0.001		<i>t</i> ₁₅₈ = 6.23 <i>p</i> < 0.001	<i>t</i> ₃₄₁ = 2.81 <i>p</i> < 0.005
0 months	55	38.36 \pm 11.31	28	43.46 \pm 17.35	
24 months		46.80 \pm 13.41		49.11 \pm 18.33	
0 vs 24 mo. <i>t</i> test ^b		<i>t</i> ₅₄ = 12.08 <i>p</i> < 0.001		<i>t</i> ₂₇ = 5.48 <i>p</i> < 0.001	<i>t</i> ₈₁ = 2.28 <i>p</i> < 0.025

Weights are reported as means \pm standard deviations in kg.

^aUnpaired Student's *t* test: Comparisons between MPH- and ATX-treated subjects regarding weight changes between baseline and the end of the specific reference period.

^bPaired Student's *t* test: Comparisons between measurements taken at baseline and at the end of the specific reference period, within each treatment group. MPH, methylphenidate; ATX, atomoxetine; *df*, degrees of freedom.

subjects; however, the difference between the two groups was significant only for the reference periods 0–6 months and 0–12 months.

We calculated the mean value of weight before the treatment and after 6, 12, and 24 months. For MPH, at each time point, a statistically significant weight increase was detected. The mean difference from baseline was +1.21 (SD 2.66) kg at 6 months, +3.21 (SD 3.63) kg at 1 year, and +8.44 (SD 5.18) kg at 24 months (*p* < 0.001 for all periods). Similarly, a statistically significant difference was observed for ATX. The mean difference from baseline was +0.38 (SD 3.03) kg at 6 months, +2.03 (SD 4.11) kg at 1 year, and +5.65 (SD 5.44) kg at 24 months (*p* = 0.031, *p* < 0.001, and *p* < 0.001, respectively). These findings are sum-

marized in Table 3. The comparison between MPH- and ATX-treated patients with respect to weight change at 6, 12, and 24 months shows a statistically significant difference (*p* < 0.001, *p* = 0.005 and *p* = 0.025, respectively).

Height evaluation

Five hundred and seventy-four subjects were included in the analyses (Table 4). The comparison for age, sex, subtype of ADHD, and comorbidity between the group included in the analysis and the one excluded, showed a statistically significant difference only for anxiety. Two hundred and eighty-eight out of 574 (50.2%) were treated with MPH and 286 (49.8%) were treated with ATX.

Percentile variations are shown in Table 5. The proportion of subjects shifting to a lower percentile class was higher than that of those moving to a higher percentile class, but the difference was significant only for ATX subjects in the reference periods 0–12 months and 0–24 months. The difference was slightly stronger in ATX- than in MPH-treated subjects; however, the difference between the two groups never reached statistical significance.

We analyzed the mean value of height before the treatment and after 6, 12, and 24 months (Table 6). A statistically significant increase of height was detected in the MPH group. The mean difference from baseline was +2.92 (SD 2.32) cm at 6 months, +5.01 (SD 2.77) cm at 1 year, and +10.48 (SD 4.83) cm at 24 months (*p* < 0.001 for all periods). For ATX, the difference from baseline was +2.64 (SD 2.50) cm at 6 months, +4.09 (SD 2.80) cm at 1 year, and +8.31 (SD 5.31) cm at 24 months (*p* < 0.001 for all periods). At any period, height increase in the ATX group was lower than the corresponding increase observed in the MPH group, but the difference was significant only after ≥ 1 year of treatment (*p* = 0.176, *p* = 0.004, and *p* = 0.050 for 6, 12, and 24 months, respectively).

Z-score for height

When considering height z-scores, the mean difference from baseline for MPH was –0.001 (SD 0.334) at 6 months, –0.104 (SD 0.381) at 12 months, and –0.175 (SD 0.660) at 24 months (*p* = 0.961, *p* < 0.001, and *p* = 0.055 for 6, 12, and 24 months, respectively). For ATX, the difference from baseline was –0.037

TABLE 4. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF SUBJECTS STRATIFIED BY GROUPS INCLUDED AND NOT INCLUDED IN THE HEIGHT ANALYSIS

Variables	Included in the analysis 574 subjects	Not included in the analysis 1184 subjects
Gender, <i>n</i> (%)		
Male	500 (87.1)	1058 (89.3)
Female	74 (12.9)	126 (10.7)
Age class, <i>n</i> (%)		
<11 years	340 (59.3)	663 (56.0)
11 to <15 years	200 (34.8)	413 (35.0)
≥ 15 years	34 (5.9)	105 (9.0)
Type of ADHD, <i>n</i> (%)		
ADHD – I	33 (5.7)	61 (5.1)
ADHD – H	27 (4.7)	59 (4.9)
ADHD – C	514 (89.6)	1045 (90.0)
Presence of comorbidity		
Oppositional defiant disorder	243 (42.3)	467 (39.4)
Conduct disorder	33 (5.7)	78 (6.6)
Depression	33 (5.7)	81 (6.8)
Anxiety	69 (12.0)	194 (16.4)
Learning disorder	265 (46.2)	483 (40.1)

ADHD, attention-deficit/hyperactivity disorder; ADHD-I, Subtype Inattentive ADHD; ADHD-H, Subtype Hyperactive ADHD; ADHD-C, Subtype Combined ADHD.

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TABLE 5. PERCENTILE CHANGES OF PATIENTS' HEIGHT AT DIFFERENT REFERENCE PERIODS STRATIFIED BY TYPE OF DRUGS

	From 0 to 6 months (n 288 MPH; n 286 ATX) Percentile			From 0 to 12 months (n 167 MPH; n 139 ATX) Percentile			From 0 to 24 months (n 55 MPH; n 55 ATX) Percentile		
	decreased	unchanged	increased	decreased	unchanged	increased	decreased	unchanged	increased
Methylphenidate (MPH)	54 (18.8%) Binomial test $\chi^2 = 0.99$	185 (64.2%) test $df = 2$	49 (17.0%) $p = 1.000$	46 (27.5%) Binomial test $\chi^2 = 3.31$	91 (54.5%) test $df = 2$	30 (18.0%) $p = 0.099$	17 (30.9%) Binomial test $\chi^2 = 1.45$	25 (45.5%) test $df = 2$	13 (23.6%) $p = 0.292$
Atomoxetine (ATX)	63 (22.0%) Binomial test $p = 0.138$	178 (62.2%) test $p = 0.609$	45 (15.7%) $p = 0.001$	48 (34.5%) Binomial test $p = 0.001$	75 (54.0%) test $p = 0.191$	16 (11.5%) $p = 0.001$	14 (40.0%) Binomial test $p = 0.032$	16 (45.7%) test $p = 0.485$	5 (14.3%) $p = 0.032$
MPH vs ATX									

The binomial test refers to the comparison between frequencies of percentile decreased and increased subjects, based on the null hypothesis of equal distribution between the two categories. The χ^2 test refers to the comparison between the distributions of MPH- and ATX-treated subjects in the percentile change categories.

(SD 0.375) at 6 months, -0.229 (SD 0.399) at 12 months, and -0.441 (SD 0.734) at 24 months ($p = 0.093$, $p < 0.001$, $p = 0.001$ for 6, 12, and 24 months, respectively). At any period, height z-score decrease in the ATX group was higher than the corresponding decrease observed in the MPH group, but the difference was significant only at 1 year of treatment ($p = 0.220$, $p = 0.006$, and $p = 0.203$ for 6, 12, and 24 months, respectively). The results are summarized in Table 7.

Discussion

This observational study assessed the impact of MPH and ATX on growth. The study showed a different growth rate between the two drugs, with ATX-treated patients growing significantly more slowly than MPH-treated patients.

With regard to weight, there was a significant trend for weight increase for both drugs. For the effect on height we observed a statistically significant decrease, evaluated in percentiles, for both drugs. However, comparing the effect between the two drugs on height decrease, a statistically significant difference were observed only at 12 months.

Although the two variables, weight and height, are both important in the assessment of growth, height is more important because, once growth stops at the end of adolescence, height cannot increase any more, whereas weight changes throughout life.

Therefore, in order to more accurately assess growth with respect to height, we used the z-score that correlates with chronological age and gender.

The z-score values after 12 and 24 months of therapy were more reduced in the ATX group than in the MPH one, but a significant difference was detected only at 12 months. At 24 months of follow-up, a greater difference in z-score between the two groups was observed, but it is not statistically significant, because the number of subjects included in this subanalysis, in the two groups, was lower. Therefore, it is possible to state that, in the first year of treatment, ATX causes a significantly greater growth delay than MPH. Additionally, both drugs showed a cumulative effect over time. After 24 months, the z-score had halved for both groups. Our results are in accordance with other studies (Spencer et al. 2005; Charach et al. 2006), in which a slowdown of growth rate in long-term treated patients was observed. Although this finding is also confirmed by a recent review (Faraone 2008), a recent naturalistic study did not support any association between deficits in growth process and psychostimulant treatment in ADHD patients (Villarreal et al. 2010).

As for ATX, a meta-analysis of long-term studies of ATX in children showed that the stronger negative effect occurred after 18 months of treatment, and that then this effect decreased with time (Spencer et al. 2005). A recent randomized, double-blind, placebo-controlled study of a Japanese pediatric population showed that the mean height increases in the ATX group were lower than those in the placebo group (Takahashi et al. 2009). On the other hand, one placebo-controlled trial did not show clinically significant effects on growth rate with ATX (Donnelly et al. 2009).

Our results should be considered in the light of study limitations. First, it is not clear whether the observed slowdown in growth is a transient effect or a permanent potential reduction for individual growth with respect to the final height. As our observation time was only 24 months of follow-up, we were not able to evaluate if the negative effect on growth persisted after 24 months of treatment. Second, we could not assess if the negative effect observed on height would persist after permanent discontinuation of drugs (Safer et al. 1975). Unfortunately, our study did not include a specific follow-up

TABLE 6. HEIGHT OF PATIENTS STRATIFIED BY TYPE OF DRUGS AT DIFFERENT TIMES FROM ENROLMENT

	MPH n	Mean \pm SD (cm)	ATX n	Mean \pm SD (cm)	MPH vs ATX t test ^a
0 months	288	140.90 \pm 15.12	286	143.02 \pm 17.01	$t_{572} = 1.36$ $p = 0.176$
6 months		143.82 \pm 15.22		145.66 \pm 17.04	
0 vs 6 mo. t test ^b		$t_{287} = 21.36$ $p < 0.001$		$t_{285} = 17.87$ $p < 0.001$	
0 months	167	141.22 \pm 15.50	139	144.01 \pm 16.89	$t_{304} = 2.87$ $p = 0.004$
12 months		146.23 \pm 15.73		148.10 \pm 17.00	
0 vs 12 mo. t test ^b		$t_{166} = 23.34$ $p < 0.001$		$t_{138} = 17.25$ $p < 0.001$	
0 months	55	140.45 \pm 14.49	35	145.49 \pm 17.57	$t_{88} = 1.99$ $p = 0.050$
24 months		150.93 \pm 15.04		153.80 \pm 18.18	
0 vs 24 mo. t test ^b		$t_{54} = 16.08$ $p < 0.001$		$t_{34} = 9.26$ $p < 0.001$	

Heights are reported as means \pm standard deviations in cm.

^aUnpaired Student's *t* test: Comparisons between MPH and ATX-treated subjects regarding weight changes between baseline and the end of the specific reference period.

^bPaired Student's *t* test: Comparisons between measurements taken at baseline and at the end of the specific reference period, within each treatment group.

MPH, methylphenidate; ATX, atomoxetine; *df*, degrees of freedom.

for subjects with permanent discontinuation of treatment. Third, ~60% of subjects could not be included in the statistical analyses. To understand the relative impact of this issue on the results, we compared "population included" versus "population not included" in the statistical analysis, following some factors, such as age classes, sex, subtype of ADHD, and comorbidity. Statistically significant differences were observed only for depression in the weight analysis and for anxiety in the height analysis. Therefore, we believe that the population included in the analysis was representative of the whole population enrolled in the Italian ADHD National Registry.

Conclusions

The long-term effects of therapies for chronic diseases represent one of the most important issues in the evaluation of the profile benefit/risk. Our study highlights that the use of MPH and ATX in children and adolescents with ADHD seems not to be the cause of permanent growth effects. Both drugs cause a moderate slowdown

in the height velocity highlighted by the values of the *z*-score. However, this effect does not seem to be permanent, and there is no significant difference between ATX and MPH. On the other hand, both drugs cause an increase in the average weight in pharmacologically treated patients. After 2 years of pharmacological treatment, we have observed an average weight about +5 SD from the 50th percentile. This finding should be confirmed by a randomized controlled study with two active drug arms and one control group.

Clinical Significance

Regular monitoring of growth parameters (parent's height, height, and weight measurements) is recommended for all patients, but it should be strongly recommended for subjects treated with ADHD drugs. So far, attention has been focused on the effect of ADHD medications on height growth. In view of our findings, it is necessary to devote the same attention to the risk of onset of obesity in patients treated with these drugs.

TABLE 7. HEIGHT Z-SCORES OF PATIENTS STRATIFIED BY TYPE OF DRUGS AT DIFFERENT TIMES FROM ENROLMENT

	MPH n	Mean \pm SD	ATX n	Mean \pm SD	MPH vs ATX t test ^a
0 months	288	0.35 \pm 1.19	286	0.32 \pm 1.27	$t_{572} = 1.23$ $p = 0.220$
6 months		0.35 \pm 1.16		0.27 \pm 1.20	
0 vs 6 mo. t test ^b		$t_{287} = 0.05$ $p < 0.961$		$t_{285} = 1.68$ $p < 0.093$	
0 months	167	0.37 \pm 1.22	139	0.55 \pm 1.21	$t_{304} = 2.79$ $p = 0.006$
12 months		0.27 \pm 1.19		0.32 \pm 1.16	
0 vs 12 mo. t test ^b		$t_{166} = 3.54$ $p < 0.001$		$t_{138} = 6.77$ $p < 0.001$	
0 months	55	0.36 \pm 1.21	35	0.84 \pm 1.22	$t_{88} = 1.27$ $p = 0.203$
24 months		0.18 \pm 1.12		0.40 \pm 1.30	
0 vs 24 mo. t test ^b		$t_{54} = 1.96$ $p < 0.055$		$t_{34} = 3.55$ $p < 0.001$	

^aUnpaired Student's *t* test: Comparisons between MPH and ATX-treated subjects regarding weight changes between baseline and the end of the specific reference period.

^bPaired Student's *t* test: Comparisons between measurements taken at baseline and at the end of the specific reference period, within each treatment group.

MPH, methylphenidate; ATX, atomoxetine; *df*, degrees of freedom.

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REVIEW ARTICLE

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Headache and comorbidity in children and adolescents

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Abstract

Headache is one of the most common neurological symptom reported in childhood and adolescence, leading to high levels of school absences and being associated with several comorbid conditions, particularly in neurological, psychiatric and cardiovascular systems. Neurological and psychiatric disorders, that are associated with migraine, are mainly depression, anxiety disorders, epilepsy and sleep disorders, ADHD and Tourette syndrome. It also has been shown an association with atopic disease and cardiovascular disease, especially ischemic stroke and patent foramen ovale (PFO).

Keywords: Headache; Comorbidity; Children; Adolescents

Review**Introduction**

Headache is one of the most common somatic complaints in children and adolescents [1]. The prevalence is estimated to be 10–20% in the school-age population, with progressive increase with age, up to values about 27–32% at the age of 13–14 years (considering monthly crisis), 87–94% (considering the presence of headache at least once a year).

Until puberty, it hasn't been seen gender differences (with a slight male predominance), at a later stage it has been noted an increase among females with a ratio of 2.5:1, except that lasts into adulthood [2,3]. Prevalence of migraine in the pediatric population ranges from 3,3% to 21,4% and it increases from childhood to adolescence [4].

Children and adolescents with headache, and in particular migraine, have worse outcomes, compared to those without migraine, as far as quality of life and school attendance [5] are concerned and they are more likely to have other somatic symptoms (e.g. abdominal pain) [6], anxiety and mood disorders, such as depression [7,8]. Due to its negative impact, on the World Health Organization's ranking of causes of disability, headache disorders are

brought into the 10 most disabling conditions for the two genders, and into the five most disabling for women [9].

In fact, primary headaches, and in particular migraine, is associated with several comorbid conditions.

Comorbidity is the presence of coexisting additional condition in a patient with particular disease index, or the association of non-random two disorders [10].

In children and adolescents, headache and migraine are commonly associated with various diseases, such as psychiatric and neurological comorbidity, in particular depression and anxiety, epilepsy, sleep disorders, ADHD. It also has been shown an association with atopy, cardiovascular disease, especially ischemic stroke and PFO [11–14].

Headache and psychiatric disorders: anxiety and depression

Since past decades, numerous population- and hospital-based studies have revealed a relationship between migraine or headache and psychopathology in children [15–17]. Depression is more prevalent in headache patients than in the headache-free population [18]. Recently, Pavone et al. (2012) [19] studied the frequency of some comorbidities in primary headaches in childhood.

They enrolled two hundred and eighty children (175 males and 105 females), aged 4 to 14 years, affected by primary headaches. In direct interviews, parents and children gave information about the association of their

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headaches with different conditions. The Authors found a significant association of primary headache with anxiety and depression.

Migraine is probably the best studied pain disorder in the context of comorbidity with anxiety and/or depression [20]. In a psychiatric setting Masi and colleagues [21], in an exploratory study, examine the prevalence of somatic symptoms in a sample of 162 Italian children and adolescents from emotional and/or behavioral disorders. The sample was divided according to gender (96 males, 66 females), age (70 children younger and 92 adolescents older than 12 years), and psychiatric diagnosis (Anxiety, Depression, Depression/Anxiety, Other). The Authors observed that headache was the most frequent somatic symptom in children and adolescents referred for anxiety, depression and behavioral disorders, with a prevalence of females.

Cahill and Cannon [22] defined migraine as a subtype of headache of particular interest for psychiatrists, as they found a linkage between migraine, psychiatric disorders (mainly anxiety and depression), personality traits and stress.

The nature of the relationship between migraine and anxiety is still not clear and we do not know if that relationship is specific to migraine or related to attack frequency [23], even if some evidence confirms that linkage [24]. It is well known that the risk of migraine is higher in patients with comorbid anxiety and/or depression [25] and that anxiety predicts the persistence of migraine and tension-type headache [26]. While only phobic disorder seems to be a predictor of the onset of migraine [27], anxiety, more than depression, predicts long-term migraine persistence, headache-related disability and reduces perceptions of efficacy with acute treatment [26,28]. Phobic disorder is also associated with more frequent and longer migraine attacks, particularly among males [29].

The increased risk of anxiety disorder in children and adolescents with migraine, compared to patients without migraine, is noticed in many studies. Arruda and Bigal [5], in their population-based study, confirmed the higher prevalence of anxious symptoms in children and adolescents with migraine.

In a meta-analysis of 10 studies published between 1996–2011 (406 patients, mean age 11.6 ± 2.3 ys) Ballottin and colleagues [23] found that migraine children show more psychological symptoms, detected by using Child Behavior Checklist (CBCL), than healthy controls. They also emphasized the need for studies to compare migraine children with children affected by other chronic pain in order to understand whether the psychopathological profile is migraine-related or chronic pain-related.

Some studies suggest that psychiatric disorders might not specifically relate to migraine, but to chronic illness in general: comparing migraine and chronic non-headache

pain samples, Cunningham [30] found no difference in anxiety and depression levels between the two groups with chronic pain, with respect to pain-free controls. Another study [6] comparing headache patients and patients with recurrent abdominal pain did not find differences by the psychological point of view (internalizing vs. externalizing disorders). One of the hypotheses for the comorbidity is that common genetic and/or environmental risk factors may underlie both migraine and psychiatric disorders [27].

Gonda and colleagues [31] found that high levels of anxiety and migraine were associated with specific gene polymorphism, supporting the hypothesis of a shared genetic linkage between these two conditions.

Instead other studies show no correlation between migraine, anxiety and depression, as Kowal and Pritchard [32] that studied twenty-three volunteer subjects, compared with 23 (matched) control subjects on self and parental ratings of anxiety, depression, shyness-sensitivity, sleeping difficulties, perfectionism, psychosomatic problems (unrelated to headache), other behavioural disturbances, major life stress events and parental expectations (i.e. achievement orientation). Results indicated that the headache children showed significantly higher shyness-sensitivity, psychosomatic problems and behavioural disturbances and significantly lower parental expectations than the control group children. No other differences were found. While none of the variables were predictive of the frequency or intensity of head pain, measures of anxiety, perfectionism, and life stress events contributed significantly to the prediction of the severity of head pain. Also the study by Laurell et al. [33] show conflicting data. The Authors interviewed 130 schoolchildren and their parents and showed a predominance of comorbidity with other pains rather than psychological and social problems.

In addition to migraine, Chronic daily headache (CDH), defined as 15 or more headaches per month, is associated with increased functional disability and impaired quality of life [34]. Functional disability in children with recurrent headache has also been shown to be a risk factor for psychiatric conditions such as depression [35]. While research in the area of adult headache has made great strides, little is known about the prevalence of psychiatric comorbidity in children with chronic headache conditions. Some researchers have suggested that children with headaches are at increased risk for psychological adjustment problems, including symptoms of anxiety and depression [36,37]. A single published study of a large sample of school-children in Taiwan that did utilize standardized interviews, written by Wang SJ et al. [15], indicated that nearly half (47%) of the sample of 122 children (out of more than 7000 children) who reported chronic headaches had one or more psychiatric disorders, primarily mood or anxiety disorders. Two years later the same Authors identified a higher frequency of suicidal ideation in younger adolescents with

migraine with aura or high headache frequency. These associations were independent of depressive symptoms [38]. Parisi P. [39] stressed that antidepressant and antiepileptic usage in adolescents was potentially associated with an increasing suicide risk and that these two medications are frequently used in adolescents with migraine. Moreover, Wang SJ et al. [38] did not exclude the diagnosis of early onset juvenile bipolar disorders (JBD). Although the onset of JBD before the age of 10 is rare and the first manifestation occurs most frequently between the ages of 13 and 15, the diagnosis of JBD is more difficult in children and adolescent populations vs the adult population due to varying symptoms. For example, in children and adolescents, dysphoria is more likely than a euphoric or depressive mood. Asymptomatic intervals rarely exist, yet rapid cycling prevails. In addition, it has been shown that antidepressants in JBD-affected children can have severe adverse effects, particularly the amplification of suicidal ideation. Parisi P., in this respect, indeed, stressed that the possibilities of manic switching and occurrence of suicidal ideation have to be closely monitored when clinicians prescribe antidepressants for treatment of either migraine or depression in adolescents.

Slater et al. (2012) [34] assessed comorbid psychiatric diagnoses in youth with CDH and examined relationships between psychiatric status and CDH symptom severity, as well as headache-related disability. Results showed that 29.6% of CDH patients met criteria for at least one current psychiatric diagnosis. Of those, anxiety disorders were the most common (16.6% of the sample). Mood disorders, on the other hand, were less prevalent (9.5%). The most common anxiety diagnoses were specific phobia (14 of 169), generalized anxiety disorder (10 of 169) and obsessive compulsive disorder (eight of 169). Of the 16 participants with a depressive disorder diagnosis, eight had major depressive disorder, four had a diagnosis of dysthymia, and four met criteria for other mood disorders.

Moreover, 34.9% met criteria for at least one lifetime psychiatric diagnosis. No significant relationship between psychiatric status and headache frequency, duration, or severity was found. However, children with at least one lifetime psychiatric diagnosis had greater functional disability and poorer quality of life than those without a psychiatric diagnosis.

It is, furthermore, important to consider the impact of headache on family life and dynamics.

Children with migraine seem to be characterized by a higher prevalence of familial headache recurrence and parents' psychiatric disorders than children with other headache subtypes [40]. Only in the case of migraine, higher familial headache recurrence correlates with higher psychiatric comorbidity in children.

The association between migraine and anxiety leads us to think of the need for an integrated, medical and

psychological, approach to the taking care of these young patients and their families.

Headache and sleep disorders

The existence of an intimate relationship between sleep and headache has been recognized for over a century, although the nature of this association is still enigmatic. It is known as sleep deprivation, or, on the contrary, a prolonged sleep, can favor the onset of headache, in particular migraine attack [41]. On the other hand, in many cases, and especially in children, sleep, spontaneous or induced by hypnotics, constitutes the decisive factor for resolution of a migraine attack [42]. Also melatonin seems to effectively reduce the number, intensity and duration of headache attacks per month in the children but the mechanism remains unclear, even though there is much evidence to support the analgesic and anti-inflammatory effects of melatonin [43].

Headaches are known to occur during sleep, after sleep, and in relationship with various sleep stages. Nocturnal migraine attacks can be a result of disrupted sleep, and primary headaches may also emerge during nocturnal sleep, causing sleep disruption [44].

About the variety of phenomena that can disrupt the sleep macrostructure and can impact its restorative function, the periodic limb movements disorder (PLMD) can be considered as the most powerful. No studies are known about the role of PLMD in the pathophysiology of migraine in children. Esposito et al. [45] assess the prevalence of PLMD and migraine and their relationship with disability and pain intensity in a pediatric sample, referred for migraine without aura by pediatricians. This study indicates the potential value of the determination of the PLMD signs, and the importance of the nocturnal polysomnography evaluation in children affected by migraine, particularly when the clinical and pharmacological management tend to fail in the attacks control.

Children who suffer from headache have usually a high rate of sleep difficulties, such as insufficient sleep, co-sleeping with parents, difficulties falling asleep, anxiety related to sleep, restless sleep, night waking, nightmares, and fatigue during the day [46]. Furthermore, an higher prevalence of parasomnias in children, particularly of sleepwalking, bedwetting and pavor, has been documented in migraine patients than in controls [47,48]. The prevalence of sleepwalking in migraineurs seems to swing between 30% and 55% [49]. Different studies propose a model of interaction between headache and sleep [50]. Table 1 shows a model combining clinical data and experimental evidence.

To date, there are no epidemiological studies to investigate systematically specific comorbidity between headache and the spectrum of sleep disorders. The lack of such

Table 1 Models of relations between sleep and headache

1	Sleep as trigger factor for headache (excessive, reduced or disrupted, increased deep sleep)
2	Sleep as relieving factor for headache
3	Sleep disturbance as cause of headache (es. sleep apnea)
4	Headache as cause of sleep disturbance (es. attacks occurring during sleep)
5	Sleep disorders in headache patients (parasomnias, sleepwalking)
6	Sleep related headache: <ol style="list-style-type: none"> Temporal relationship (during or after sleep) Sleep stage relationship: <ol style="list-style-type: none"> REM sleep (migraine, cluster headache, chronic paroxysmal hemicrania) Slow-wave sleep (migraine)
7	Headache/sleep association: <ol style="list-style-type: none"> Intrinsic origin (modulation through the same neurotransmitters) Extrinsic origin (i.e. fibromyalgia syndrome) Reinforcement (bad sleep hygiene)

studies is compounded by the difficulties of classification of the two disease entities.

Among the epidemiological studies carried out so far, who have analyzed the relationship between sleep and headache, there is a European study, performed by 18,980 telephone interviews. This study showed the presence of chronic headache in the morning in 7.6% of subjects [51]. These, also, than non-sufferers, had more frequently sleep disorders including insomnia, circadian rhythm disorders, snoring, sleep-related breathing disorders, frightening dreams and other dyssomnia.

Headache and epilepsy

Migraine and epilepsy are the commoner brain diseases and comorbidity of these conditions is well known. This comorbidity is most frequent in childhood and adolescence.

The International Classification of Headache Disorders (ICHD-2) committee recognizes three nosographic entities concerning the relationship between epilepsy and headache: migralepsy, hemicrania epileptica, post-ictal headache [52].

Recent scientific evidences on the ictal epileptic headache have demonstrated that the 'migralepsy' concept is exceptional or even it does not exist [53]. On the other hand, migralepsy is neither included in the currently used International League Against Epilepsy (ILAE) seizure classification nor in the recent recommendations of the ILAE Commission on Classification and terminology. In particular, migralepsy, which in the recent ICHD-II is defined as a seizure developing during or within 1 h of a migraine aura, is extremely rare. The concept of migralepsy,

according to the current definition, is too narrow and inadequate and it should be revised keeping in the mind that headache or visual symptoms can be the epileptic "aura" of a seizure [54].

Parisi et al. [52] suggest to add, to the forthcoming ICHD-3 classification, the term "ictal epileptic headache" (IEH) which defines a condition diagnosed when a headache attack is the only clinical feature of epileptiform discharges [52-56].

The classification criteria for "ictal epileptic headache" (IEH), was based on twelve well-documented cases that have been published in the literature. The "migraine-epilepsy" sequence, defined, as said, "migralepsy", may often merely be a seizure starting with an ictal headache, followed by a sensory-motor partial or generalized seizure, which fits into the codified "Hemicrania Epileptica" [53,57].

To date, headache and epilepsy classifications have ignored each other. In the International League Against Epilepsy (ILAE) classification, headache is considered exclusively as a possible semiological ictal phenomenon among the "non-motor" features. In particular, headache is described as a "cephalic" sensation and is not considered as the sole ictal expression of an epileptic seizure. Moreover, headache is not classified as a "pain" (among the "somatosensory" features) or "autonomic" sensation, whereas signs of involvement of the autonomic nervous system, including cardiovascular, gastrointestinal, "vasomotor" and thermoregulatory functions, are classified as "autonomic" features. Now, although still considered a controversial issue, we must consider that headache pain could originate in the terminal nervous fibers ("vasomotor") in cerebral blood vessels; consequently, headache should be classified as an "autonomic" sensation in the ILAE Glossary and Terminology. Headache could thus be interpreted as the sole expression of an epileptic seizure and classified as an autonomic seizure [53].

In according to these criteria, Parisi et al. [58] propose the term "ictal epileptic headache" for cases in which headache is the sole ictal manifestation, whereas the term "ictal headache" should be applied when the headache, whether brief or long-lasting, is part of a more complex seizure including other sequential or overlapping (sensory-motor, psychiatric or non-autonomic) ictal manifestations.

This new classification proposal (headache as an isolated ictal autonomic manifestation in IEH) has very different prognostic implications because the outcome in people with long-lasting autonomic status epilepticus is very different (i.e., benign) from that of people with additional ictal motor-sensitive semiology. In addition, headache as an autonomic phenomenon is crucial when attempting to understand why headache may be the sole ictal epileptic manifestation: the reasons have been thoroughly explained in Panayiotopoulos syndrome, whereas the

threshold required to trigger an ictal autonomic phenomenon is believed to be lower than that required to trigger sensitive sensorial or motor ictal semiology [53].

The criteria of IEH have been proposed by Belcastro et al. [59] to identify the case of headache (as sole ictal manifestation) of epileptic origin in order to promptly obtain an EEG recording and confirm the diagnosis. Table 2, taken from the paper of Parisi et al. [52], shows the proposed criteria for ictal epileptic headache (Diagnostic criteria A–D must all be fulfilled to make a diagnosis of 'IEH').

This clinical picture is extremely rare and has only been documented in about 10–12 cases and its epileptic nature is documented with ictal EEG. For this reason, it is difficult to obtain firm conclusions about the frequency of IEH based on epidemiological studies. Using these criteria, we will be able to clarify if IEH represents an underestimated phenomenon or not [59].

Regarding the third entity concerning the relationship between epilepsy and headache, the post-ictal headache, a multicentric Italian study from 2006 at 2009 on 142 children, shows that post-ictal headaches were most frequent (62%). Pre-ictal headaches were less common (30%). Inter-ictal headaches were described in 57.6%. Clear migrainous features were present in 93% of pre-ictal and 81.4% of post-ictal headaches. Inter-ictal headaches meet criteria for migraines in 87%. The association between partial epilepsy and migraine without aura is most common and reported in 82% of our patients with peri ictal headache and in 76.5% of patients with post-ictal headache [60]. The term "hemispheric epileptic" should be maintained in the ICHD-II, introduced into the ILAE, and be used to classify all cases in which an "ictal epileptic headache" "coexists" and is associated synchronously or sequentially with other ictal sensory-motor events [55].

As regards the possible causes of comorbidity, the first hypothesis provides a causal relationship of migraine and epilepsy, which seems, however, unlikely considering that some epileptic syndromes such as benign partial epilepsies

are observed more frequently [61]. If the association of the two disorders were purely random, the expected prevalence of epilepsy was 1% in migraineurs and the prevalence of migraine was 12% in epileptics, while the literature reports prevalence data significantly higher than expected on basis of random association. The risk for unprovoked seizures was increased in children with migraine with aura and not in patients with migraine without aura [62].

Several epidemiological studies indicate an association of migraine and epilepsy with an increased prevalence of migraine in patients with epilepsy and vice versa. In particular, the prevalence of epilepsy in patients with migraine varies from 1 to 17%, with an average of 5.9%, but this percentage greatly exceeds that of the general population that is approximately 0.5–1%.

The overall prevalence of migraine in children with epilepsy varies from 8 to 15%, with values also increased in children with central-temporal EEG spikes (63%) and epilepsy with absences (33%) [63,64]. The risk of migraine is more than twice as high in subjects with epilepsy both in probands than in relatives, compared to people without epilepsy [65].

As a second hypothesis has been suggested a causal unidirectional relationship, for instance in case of migraine can cause cerebral ischemia or cerebral damage, and consequently epilepsy, or in the case of "migralepsy", where migraine aura can trigger a seizure. More often a seizure triggers an attack of headache post-critical, often with migraine characteristics, in this case it has been hypothesized that epilepsy can trigger migraines through activation of the trigeminal-vascular system or through mechanisms-encephalic trunk [66].

However, the unidirectional hypothesis has been contradicted in a study for verified the relationship between migraine and epilepsy in 395 adult seizure patients, conducted by Marks et al. [67], since in the majority of patients with migraine and epilepsy (66/79, 84%) attacks were completely independent. A third hypothesis requires that common environmental risk factors, such as head injury, can cause both migraine and epilepsy. In fact, it has been found an increased risk of migraine in people with epilepsy caused by head trauma, and that in each subgroup of epilepsy, defined on the basis of seizure type, age at onset, etiology, and family history [68]. On the other hand, the presence of shared environmental factors do not explain the increased risk of migraine in patients with idiopathic epilepsy and several studies have documented the association between migraine and rolandic epilepsy and idiopathic occipital epilepsy [69,70].

Headache may occur before, during or after an epileptic seizure, as well as vomiting. In idiopathic occipital epilepsy, crises are, in fact, often characterized by

Table 2 Proposed criteria for ictal epileptic headache (IEH)

A.	Headache lasting seconds, minutes, hours or days;
B.	Headache that is ipsilateral or contralateral to lateralized ictal epileptiform EEG discharges (if EEG discharges are lateralized);
C.	Evidence of epileptiform (localized, lateralized or generalized) discharges on scalp EEG concomitantly with headache; different types of EEG anomalies may be observed (generalized spike-and-wave or polyspike-and-wave, focal or generalized rhythmic activity or focal subcontinuous spikes or theta activity that may be intermingled with sharp waves) with or without photoparoxysmal response (PPRs)
D.	Headache resolves immediately after iv. antiepileptic medication

vomiting associated with visual symptoms, focal seizures and headache.

The existence of a possible constitutional common ground between migraine and epilepsy was initially proposed on the basis of significantly greater familiarity of migraine in epileptics (28%) and for epilepsy in migraineurs (2–3%) [70].

The genetic hypothesis (fourth hypothesis) was tested by Ottman et al. [65], which have suggested a higher incidence of migraine in families with genetic forms of migraine than those with non-genetic forms and that the relatives of patients with migraine and epilepsy had an increased incidence of epilepsy compared to the relatives of patients with only epilepsy. However, this hypothesis was not confirmed by other studies [68].

Subsequent work reported data in favor of possible genetic factors common to the two conditions. In fact, in some families with idiopathic temporal lobe epilepsy was found a higher prevalence of migraine [71,72]. An extended family with several individuals with occipital and temporal lobe epilepsy was also featured, which segregated with an autosomal dominant mode of transmission; epileptic patients had migraines with aura are independent of seizures [73].

Most obvious is the association between migraine with aura (MWA) and epilepsy. In fact, in a study of 134 children and adolescents with headache, there was a high prevalence of MWA (30.4%) than other types of primary headache in children with seizures [74]. Another study of population-based case-control study documented that the risk of seizures was increased in children with MWA and not in those with migraine without aura (MOA) [75]. In addition, in a study of adult patients, the frequency of MWA was significantly higher in patients with epilepsy in comorbidity (41%) compared to patients only with migraine (25.8%) [76].

Finally, considering the comorbidities as a result of an alteration in brain excitability, Leninger et al. [76] investigated whether the clinical features associated with diffuse cortical depression (the so-called "Spreading Depression," CSD) were more severe in patients with comorbidities. Despite the frequency of epileptic seizures and syndromes did not differ between patients with epilepsy alone, compared to subjects with comorbidity, migraine with aura, worsening pain with physical activity, phonophobia and photophobia were significantly more frequent in patients with comorbidities compared with patients with epilepsy or migraine alone.

These differences are in favor of the hypothesis that the link between migraine and epilepsy is based on the CSD as an expression of neuronal hyperexcitability. The altered neuronal excitability may cause an increased sensitivity to the CSD resulting in an increased activation of the trigeminal nociceptive fibers and consequently in more severe migraine attacks [76].

Therefore it is likely that the altered neuronal excitability threshold, involved in migraine and epilepsy, and due to altered levels of neurotransmitters, is attributable to genetic factors, in particular the disorders of membrane ion channels, the so-called channelopathies.

The epilepsy and migraine, in fact, share common pathogenetic mechanisms partially related to the dysfunction of ion channels, it is assumed, therefore, that channelopathies may be the link between epilepsy and migraine, particularly when these disturbances are in comorbidity.

However, when headache and epilepsy overlap as a result of the crossing of the cascade of events at the cortical level, in both of the events (CSD and epileptic focus), their onset and propagation are triggered when these events reach a certain threshold, which is lower for CSD than for seizure. These two phenomena may be triggered by more than one pathway converging (at cortical level) upon the same destination: depolarization and hypersynchronization [53].

Finally, further studies are warranted to better delineate the complex link between epilepsy and migraine.

Headache and general medical conditions

Compared to comorbidity between headache and general medical conditions, an interesting epidemiological study, led by Lateef et al. [77] on the child population, highlights the correlation between headache and other general medical conditions, including asthma, hay fever and frequent ear infections. The 41.6% of children with headache had at least one of these conditions, and in general, the group examined had a probability of 3.2 times higher to present two of the above conditions and a probability of 13.6 times greater to submit all three. The increased comorbidity between headache and general medical conditions was found from 4 to 11 years.

Other conditions most frequently observed in children with frequent or severe headaches are: ADHD, especially as regards hyperactive/impulsive behavior [78], learning disabilities, stuttering, anemia, obesity, bowel disease. Regarding the girls, it was found that most of those who had frequent headaches had their first menstrual cycle before the age of 12 years [77].

It was also found a higher comorbidity of headache, in particular migraine, with atopic disorders (asthma, rhinitis or eczema), studied in a sample of children presenting with such disorders. The prevalence of migraine was significantly higher in children with atopic disorders than those without. In particular, the greater association was detected with rhinitis [12].

Recent researches suggest that obesity was significantly correlated with migraine frequency and disability in children, as well as in adult population studies. Translational and basic science research shows multiple areas of overlap

between migraine pathophysiology and the central and peripheral pathways regulating feeding. Specifically, neurotransmitters such as serotonin, peptides such as orexin, and adipocytokines such as adiponectin and leptin have been suggested to have roles in both feeding and migraine. A relationship between migraine and body mass index exists, and therefore, interventions to modify body mass index may provide a useful treatment model for investigating whether modest weight loss reduces headache frequency and severity in obese migraineurs [79].

The effect of obesity and weight change on headache outcomes may have important implications for clinical care.

Recently, Verrotti et al. [80] investigated the real impact of a weight loss treatment on headache in a sample of obese adolescents. In all, 135 migraineurs, aged 14–18 years, with body mass index (BMI) greater than or equal 97th percentile, participating in a 12-month-long program, were studied before and after treatment. The program included dietary education, specific physical training, and behavioral treatment.

Decreases in weight, BMI, waist circumference, headache frequency and intensity, use of acute medications, and disability were observed at the end of the first 6-month period and were maintained through the second 6 months. Both lower baseline BMI and excess change in BMI were significantly associated with better migraine outcomes 12 months after the intervention program.

So, initial body weight and amount of weight loss may be useful for clinicians to predict migraine outcomes [80].

Headache and cerebro and cardio-vascular diseases

Although migraine is an accepted cause of cerebral infarction in adults, this association is not recognized in children. The mean annual incidence of stroke in children is about 2.5 per 100,000 [78].

The causes of cerebral infarction in children may include: heart disease, vascular disease, blood disorders, primary hypercoagulable states or congenital metabolic disorders, but 50% of strokes are considered idiopathic [81].

In the adult population is generally accepted that cerebral infarction may occur during a migraine attack [82]. In young adults, ischemic strokes could be the result of migraine in a percentage ranging from 10% to 27% [83]. In contrast, in children, the diagnosis of stroke caused by migraine is still questioned, in fact, until now, only a few cases have been reported in subjects under the age of 16 years [84,85]. In most patients, the ischemic stroke occurred in a middle cerebral artery territory [85] but may be involved also areas of the brain sprayed from basic.

In particular, there appears to be a complex relationship in a bidirectional association between migraine and stroke, including migraine as a risk factor for cerebral ischemia, migraine caused by cerebral ischemia, migraine as a cause of stroke, the presence of a common cause for

migraine and cerebral ischemia or migraine associated with subclinical vascular injury of the brain.

Some studies of young adults seem to confirm this association [86,87]. A history of migraine with aura seems to be more common among victims of ischemic stroke than among controls and an acute attack of migraine may precede, accompany or follow a thromboembolic transient ischemic attack or a stroke, this seems to occur more often among migraineurs compared patients without migraine [88,89]. Adults suffering from migraine with aura are at increased risk of cardiovascular disease and stroke [90], but it is necessary to consider that in adults, the analysis of this association is complicated by a frequent presence of additional risk factors such as smoking, hypertension and diabetes mellitus. In children, these and other potential confounding factors are much less common. There are relationships arising from small clinical samples of pediatric age who demonstrate the association of migraine with dyslipidemia [91], hyperhomocysteinemia and genetic variants related to homocysteine which appear to be risk factors for the development of stroke in children [92].

Furthermore, in a national representative sample of children, the severe or recurrent headache was associated with higher levels of adiposity measured by the body mass index (BMI) [77].

In general, below the age of 55, migraine with aura is a risk factor for ischemic strokes. However, it's important to point out that part of the latter, can be linked to the presence of a patent foramen ovale (PFO).

The PFO is the result of incomplete fusion of the septum "primum" and "secundum", which normally occurs shortly after birth, when the left atrial pressure exceeds that of the right atrium.

Epidemiological studies have shown a clear comorbidity between migraine with aura and PFO. In fact, the available data suggest that PFO is more common in women with migraine with aura (present in about 50% of cases) and that migraine with aura is more common in patients with PFO [93-95]. The mechanism underlying the possible relationship between migraine and PFO is not yet very clear: is there a causal relationship with migraine attacks, or have common genetic factors? The pathophysiological mechanism is considered a passage of microemboli and vasoactive chemicals through the PFO, which would circumvent the filtering pulmonary triggering migraine symptoms. The widespread cortical depression, which is the mechanism behind the migraine aura, could be favored by the presence of a PFO. Among the various hypotheses, it seems interesting to Pierangeli et al., who claim that a particular genetic predisposition could lead to a co-development of atrial septal abnormalities and migraine [96]. In fact, if the aura has occurred due to a malfunction of the

cerebral perfusion, the symptoms should occur with a sudden onset and not gradual. It's likely that the association of migraine and PFO is random, given the frequency of both disorders.

Recently, Steenblik et al. [97] sought to examine the familial risk of isolated interatrial shunt, caused by either atrial septal defect or patent foramen ovale, and explore associated comorbidities of stroke, transient ischemic attack (TIA), and migraine using a population database.

They found that there is a strong familial inheritance pattern for isolated interatrial shunt, with significantly higher risk of interatrial shunt among affected patients' siblings, first-, and second-degree relatives. Relatives of affected individuals also had a higher risk of TIA, a trend toward an increased risk for stroke, but no increased risk of migraine headache.

The relevance of genetic factors with respect to the preparation and transmission of PFO and migraine with aura is still under discussion [98-100].

Headache and tourette syndrome

Tourette syndrome (TS) is recognized as one of the most common childhood movement disorders, characterized by motor and phonic tics often associated with neurobehavioral comorbidities, such as obsessive-compulsive disorder. Neurotransmitter dysregulation, particularly involving the serotonin system, has been implicated in the pathogenesis of TS, obsessive-compulsive disorder, and migraine headache. The frequency of migraine headache in a clinic sample of TS subjects was nearly 4-fold more than the frequency of migraines reported in general population. In particular, of 100 patients with TS, 25 (25.0%) satisfied the diagnostic criteria for migraine headache, significantly greater than the estimated 10% to 13% in general adult population and the estimated 2% to 10% in general pediatric population [101].

The first study that has examined the comorbidity between Tourette syndrome and headache was conducted by Barabas et al. (1984) [102]. The authors studied the incidence of migraine among children with Tourette's Syndrome (TS). Among 60 children with TS (mean age of 11.9 yrs), migraine was prevalent in 26.6%. This figure is substantially greater than that reported for general population of school-aged children (4.0–7.4%) or for 2 control groups consisting of 72 children with seizure disorders and 62 children with learning disabilities. The prevalence rates for these two control groups were 11.3% and 8.0%, respectively.

Subsequently, in 1986, Lacey D.J. [103] have shown a correlation between Tourette's syndrome and several other disorders in children, including: thought and behavioral disorders, sleep disturbances, headaches, and school difficulties-including attention deficit disorder.

A recent study of Ghosh et al. (2012) [104] analyzed the frequency of occurrence of headaches in children and adolescents with TS to address their possible inclusion as a comorbidity.

Using a prospective questionnaire, administered directly, the author interviewed a total sample size of 109 patients with TS ≤ 21 years of age. The questionnaires were then analyzed according to the International Headache Society's diagnostic criteria. The author found that headaches were present in 55% of patients, with two most common headache types being migraine headaches and tension-type headaches. The rate of migraine headache within the TS group was found to be 4 times greater than that of general pediatric population, as reported in literature. In addition, the rate of tension-type headache was found to be more than 5 times greater than that of general pediatric population. Overall, the high rates of migraine and tension-type headache within this population support the proposition that headaches are a comorbidity of TS.

Headache and ADHD

Primary headache syndromes (eg, migraine and tension-type headache [TTH]) and attention-deficit/hyperactivity disorder (ADHD) are prevalent in childhood and may cause impairment in social and academic functioning.

In particular, Migraine and ADHD are highly prevalent, affecting between 5 to 10% of the pediatric population [4,105]. Coincidentally, the burden caused by both neuropsychiatric disorders reaches a common range of negative outcomes impairing quality of life [106,107], school achievement [108,109], social [7,110], and family functioning [111,112]. Thus, studying the association of both conditions is of utmost clinical importance.

According to a systematic review of clinical studies on psychological functioning and psychiatric comorbidity of migraine in children, there is no evidence that ADHD is more frequently diagnosed in this group compared with no headache controls [7].

In a cross-sectional epidemiological study specifically designed to examine this association, we have found that migraine are not comorbid to ADHD overall, but are comorbid to hyperactive-impulsive behavior [88]. In this study ADHD was assessed according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria by the validated Brazilian version of the Multimodal Treatment Study of Children with ADHD – Swanson, Nolan, and Pelham IV (MTA-SNAP-IV) scale [113] fulfilled by parents and teacher. Mental health status was assessed with the validated Brazilian version of the Child Behavior Checklist (CBCL) [114]. The prevalence of ADHD was not significantly different comparing children with migraine to controls (no headache). For inattention symptoms,

no significant differences were found. The prevalence of hyperactivity-impulsivity symptoms was 8.1% in children without headache, 23.7% in children with migraine (relative risk [RR] = 2.6; 95% confidence interval [CI] = 1.6–4.2), and 18.4% in children with probable migraine (RR = 2.1; 95% CI = 1.4–3.2). According to the multivariate analyses, ADHD or inattention symptoms were not predicted by headache subtypes or headache frequency. On the other hand, hyperactivity-impulsivity symptoms were significantly associated with any headache ($p < 0.01$), tension-type headache (TTH) ($p < 0.01$), or migraine ($p < 0.001$) [88].

An association between childhood migraine and inattention symptoms have been reported by some population [115,116] and clinical [6] studies. However, the findings must be understood in the context of some methodological limitations. The behavior rating scales adopted by these studies add symptoms of inattention and hyperactivity/impulsivity in the same domain preventing the distinction between them. Among the 11 questions comprising the attention domain in the CBCL, only three capture symptoms of inattention (*"Can't concentrate, can't pay attention for long"*, *"Daydreams or gets lost in his/her thoughts"*, and *"Stares blankly"*). The remaining questions focus on hyperactivity, impulsivity, executive dysfunctions and lack of coordination (*"Acts too young for his/her age"*, *"Can't sit still, restless, or hyperactive"*, *"Confused or seems to be in a fog"*, *"Impulsive or acts without thinking"*, *"Nervous, high strung, or tense"*, *"Nervous movements or twitching"*, *"Poor school work"*, and *"Poorly coordinated or clumsy"*) [117]. Likewise, of the five questions that encompass the hyperactivity scale of the Strengths and Difficulties Questionnaire (SDQ), two are destined to identify inattention symptoms and three to hyperactivity/impulsivity [118]. Adopting the MTA-SNAP-IV scale we could separate both dimensions of ADHD symptoms in our study [88].

In accordance to our findings, neuropsychological studies with clinical samples have found no attentional impairment in children with migraine compared to controls, in spite of a rather impulsive response profile [119–121].

Given the possible comorbidity between migraine and hyperactivity-impulsivity symptoms, providers and educators should be aware of the association.

Conclusions

Primary Headaches In Childhood and Adolescence are often associated with, and deeply influenced by, many comorbid situations.

In this review are analyzed the most relevant of them.

It is fundamental to take care of any kind of comorbidity to establish the most effective treatment strategy.

Competing interest

The authors declare that they have no competing interest.

Authors' contributions

All authors contributed to the writing of each paragraph of the manuscript. All authors read and approved the final manuscript.

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8° RASSEGNA
 SUL CINEMA PER L'INFANZIA
 E PER L'ADOLESCENZA

Grandi SPERANZE

Storie di bambini
 tra **SOGNI** e **BISOGNI**

A cura di Stefano Conte
 Neuropsichiatra Infantile
 U.S.C. di Neuropsichiatria Infantile - A.O. Papa Giovanni XXIII

1 Giovedì 10 ottobre 2013
 ore 20.30
La guerra è dichiarata
 di Valérie Donzelli
 Interverrà Pieremilio Comelli,
 Pediatra - Sezione di Emato-Oncologica
 U.S.C. di Pediatria - A.O. Papa Giovanni XXIII

2 Giovedì 17 ottobre 2013
 ore 20.30
Tomboy
 di Céline Sciamma
 Interverrà Andrea Ualesini,
 Caporedattore de «L'Eco di Bergamo»

3 Giovedì 24 ottobre 2013
 ore 20.30
Sister
 di Ursula Meier
 Interverrà Rossana Bonadei,
 Docente di Letteratura Inglese e Studi Culturali
 Università degli Studi di Bergamo

4 Giovedì 31 ottobre 2013
 ore 20.30
Monsieur Lazhar
 di Philippe Falardeau
 Interverrà Paolo Scotti,
 Psicologo e Mediatore Familiare
 Centro per il Bambino e la Famiglia - ASL di Bergamo

La rassegna propone, attraverso la visione
 e la successiva discussione di quattro film,
 una riflessione su alcuni temi che riguardano
 l'infanzia di oggi, quali la malattia,
 le discriminazioni, l'emarginazione e
 l'importanza dell'istruzione e dell'insegnamento.

CINEMA CAPITOL
 BERGAMO, VIA T. TASSO 41

LA PARTECIPAZIONE ALLE SERATE È RICONOSCIUTA
 DAL CENTRO SERVIZI DI BERGAMO COME MONTE ORE
 DESTINATO ALL'AGGIORNAMENTO DEGLI INSEGNANTI



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Nepios
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 Associazione a tutela dell'infanzia

**I TEMI PRINCIPALI DEI FILM VERRANNO
 COMMENTATI E DISCUSSI INSIEME
 AD ESPERTI CHE CONOSCONO
 - ANCHE ATTRAVERSO LA LORO
 ESPERIENZA QUOTIDIANA - LA REALTÀ
 DELLE PROBLEMATICHE PROPOSTE.**

CINEMA CAPITOL
 BERGAMO, VIA T. TASSO 41

8° RASSEGNA SUL CINEMA PER L'INFANZIA E PER L'ADOLESCENZA

Grandi SPERANZE

Storie di bambini tra SOGNI e BISOGNI



Alfede di ogni associazione c'è innanzitutto un
 in, una persona spinta ad offrire il proprio impegno.
 Quando nasce la volontà di servire l'altro, inizia la ricerca dell'appoggio
 di un gruppo, per operare insieme e diventare una presenza sociale con-
 creta. Così nel 2001 è nata a Bergamo **Nepios**, un'associazione senza sco-
 po di lucro a tutela dell'infanzia e della famiglia. **Nepios** opera grazie a
 un fondo incrementato dai contributi diretti dell'associazione e di terzi pub-
 blici o privati. Incoraggia e gestisce iniziative di carattere culturale, di-
 creativo e di sensibilizzazione sociale, a tutte le repliche ulteriori fondi da
 destinare a progetti in linea con gli scopi statutari. Opera in stretta col-
 laborazione con le istituzioni cittadine ed è sostenuta dalla gene-
 rosità delle imprese del territorio bergamasco, che sempre si dimostra-
 no sensibili alle iniziative del territorio.

1

10 ottobre 2013, ore 20.30
La guerra è dichiarata

di Valérie Donzelli con Valérie Donzelli, Jérôme Elkaim, Gabriel Elkaim, Cé-
 sar Deseux, Brigitte Sy - Sceneggiatura di Valérie Donzelli e Jérôme e Elkaim -
 Francia - 2012 - Sacher Distribuzione - 96 minuti.

Romeo e Julietta sono due giovani che si incontrano ad una festa, sembrano
 davvero destinati ad una vita felice di coppia sconosciuta e loro nomi di butte-
 siano. Ricercheranno con loro le strade di una Parigi tumultuosa, con-
 siderano il loro amore libero evolvendosi e culminando con l'arrivo di un figlio.
 La nascita di Adamo determina ovviamente cambiamenti e nuove prospettive
 all'interno del loro rapporto ma inaspettatamente, al compimento di 18 me-
 se del bimbo, qualcosa si inclina. Il futuro familiare assume colori cupi per
 l'improvvisa scoperta della malattia di Adamo, giocata dai sanitari senza
 grandi speranze di sopravvivenza. Tuttavia Romeo e Julietta non si arren-
 dono e giorno dopo giorno, nella speranza di una possibile guarigione viene
 continuamente alimentata dall'insopprimibile desiderio di reagire di fronte
 alle avversità con una prorompente vitalità. "La guerra è dichiarata" non è un
 racconto di dolore e tanto meno di rassegnazione ma è una grande storia
 d'amore e di ottimismo, elementi indispensabili per sopravvivere alle costanti
 problematiche che un percorso di guarigione comporta. Il film nasce dalla
 necessità di voler comunicare questo dramma familiare, realmente vissuto
 dalla coppia Donzelli - Elkaim. La matrice autobiografica consente agli autori
 di poter trattare queste tematiche con grande coraggio, libertà ma anche con
 una spudorata leggerezza senza tuttavia essere superficiali. Ogni sequenza
 sprigiona un desiderio di coinvolgere emotivamente lo spettatore che è come
 trascinato, senza alcuna furbata o facile ricatto ma anzi con grande affetto,
 nel vertice delle mille piccole cose di una giovane coppia di genitori che cerca di
 salvare la vita del loro piccolo bimbo. L'assoluta libertà narrativa, la capacità
 di mischiare ed integrare perfettamente più generi cinematografici, la per-
 fetta adesione al ruolo degli attori sono tra i grandi pregi di questa pellicola. "La
 guerra è dichiarata" ha inoltre un altro grande merito che è quello di far rivive-
 re, per qualche momento, l'intimità poetica del cinema dei maestri come
 l'innocenza di *L'Inferno* o *Jacques Demy* verso i quali questo film sembra essere un
 commosso e straziato omaggio.

2

17 ottobre 2013, ore 20.30
Tomboy

di Céline Sciamma con Zoé Héran, Jeanne Disson, Malou Lévana, Sophie e
 Cattan, Mathieu Demy - Sceneggiatura di Céline Sciamma - Francia 2011 -
 Teodora Film - 78 minuti.

Laure è una bambina di 10 anni, ha una sorellina Jeanne vivace e spiritosa,
 una famiglia accogliente ed apparentemente serena (la mamma è in attesa
 del terzo figlio e il padre è sensibile ed è disponibile verso le bimbe). La fa-
 miglia si è appena trasferita in un nuovo quartiere di una grande città della
 Francia presumibilmente Parigi. Laure inizia ad ambientarsi, è estate e quin-
 di ha tutto il tempo per creare nuove amicizie. Compie un taglio di capelli
 non particolarmente femminile, una preferenza per vestiti decisamente mas-
 schili, un po' per gioco o per curiosità, Laure decide di presentarsi ai suoi coe-
 tanei come un maschio con il nome di Michael facendo forza anche sulla sua
 prestanza fisica e sulle buone abilità calcistiche. Il cambio di genere com-
 porta per Laure la gestione di non pochi problemi "pratici", non ultimo un inizia-
 le interessamento sentimentale di una bambina del gruppo verso di lei. No-
 nostante notevoli sforzi ed opportuni accorgimenti, la situazione inevitabi-
 lmente precipita e Laure sarà costretta dalla madre a rivelarsi come bambina
 suscitando ovviamente reazioni contrastanti nel gruppo dei piccoli amici.
 "Tomboy" (parola inglese traducibile come "ragazzo mancato") è il secondo
 lungometraggio di una giovane regista francese di origine italiana che è ri-
 scia nell'impresa di realizzare un film inteso come esplorazione del mondo in-
 fanziale con il pudore ed il rispetto di uno sguardo adulto attento e partecipe
 nel cogliere le inquietudini della piccola Laure e dei suoi nuovi amici. Il film
 non ha alcuna pretesa di fornire spiegazioni psicologiche o sociologiche né
 sposare particolari interpretazioni o tesi su un argomento peraltro così di-
 licato ma cerca di esplorare e di restituirci la complessità della costruzione
 dell'identità sessuale attraverso le emozioni e gli sguardi dei piccoli protagoni-
 sti. Il bel finale lascia allo spettatore la speranza che Laure/Michael possa
 essere accettata/o per quello che deciderà in futuro di essere nella con sape-
 volezza tuttavia che e ciò non sarà sempre facile come i recenti fatti di cronaca
 sempre più insegnano.

3

24 ottobre 2013, ore 20.30
Sister

di Ursula Meier con Léa Seydoux, Kacey Mottet Klein, Martin Compston, Gillian Anderson, Yann Tregouet, Jean-François Stévenin - Sceneggiatura: Ursula Meier, Antoine Jaccoud, Gilles Taurand - Francia / Svizzera - 2012 - Teodora Film/ Spazio Cinema - 94 minuti.

Simon ha 12 anni vive in un desolato paese ai piedi del massiccio dello Giura in Svizzera. Durante il giorno nel periodo invernale, frequenta regolarmente le vicine stazioni sciistiche dove cerca di mischiarsi tra turisti non per alimentare personali passioni sportive o per cercare di fare nuove amicizie, ma solo per derubare i villeggianti fondamentalmente della loro attrezzatura sportiva ma anche del cibo contenuto nei loro zaini in custodia. Simon ruba per mangiare e per garantire anche il sostegno a quella che vive e presentata come sua sorella maggiore, giovane inquieta ed inaffidabile, che invece di prendersi cura di Simon, appare lei stessa incapace di stabilire adeguate strategie di sopravvivenza per cui dalla vita sembra accumulare solo amarezze e soprusi. Simon è diverso, è convinto che attraverso la sua attività il legale possa acquisire uno specifico ruolo, possa avere un miglioramento del suo livello sociale ma soprattutto con i modesti guadagni, Simon rivendica la necessità di un riconoscimento affettivo che colmi la sua solitudine abbandonica. Progressivamente con grande sensibilità ed umanità (la giovane regista è appena al suo secondo film dopo l'eccezionale esordio del film "Home" del 2008) ci addentriamo nel complesso rapporto che lega Simon e Louise e per scoprire il loro segreto più profondo forse la radice del loro malessere. Sostentuto dall'eccezionale interpretazione dei due giovani protagonisti, "Sister" è un film appassionante e colmo di richiami alla memoria il rigore del cinema di Bresson e dei Fratelli Dardenne e ma ha anche la tenerezza di un racconto dickensiano. Il film ha vinto l'Orso d'Argento al 62° Internazionale Filmfestival di Berlino.

LE RECENSIONI DEI FILM SONO A CURA DI STEFANO CONTE

4

31 ottobre 2013, ore 20.30
Monsieur Lazhar

di Philippe Falardeau con Mohamed Fellag, Sophie Nélisse, Émilien Néron, Danièle Proulx - Sceneggiatura di Philippe Falardeau tratto dall'opera teatrale "Bashir Lazhar" di Evelyne De La Chenelière - Canada - 2011 - Rai Cinema 01 Distribuzione - Officine Ubu - 94 minuti.

In una scuola elementare di Montreal, viene ritrovato il corpo senza vita di una insegnante appesa ad un cappio, questo fatto drammatico ed inaspettato getta nello sconforto la comunità scolastica ed i bambini in particolare non riescono a trovare una spiegazione per comprendere questo gesto che pesa su tutti i loro sensi di colpa. A sostituire la giovane maestra, si propone in modo convincente, Bashir Lazhar un emigrato algerino che rivivendo una lunga esperienza come insegnante per aver svolto questo mestiere nel suo paese di origine per vent'anni. In realtà da subito sorgono dei dubbi circa l'effettiva carriera del nuovo, non più giovane, insegnante in quanto soprattutto la metodologia didattica viene giudicata piuttosto obsoleta. Vengono di fatto proposti autori francesi classici (Balzac, Molière) ma è anche per alcuni comportamenti che Lazhar viene ripreso dai colleghi e dai genitori. Per comunicare con i bambini, il maestro talvolta ricorre anche ad un coinvolgimento fisico (abbraccia gli scolari per consolarli, li riprende in qualche occasione anche con lievi schiaffetti). Nonostante l'approccio spesso discutibile e la sua goffaggine, i bambini progressivamente si affezionano a Lazhar riconoscendo dietro alla sua maschera sofferta e riservata, una sincerità di intenti e soprattutto il coraggio di non nascondersi mai di fronte alle avversità della vita. Quando progressivamente scopriamo la sua condizione di profugo e i suoi dolori familiari, comprendiamo anche noi la coerenza dei suoi insegnamenti. In modo asciutto e quasi documentaristico, continuamente vitalizzato dalla straordinaria spontaneità del protagonista e dei suoi allievi, "Monsieur Lazhar" si impone alla nostra memoria anche come una affettuosa e poetica riflessione sulla difficoltà degli adulti di riuscire a proteggere i bambini di fronte alle ingiustizie della vita e sul senso più profondo che dovremmo dare alla parola educazione.



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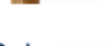
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