NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD NOVEMBRE 2015

Acta Neurol Belg. 2015;115:657-63.

ADHD, AUTISM AND NEURORADIOLOGICAL COMPLICATIONS AMONG PHENYLKETONURIC CHILDREN IN UPPER EGYPT.
Saad K, Elserogy Y, Abdel rahman AA, et al.

The aim of this study is to evaluate the neuropsychological status in a cohort of children with early and continuously treated phenylketonuria in Assiut, Upper Egypt. The study was implemented in seventy-eight phenylketonuria (PKU) children. Only 34 patients met the inclusion criteria. Investigated patients were evaluated according to detailed history, neurological examination, Childhood Autism Rating Scale, full scale Intelligence Quotient, attention deficit hyperactivity disorder, electroencephalography and magnetic resonance imaging (MRI). This study concluded that the prognosis for early diagnosed children with PKU treated from the first weeks of life is generally good. However, they are at increased risk for neurological complications and behavioral problems. So, neonatal screening for PKU is highly recommended in Egypt, for early detection and management. In addition, neuropsychological and MRI assessments in PKU children should be done

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Per la ricerca degli articoli pubblicati nella letteratura scientifica nel mese in esame sono state consultate le banche dati Medline, Embase, PsycINFO e PsycArticle utilizzando le seguenti parole chiave (o i loro sinonimi): 'Attention deficit disorder', 'Attention deficit hyperactivity disorder', 'Infant', 'Child', 'Adolescent', 'Human'. Sono qui riportate le referenze considerate rilevanti e pertinenti.

Afr J Psychiatry (South Africa). 2015;18.

COGNITIVE DEFICITS FEATURE OF MALE WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER-BASED ON THE STUDY OF WISC-IV.

Jiang W, Li Y, Du Y, et al.

Objective: This study aims to explore the characteristics of children with attention deficit hyperactivity disorder (ADHD) in the Fourth Edition of Wechsler Intelligence (WISC-IV).

Methods: The boys with ADHD were tested by WISC-IV, and the comparisons with healthy children were performed.

Results: The total IQ, (t=-4.964, P < 0.001), general ability index (t=-2.443, P=0.016) and cognitive efficiency index (t=-5.810, P < 0.001) of the study group were significantly lower than that of the control group, of which, the working memory (t=-5.354, P < 0.001), processing speed (t=-4.593, P < 0.001) and its various sub-tests scores of the subscales for cognitive processing efficiency index were significantly lower than that of the control group. The incidence of the "relatively low cognitive efficiency" feature of the study group (69.23%) was significantly higher than that of the control group (46.15%) (X2=6.923, P=0.009). The performance of the learning factor in the study group was correlated with the total IQ and working memory of WISC.

Conclusions: Children with ADHD have intellectual characteristics of relatively low cognitive efficiency

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Afr J Psychiatry (South Africa). 2015;18.

RELIABILITY AND VALIDITY OF A PARENT-ASSESSED IMPULSIVENESS SCALE FOR CHINESE CHILDREN.

Li F, Su L-Y, Geng Y-G.

Objective: The aim of this study was to investigate the reliability and validity of a version of the Barratt Impulsiveness Scale assessed by children's parents.

Methods: The test-retest reliability, split-half reliability, and homogeneity reliability were tested. Construct validity (including internal consistency and factor structure) and criterion validity were tested. The criterion validity examined the correlation with hyperactivity and impulsive factors of the CBCL and Conners' scales and the score differences between the control and the diagnosed groups were compared.

Results: The test-retest reliability was 0.825. The split-half correlation coefficient was 0.722. The internal factors consistency a coefficient of the scale was 0.387 for attention, 0.641 for motion, 0.643 for non-plan, and the total score was 0.794. The score was related with Conners' hyperactivity and impulsivity factors and CBCL's corresponding factors. This assessed scale included six factors. The scores of the comparison group were significantly higher than those of the control group.

Conclusions: The reliability and validity of the Impulsiveness Scale assessed by parents were ideal and consistent with psychometric requirements

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Afr J Psychiatry (South Africa). 2015;18.

EVALUATION OF BUPROPION AND VENLAFAXINE IN CHILDREN WITH ADHD.

Hashemian P, Nazemian A.

Background: As it is defined stimulants are the first choice in the treatment of ADHD patients but some patients cannot use it because of side effects or poor response. It seems we need to use drugs from antidepressant group like venlafaxine and bupropion that have the same effect and define which one is more effective. In this study these are answered. Therefore 40 children with ADHD between 7 to 11 years old were selected after psychiatric interview and received ADHD and Conner's rating scale. The first group took venlafaxine and the second group took bupropion. The two groups were evaluated as pre- and post-test by Conner's and ADHD rating scale.

Result: Bupropion and venlafaxine were both effective on those children and their efficacy were compared in the entire sample and for boys and girls separately by using one-way analysis of covariance. There was no significant difference between the two groups in general and separately within males and females of the two groups.

Discussion: This article shows that venlafaxine and bupropion are both effective on decreasing symptoms of ADHD. The response rates are the same in the two groups

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Afr J Psychiatry (South Africa). 2015;18.

COGNITIVE SHIFTING IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A NEAR INFRARED SPECTROSCOPY STUDY.

Yasumura A, Yamamoto H, Yasumura Y, et al.

Background: Executive function is an assemblage of high-level cognitive domains (inhibition, working memory, planning, fluency, and shifting) that facilitate the inhibition of incorrect behaviors and the selection of appropriate behaviors according to context and goals. A deficit in cognitive shifting might be a core symptom of attention-deficit hyperactivity disorder. However, previous studies addressing this issue used neurobehavioral tests, which might not be specific enough to measure cognitive shifting. The purpose of the present study was to compare cognitive shifting among children with attention-deficit hyperactivity disorder and typically developing children using a Dimensional Change Card Sort task while simultaneously measuring patterns of neural activity in the prefrontal cortex.

Methods: We recruited 22 children diagnosed with attention-deficit hyperactivity disorder and 37 typically developing children as controls matched on age, gender, language ability, and non-verbal intelligence quotient. Participants performed the computer-based Dimensional Change Card Sort task, while prefrontal cortical activity was measured with near-infrared spectroscopy.

Results: Children with attention-deficit hyperactivity disorder exhibited more incorrect answers, similar reaction times, and less prefrontal activity as compared to the typically developing children.

Conclusion: The Dimensional Change Card Sort task results revealed deficits in cognitive shifting among children with attention-deficit hyperactivity disorder. This was particularly observed through the appearance of several performance errors and with decreases in prefrontal brain activity

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Afr J Psychiatry (South Africa). 2015;18:1-2.

ZIPRASIDONE MONOTHERAPY FOR TOURETTE SYNDROME WITH COMORBID ADHD.

Naguy A, At-Tajali A.

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Am J Med Genet Part B Neuropsychiatr Genet. 2015;168:730-38.

THE CLINICAL PRESENTATION OF ATTENTION DEFICIT-HYPERACTIVITY DISORDER (ADHD) IN CHILDREN WITH 22Q11.2 DELETION SYNDROME.

Niarchou M, Martin J, Thapar A, et al.

Background: Although attention deficit-hyperactivity disorder (ADHD) is the most prevalent psychiatric disorder in children with 22q11.2DS, it remains unclear whether its clinical presentation is similar to that in children with idiopathic ADHD. The aim of this study is to compare the ADHD phenotype in children with and without 22q11.2DS by examining ADHD symptom scores, patterns of psychiatric comorbidity, IQ and gender distribution.

Methods: Forty-four children with 22q11.2DS and ADHD (mean age=9.6), 600 clinic children (mean age=10.8) and 77 children with ADHD from a population cohort (mean age=10.8) participated in the study. Psychopathology was assessed using parent-report research diagnostic instruments.

Results: There was a higher proportion of females in the 22q11.2DS ADHD sample in relation to the clinical sample (¤ç2=18.2, P<0.001). The 22q11.2DS group showed a higher rate of ADHD inattentive subtype (¤ç2=114.76, P<0.001), and fewer hyperactive-impulsive symptoms compared to the clinical group (z=8.43, P<0.001). The 22q11.2DS ADHD group parents reported fewer oppositional defiant disorder/conduct disorder symptoms (z=6.33, P<0.001) and a higher rate of generalized anxiety disorder (¤ç2=4.56, P=0.03)

in relation to the clinical group. Two percent of the 22q11.2 DS ADHD sample had received ADHD treatment. The results were similar when the 22q11.2 ADHD group was compared to the population cohort ADHD group. **Conclusions**: The clinical presentation of ADHD and patterns of co-morbidity in 22q11.2DS is different from that in idiopathic ADHD. This could lead to clinical under-recognition of ADHD in this group. Examining psychopathology in 22q11.2DS can provide insights into the genetic origins of psychiatric problems with implications beyond the 22q11.2DS population

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American Journal of Respiratory and Critical Care Medicine. 2015;191.

ABNORMAL SWEAT CHLORIDE ELEVATION IN ATTENTION DEFICIT HYPERACTIVITY DISORDER PATIENTS TAKING STIMULANT MEDICATION.

Carrion A, Whitworth J, Stokes DC.

Introduction: The gold standard confirmation method for suspected cystic fibrosis (CF) is sweat chloride using pilocarpine iontophoresis. False positive results can occur due to multiple causes, including poor technique. Multiple conditions have also been associated with a falsely elevated sweat chloride. In addition, medications like topiramate can alter sweat rate and falsely elevate sweat chloride. We encountered two children referred for elevated sweat chloride levels and possible CF. Work up for CF clinical disease was negative. In reviewing their history, both patients were receiving stimulant medications for Attention Deficit Hyperactivity Disorder (ADHD).

Case 1: Seven-year-old male was seen by his pediatrician for history of recurrent cough and otitis media. He had a normal newborn screening for CF and absence of gastrointestinal symptoms. His medications were methylphenidate 27 mg daily, inhaled beclomethasone daily and albuterol prn. Clinical exam, chest radiograph and lung function tests were all normal. Two sweat chloride determinations revealed duplicate intermediate values of 40 mmol/L, 40 mmol/L, 45 mmol/L and 46 mmol/L. CF genotyping analysis was negative for CFTR mutations.

Case 2: Six-year-old male with a history of abnormal stool pattern (primarily constipation) was sent for sweat testing. His medications were dextroamphetamine 10mg daily and polyethylene glycol daily. Clinical exam and chest radiograph were normal, as was stool elastase. Sweat chloride values were intermediate at 47 mmol/L and 48 mmol/L. CF genotyping analysis was negative for CFTR mutations.

Discussion: We report two cases of school-aged males with ADHD on stimulant medication, with elevated sweat chloride results. The association between stimulants and abnormal sweat chloride has not been previously reported. Sweat testing for the presence of stimulant derivatives has been an alternative to urine testing for monitoring their use or misuse, indicating that these drugs are excreted in sweat. The mechanism for the elevation in sweat chloride in these two patients is unclear

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Ann Neurol. 2015;78:S166.

METHYLPHENIDATE EXTENDED-RELEASE ORAL SUSPENSION (MEROS) IMPROVES ADHD-RATING SCALE AND PERMANENT PRODUCT MEASURE OF PERFORMANCE SCORES IN CHILDREN WITH ADHD.

Palumbo DR, Belden HW, Berry SA.

Objective: This study evaluated the efficacy and performance effect of Methylphenidate Extended-Release Oral Suspension (MEROS; Quillivant XR [methylphenidate HCl]), a long-acting liquid for the treatment of children with ADHD.

Methods: This randomized, double-blind (DB), placebocontrolled, crossover study enrolled 45 patients 6-12 years of age with ADHD. Following an open-label (OL) doseoptimization phase, patients were randomly assigned to 1 week of MEROS treatment followed by 1 week of placebo (or the opposite) during the DB phase. Each week of DB treatment was followed by a laboratory classroom session during which PERMP scores were measured predose and 0.75, 2, 4, 8, 10 and 12 hours postdose. ADHD Rating Scale (ADHD-RS) scores were assessed at screening, baseline, and all visits during the OL period. Treatment response was defined as a ΓëÑ50% improvement in ADHD-RS score from baseline. Safety was assessed using adverse events (AEs).

Results: A total of 45 patients were enrolled. MEROS treatment resulted in improvements in ADHD-RS scores (total and subscales) at weeks 1-4 compared with baseline. At week 4, 87.2% of children who received MEROS had achieved treatment response. PERMP scores (number of problems attempted and number correct) were significantly higher with MEROS versus placebo as early as 45 minutes (P<0.0001) and at each time point through 12 hours postdose (P<0.002). The most commonly reported AEs were decreased appetite, upper abdominal pain, affect lability, initial insomnia, insomnia, and headache.
Conclusions: These findings suggest MEROS is safe and effective in improving ADHD-RS and PERMP scores in children with ADHD

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Ann Neurol. 2015;78:S209.

THE IMPACT OF ADHD AND OCD SYMPTOMATOLOGY ON PARENTING STRESS IN CHILDREN WITH TOURETTE SYNDROME AND IN TYPICALLY DEVELOPING CHILDREN.

Stewart SB, Greene DJ, Lessov-Schlaggar CN, et al.

Objective: The most common neuropsychiatric comorbidities in children with Tourette Syndrome (TS) are attention deficit hyperactivity disorder (ADHD) and obsessivecompulsive disorder (OCD). We sought to determine the impact of tic severity in children with TS on parenting stress and the impact of comorbid ADHD and OCD symptomatology on parenting stress in children with TS and with typical development.
Methods: Seventy-four children with TS and 48 unaffected children were included. Standardized measures of parenting stress, tics severity, and OCD and ADHD symptomatology were administered. Group differences were examined. Correlations between measures and multivariate linear regressions were conducted separately in the TS and typically developing groups.
Results: The TS group had higher parenting stress compared to typically developing controls. Parenting stress and ADHD symtomatology in both groups were correlated. In the TS group, OCD symptoms were correlated with the parenting stress. In multivariate regressions, a higher severity of ADHD and OCD, but not tic severity, independently contributed to increased parenting stress. This suggests that comorbid symptomatology, but not tic severity, is associated with parenting stress. In the typically developing group, subthreshold ADHD symptoms also contributed to increased parenting stress, suggesting some generalizability of parenting stress with childhood neurodevelopmental symptomatology.
Conclusions: First, treating tics in isolation will likely not address the elevated parenting stress reported by parents of children with TS. Second, the negative impact of ADHD symptoms on parenting stress extends to typically developing children. Clinicians should consider addressing comorbid ADHD and OCD symptoms in addition to tic severity, even in children without formal diagnoses

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Applied Neuropsychology: Child. 2015 Oct;4:230-36.

COGNITIVE AND ADAPTIVE SKILL PROFILE DIFFERENCES IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER WITH AND WITHOUT COMORBID FETAL ALCOHOL SPECTRUM DISORDER.

Boseck JJ, Davis AS, Cassady JC, et al.

Children with fetal alcohol spectrum disorder (FASD) often present with comorbid attention-deficit hyperactivity disorder (ADHD), which can complicate diagnosis and treatment planning. This study investigated the cognitive and adaptive profiles of 81 children with ADHD/FASD and 147 children with ADHD. Multivariate analysis of variance and follow-up discriminant analysis indicated that the two groups had similar profiles on the Wechsler Intelligence Scale for Children-Fourth Edition and Vineland Adaptive Behavior Scales, although the children with comorbid ADHD/FASD demonstrated significantly more impairment in verbal ability, perceptual reasoning, working memory, processing speed, and overall adaptive skills. The results suggested that when compared with children with ADHD alone, children with ADHD/FASD exhibit significantly more impaired cognitive processing and adaptive skill deficits that are essential for school

success and healthy social, behavioral, and emotional functioning. Research evaluating the profiles of these groups is likely to facilitate earlier and more accurate diagnosis and intervention

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Arch Clin Neuropsychol. 2014 Nov;29:680-90.

WORD-LEVEL READING ACHIEVEMENT AND BEHAVIORAL INATTENTION: EXPLORING THEIR OVERLAP AND RELATIONS WITH NAMING SPEED AND PHONEMIC AWARENESS IN A COMMUNITY SAMPLE OF CHILDREN.

Martinussen R, Grimbos T, Ferrari JL.

This study investigated the contribution of naming speed and phonemic awareness to teacher inattention ratings and word-level reading proficiency in 79 first grade children (43 boys, 36 girls). Participants completed the cognitive and reading measures midway through the school year. Teacher ratings of inattention were obtained for each child at the same time point. A path analysis revealed that behavioral inattention had a significant direct effect on word reading proficiency as well as significant indirect effects through phonemic awareness and naming speed. For pseudoword reading proficiency, the effects of inattention were indirect only through phonemic awareness and naming speed. A regression analysis indicated that naming speed, but not phonemic awareness, was significantly associated with teacher inattention ratings controlling for word reading proficiency. The findings highlight the need to better understand the role of behavioral inattention in the development of emergent literacy skills and reading proficiency

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Asia-Pacific Psychiatry. 2015.

RELATIONSHIPS BETWEEN BEHAVIORAL SYMPTOMS OF NON-MEDICATED CHINESE CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND PARENTING STRESS: COMPARISON OF DIFFERENT SUBTYPES AND COMORBIDITIES.

Li Y, Jiang W-Q, Du Y-S, et al.

Introduction: To identify the characteristics of behavior problems among children with attention deficit hyperactivity disorder (ADHD) and their relation with parenting stress.

Methods: The Conners Parent Symptom Questionnaire (PSQ) and Parenting Stress Index (PSI) were used to assess the symptoms and parenting stress of 132 non-medicated children with ADHD as compared with 88 healthy controls.

Results: Every PSQ factor of ADHD children was higher than in the control group; children with the combined subtype of ADHD had the highest scores in conduct and learning problems, impulsivity/hyperactivity, and overall hyperactivity index; the PSI total stress, child domain, and parent domain scores were all higher in the ADHD group than in the control group; children with the combined subtype of ADHD had the highest score in the competence subscale of the parent domain, whereas the PSI total stress score of parents of children with ADHD and comorbid oppositional defiant disorder (ODD) was higher than that of parents of children with only ADHD. The PSI total stress score was positively correlated with all PSQ factor scores. The PSQ factors of conduct problems and learning problems were found to be significant predictors in a regression analysis.

Discussion: The children with ADHD exhibited abnormal parenting stress compared with healthy controls, which was much more pronounced when the children had comorbid ODD. Furthermore, parenting stress was related with the severity of ADHD symptoms, suggesting that children with the combined subtype of ADHD require particular attention in the future

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Autism Res. 2015.

DEVELOPMENT OF PLANNING IN CHILDREN WITH HIGH-FUNCTIONING AUTISM SPECTRUM DISORDERS AND/OR ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Unterrainer JM, Rauh R, Rahm B, et al.

Planning impairment is often observed in children with high-functioning autism spectrum disorders (ASD), but attempts to differentiate planning in ASD from children with attention deficit hyperactivity disorder (ADHD) and typically developing children (TD) have yielded inconsistent results. This study examined differences between these groups by focusing on development and analyzing performance in searching ahead several steps ("search depth") in addition to commonly used global performance measures in planning. A cross-sectional consecutive sample of 83 male patients (6-13 years), subgrouped as ASD without (ASD-, n=18) or with comorbid ADHD (ASD+, n=23), ADHD only (n=42) and n=42 TD children (6-13 years) were tested with the Tower-of-London-task. For global performance, ASD+ showed the lowest accuracy in younger children, but similar performance as TD at older ages, suggesting delayed development. Typically, a prolongation of planning time with increasing problem difficulty is observed in older children as compared to younger children. Here, this was most pronounced in ASD-, but under-expressed in ADHD. In contrast to global performance, effects of search depth were independent of age. ASD-, but not ASD+, showed increased susceptibility to raised demands on mentally searching ahead, along with the longest planning times. Thus, examining both global and search depth performance across ages revealed discernible patterns of planning between groups. Notably, the potentially detrimental impact of two diagnosed disorders does not add up in ASD+ in this task. Rather, our results suggest paradoxical enhancement of performance, ostensibly attributable to disruption of behavioral rigidity through increased impulsivity, which did not take place in ASD

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BMC Psychiatry. 2015.

A QUALITATIVE PROCESS EVALUATION OF A RANDOMISED CONTROLLED TRIAL OF A PARENTING INTERVENTION IN COMMUNITY (SCHOOL) SETTINGS FOR CHILDREN AT RISK OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Taylor JA, Valentine AZ, Sellman E, et al.

Background: Interventions for parents of children experiencing emotional and/or behavioural difficulties can help to improve their children's health, educational and social outcomes. However, the desirability and acceptability of screening and offering such interventions for attention-deficit hyperactivity disorder (ADHD)-type problems are currently unclear. This article is a qualitative process evaluation of a pragmatic cluster randomised controlled trial (Trial registration: ISRCTN87634685; reported elsewhere) to assess the feasibility and acceptability of a school-based parenting intervention programme for parents and teachers of children with high levels of ADHD symptoms.

Methods: Parents (n = 22) and teaching staff (n = 29) took part in semi-structured group or individual interviews, either by telephone or face-to-face, following the main trial. Interviews were digitally-recorded, transcribed verbatim and subjected to thematic analysis.

Results: The parenting intervention was acceptable to parents and teachers, and they were enthusiastic about the need for parenting groups in the school environment and stressed the importance of parent-school collaboration. Parents generally stated a preference for universal recruitment approaches to such programmes whilst teachers described the need to target specific parents.

Conclusions: It is feasible to deliver parenting intervention programmes within or near schools. The intervention was acceptable to the majority of parents, thus retention was high, but recruitment was difficult and reaching the parents with the most need was challenging. The findings of the process evaluation identified greater benefits to families than were apparent in the main trial. Recommendations identified by parents and teaching staff may be used to inform service delivery and future research to enhance recruitment to parenting interventions in the school environment

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Br J Psychiatry. 2014 Nov;205:355-61.

FETAL GROWTH AND PSYCHIATRIC AND SOCIOECONOMIC PROBLEMS: POPULATION-BASED SIBLING COMPARISON.

Class QA, Rickert ME, Larsson H, et al.

BACKGROUND: It is unclear whether associations between fetal growth and psychiatric and socioeconomic problems are consistent with causal mechanisms. AIMS: To estimate the extent to which associations are a result of unmeasured confounding factors using a sibling-comparison approach.

METHOD: We predicted outcomes from continuously measured birth weight in a Swedish population cohort (n = 3 291 773), while controlling for measured and unmeasured confounding.

RESULTS: In the population, lower birth weight (2500 g) increased the risk of all outcomes. Sibling-comparison models indicated that lower birth weight independently predicted increased risk for autism spectrum disorder (hazard ratio for low birth weight = 2.44, 95% CI 1.99-2.97) and attention-deficit hyperactivity disorder. Although attenuated, associations remained for psychotic or bipolar disorder and educational problems. Associations with suicide attempt, substance use problems and social welfare receipt, however, were fully attenuated in sibling comparisons.

CONCLUSIONS: Results suggest that fetal growth, and factors that influence it, contribute to psychiatric and socioeconomic problems

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Brain Imaging Behav. 2015.

ABNORMAL ASYMMETRY IN FRONTOSTRIATAL WHITE MATTER IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Silk TJ, Vilgis V, Adamson C, et al.

A growing body of work utilizing structural and functional brain imaging and neurocognitive measures of executive and attentional function indicates anomalous asymmetry in ADHD. This study examined the white-matter volume and diffusion properties of frontostriatal tracts, as a function of hemisphere, in ADHD and healthy controls. Forty-three young males (21 ADHD-Combined Type and 22 controls) aged 10-18 years underwent structural and diffusion weighted MRI. Tractography applying constrained spherical deconvolution (CSD) was used to construct frontostriatal tracts between each of caudate and putamen and each of dorsolateral prefrontal, ventrolateral prefrontal and orbitofrontal cortices (DLPFC, VLPFC and OFC) in each hemisphere, to examine both volumetric and diffusion microstructure properties. Young people with ADHD did not show the right hemisphere lateralization of volume in the Caudate-VLPFC and Caudate-DLPFC tracts that was evident in controls, however the ADHD group displayed a pronounced lateralization to the left for fractional anisotropy in the Putamen-VLPFC tracts. The degree of volume asymmetry did not correlate with symptom severity; however fractional anisotropy (FA) values that were more strongly lateralized to the left in the Putamen-VLPFC white matter were associated with greater symptom severity. ADHD was associated with anomalous hemispheric asymmetries in both tract volume and underlying white-matter microstructure in major fibre tracts of the frontostriatal system. Our observations of both weaker lateralization to the right in terms of tract volume and stronger lateralization to the left in terms of FA values for the ADHD group, suggests that previous inconsistencies in the literature may reflect the influence of such asymmetries

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Cephalalgia. 2015;35:60.

ATTENTION DEFICIT AND HYPERACTIVITY DISORDER AND RESPONSE TO STIMULANTS IN CHRONIC MIGRAINEURS.

Peres M.

Chronic Migraine (CM) sufferers often present psychiatric comorbidity, mainly mood and/or anxiety disorders, being more difficult to treat. Attention Deficit and Hyperactivity Disorder (ADHD) appears not only in children but also in adults. ADHD overlaps with bipolar and anxiety disorders in the adult population and can be easily misdiagnosed. We report 12 patients with ADHD and CM diagnosis who were started in a stimulant therapy. DSM-IV and IHS criteria were met. Other patients were also diagnosed but excluded from the stimulant therapy because of bipolar disorder diagnosis, hypertension, previous history of drug abuse, previous stimulant use, insomnia, panic disorder, BMI lower than 18, and glaucoma. Patients started

lysdexamfetamine 30 mg, doses were escalated if necessary, either for headache or ADHD control. Two patients did not tolerate and stop the medication, one due to worsening of headaches and other excessive irritability. The median dose was 50 mg. At least a mild improvement in ADHD and headache were observed in all 10 patients. Four patients had more than 90% decrease in headache frequency, 4 50-90%, and 2 had less than 50% improvement. All patients had poor response to previous preventive treatments. Eight patients also reported significant improvement in anxiety levels. Weight loss occurred in all patients. ADHD may coexist with CM, if suspected, a stimulant trial most likely result in better headache control and ADHD improvement. Further trials are necessary to assess the risk and benefit of stimulant therapy in migraine and ADHD and co-existing insomnia, bipolar spectrum, and anxiety disorders

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Child Adolesc Psychiatry Ment Health. 2015.

EFFECTIVE MANAGEMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) THROUGH STRUCTURED RE-ASSESSMENT: THE DUNDEE ADHD CLINICAL CARE PATHWAY.

Coghill D, Seth S.

Attention-deficit/hyperactivity disorder (ADHD) has become a major aspect of the work of child and adolescent psychiatrists and paediatricians in the UK. In Scotland, Child and Adolescent Mental Health Services were required to address an increase in referral rates and changes in evidence-based medicine and guidelines without additional funding. In response to this, clinicians in Dundee have, over the past 15 years, pioneered the use of integrated psychiatric, paediatric, nursing, occupational therapy, dietetic and psychological care with the development of a clearly structured, evidence-based assessment and treatment pathway to provide effective therapy for children and adolescents with ADHD. The Dundee ADHD Clinical Care Pathway (DACCP) uses standard protocols for assessment, titration and routine monitoring of clinical care and treatment outcomes, with much of the clinical work being nurse led. The DACCP has received international attention and has been used as a template for service development in many countries. This review describes the four key stages of the clinical care pathway (referral and pre-assessment; assessment, diagnosis and treatment planning; initiating treatment; and continuing care) and discusses translation of the DACCP into other healthcare systems. Tools for healthcare professionals to use or adapt according to their own clinical settings are also provided

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Child Adolesc Psychiatry Ment Health. 2015;9.

THE EFFECTS OF LONG-TERM MEDICATION ON GROWTH IN CHILDREN AND ADOLESCENTS WITH ADHD: AN OBSERVATIONAL STUDY OF A LARGE COHORT OF REAL-LIFE PATIENTS.

Powell SG, Frydenberg M, Thomsen PH.

Background: Children and adolescents with ADHD treated with central stimulants (CS) often have growth deficits, but the implications of such treatment for final height and stature remain unclear.

Methods: Weight and height were assessed multiple times in 410 children and adolescents during long-term treatment with CS, which lasted between 0.9 and 16.1 years. Weight and height measures were converted to z-scores based on age- and sex-adjusted population tables.

Results: CS treatment was associated with (1) a relative reduction in body weight and a temporary halt in growth, (2) a weight and height lag after 72 months compared with relative baseline values. No relation to early start of medication (<6 years), gender, comorbid ODD/CD or emotional disorders was observed.

Conclusions: Treatment with central stimulants for ADHD impacts growth in children and adolescents, and growth should be continuously monitored in patients on chronic treatment with these medications

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Child Neuropsychol. 2015.

WORKING MEMORY AND BEHAVIORAL INHIBITION IN BOYS WITH ADHD: AN EXPERIMENTAL EXAMINATION OF COMPETING MODELS.

Alderson RM, Patros CHG, Tarle SJ, et al.

Working memory (WM) and behavioral inhibition impairments have garnered significant attention as candidate core features, endophenotypes, and/or associated neurocognitive deficits of attention-deficit/hyperactivity disorder (ADHD). The relationship between ADHD-related WM and inhibition deficits remains relatively unclear, however, with inferences about the constructs' directional relationship stemming predominantly from correlational research. The current study utilized a dual-task paradigm to experimentally examine the relationship between ADHD-related WM and behavioral inhibition deficits. A total of 31 boys (15 ADHD and 16 typically developing [TD]) aged 8-12 years completed WM (1-back and 2-back), behavioral inhibition (stop-signal task [SST]), and dual-condition (1-back/SST and 2-back/SST) experimental tasks. Children with ADHD exhibited significant, large-magnitude WM deficits for the 1-back condition but were not significantly different from children in the TD group for the 2-back, 1-back/SST, and 2-back/SST conditions. Children with ADHD also exhibited significant inhibition deficits for the SST, 1-back/SST, and 2-back/SST conditions, but the within-group effect was not significant. The findings suggest that ADHD-related stop-signal demands are upstream, or compete for, resources involved in controlled-focused attention and/or other central executive (CE), WM processes

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Child Neuropsychol. 2016;22:99-109.

EVENT RATE AND REACTION TIME PERFORMANCE IN ADHD: TESTING PREDICTIONS FROM THE STATE REGULATION DEFICIT HYPOTHESIS USING AN EX-GAUSSIAN MODEL.

Metin B, Wiersema JR, Verguts T, et al.

According to the state regulation deficit (SRD) account, ADHD is associated with a problem using effort to maintain an optimal activation state under demanding task settings such as very fast or very slow event rates. This leads to a prediction of disrupted performance at event rate extremes reflected in higher Gaussian response variability that is a putative marker of activation during motor preparation. In the current study, we tested this hypothesis using ex-Gaussian modeling, which distinguishes Gaussian from non-Gaussian variability. Twenty-five children with ADHD and 29 typically developing controls performed a simple Go/No-Go task under four different event-rate conditions. There was an accentuated quadratic relationship between event rate and Gaussian variability in the ADHD group compared to the controls. The children with ADHD had greater Gaussian variability at very fast and very slow event rates but not at moderate event rates. The results provide evidence for the SRD account of ADHD. However, given that this effect did not explain all group differences (some of which were independent of event rate) other cognitive and/or motivational processes are also likely implicated in ADHD performance deficits

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Chin J Contemp Pediatr. 2015;17:980-83.

RELATIONSHIP BETWEEN SERUM ZINC LEVELS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.

Gui-Xiang S, Bing-Hua W, Ya-Feng Z.

To study the possible relationship between serum zinc levels and attention deficit hyperactivity disorder (ADHD) in Chinese children. Methods Following a systematic search for case-control studies on the serum zinc levels in Chinese children with ADHD published between 2000 and 2015, a Meta analysis was conducted using Stata 12.0 software. Results A total of 17 studies, including 2 177 children with ADHD and 2 900 normal children, were enrolled. The Meta analysis showed that serum zinc levels in children with ADHD were lower than normal children (SMD=-1.33; 95%CI:-2.22,-0.44; P=0.003). The sensitivity analysis indicated that the results were reliable. Egger's test did not find the existence of publication bias. Conclusions Serum zinc levels may be associated with susceptibility to ADHD in children

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Chin Med J. 2015;128:2988-97.

AN OPEN-LABEL, SELF-CONTROL, PROSPECTIVE STUDY ON COGNITIVE FUNCTION, ACADEMIC PERFORMANCE, AND TOLERABILITY OF OSMOTIC-RELEASE ORAL SYSTEM METHYLPHENIDATE IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Zheng Y, Liang J-M, Gao H-Y, et al.

BACKGROUND: Attention-deficit hyperactivity disorder (ADHD) is the most common mental and behavioral disorder in school-aged children. This study evaluated the effect of osmotic-release oral system (OROS) methylphenidate (MPH) on cognitive function and academic performance of Chinese school-aged children with ADHD.

METHODS: This 12-week, prospective, multicenter, open-label, self-controlled study enrolled 153 Chinese school-aged children with ADHD and 41 non-ADHD children. Children with ADHD were treated with once-daily OROS-MPH (18 mg, 36 mg, or 54 mg). The primary endpoints were Inattention/Overactivity (I/O) with Aggression Conners Behavior Rating Scale (IOWA) and Digit Span Test at week 12 compared with baseline. Secondary endpoints included opposition/defiant (O/D) subscale of IOWA, Clinical Global Impression (CGI), Coding Test, Stroop Color-word Test, Wisconsin Card Sorting Test (WCST), academic performance on teacher-rated school examinations, and safety at week 12 compared with baseline. Both non-ADHD and ADHD children received the same frequency of cognitive operational test to avoid the possible bias caused by training.

RESULTS: A total of 128 patients were evaluated with cognitive assessments. The OROS-MPH treatment significantly improved IOWA Conners I/O subscale scores at week 12 (3.8 ± 2.3) versus baseline (10.0 ± 2.4; $P < 0.0001$). Digit Span Test scores improved significantly ($P < 0.0001$) with a high remission rate (81.1%) at week 12 versus baseline. A significant ($P < 0.0001$) improvement was observed in O/D subscale of IOWA, CGI, Coding Test, Stroop Color-word Test, WCST, and academic performance at week 12 versus baseline. Very few practice-related improvements were noticed in the non-ADHD group at week 12 compared with baseline. No serious adverse events and deaths were reported during the study.

CONCLUSIONS: The OROS-MPH treatment effectively controlled symptoms of ADHD and significantly improved academic performance and cognitive function of Chinese school-aged children with ADHD. The treatment was found to be safe and generally well-tolerated over 12 weeks

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Chinese Mental Health Journal. 2015 Sep;29:685-91.

ASSOCIATION BETWEEN LPHN3 AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHINESE HAN SUBJECTS.

Wang Y, Li HM, Liu L, et al.

Objective: To investigate the association between LPHN3 and attention-deficit/hyperactivity disorder(ADHD) in Chinese Han children.

Methods: Based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis criteria, 921 normal controls and 1052 ADHD children were included in the study. The Clinical Diagnostic Interview Scale (CDIS) was used to assess symptoms and ADHD subtypes. ADHD was divided into three subtypes, namely ADHD inattentive type (ADHD-I), ADHD hyperactive-impulsive type (ADHD-HI), and ADHD combined type (ADHD-C). The ADHD rating-scale was used to assess ADHD symptoms. Including inattentive symptoms, hyperactive symptoms, impulsive symptoms and ADHD total symptoms. Three single nucleotide polymorphisms (SNPs) of LPHNS were genotyped. Case-control studies were conducted to investigate the association of each SNP with the ADHD and the subgroups using chi-square test.

Results: rsl 1131347 was associated with ADHD $P < 0.05$, OR = 0. 86(0.76-0.98)], but the difference didn't survive significance after corrections. The frequency of minor allele C in cases and control wasO. 409 vs. 0.445. For different genders, rslll31347 was significantly associated with ADHD boys [$P < 0.05$, OR = 0. 82 (0.71-0.96)], The frequency of minor allele C in cases and control was0. 402 vs. 0.449. For different subtypes, rslll31347 was associated with ADHD-C [$P < 0.05$, OR = 0. 85(0.74-0.98)] and ADHD-C boys [$P < 0.05$, OR = 0.82(0. 70 - 0.97)], but none of the difference survived significance after corrections. The frequencies of minor allele C in cases and control were respectively 0.407 vs. 0.445 and 0.401 vs. 0.449. Genotypes distribution analysis indicated that rslll31347 was associated with ADHD in general (recessive model, $P < 0.05$), ADHD boys (additive model, $P < 0.05$; dominant model, $P < 0.05$; recessive model, $P < 0.05$), ADHD-

C(recessive model, P < 0.05) and ADHD-C boys (dominant model, P < 0.05), however, none of the difference survived significance after corrections, rsl 1131347 was nominal associated with impulsive scores (P < 0.05).
Conclusion: These findings suggest that the polymorphism of LPHNS is probably involved in the pathological mechanisms of ADHD and its core symptoms of impulsivity

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Chinesische Medizin. 2015;30:158-70.
CHINESE MEDICINE IN THE TREATMENT OF ADS!ADHS IN CHILDREN.
Schreiber HWN.
In this article the author describes the positive experience she has had using Chinese Medicine in the treatment of children diagnosed with Attention Deficit Syndromes - ADS or ADHS. First of all, she explains the illness and the causes as they are perceived by Western Medicine, and subsequently she looks at some important terms in Chinese Medicine which are of significance when talking about the psyche and attention, l.a. the mind shen, the "spiritual soul" hun, the imagination yi and the willpower zhi. She describes possible disturbances in the functional systems in which energy deficiency (depletiones, xu) has a significant role to play, and mentions important basic prescriptions and their appropriate modifications. With regard to acupuncture, acupression and tuina treatments, she indicates the important acupoints. She concludes by describing the therapy of three young patients suffering from ADS or ADHS in which the author was able to achieve a significant improvement

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Clinical Child and Family Psychology Review. 2015 Sep;18:185-217.
ADHD AND EMOTION DYSREGULATION AMONG CHILDREN AND ADOLESCENTS.
Bunford N, Evans SW, Wymbs F.
Individuals with attention-deficit/hyperactivity disorder (ADHD) experience impairments in a number of functional domains. Although current evidence-based treatments for ADHD reduce symptoms and improve academic and behavioral functioning, they have minimal impact on social functioning or on risky behaviors (see Evans et al. in J Clin Child Adolesc Psychol, 43:527–551, 2014 for review). Preliminary evidence indicates that emotion dysregulation (ED) is associated with impairments across the developmental spectrum, such as social impairment and risky behaviors, and that its relative absence/presence is differentially associated with treatment response. It thus stands to reason that by incorporating a focus on ED in interventions targeting social impairment and risky behaviors, we may be able to increase the number of youth who respond to such interventions and decrease the prevalence or degree of these impairments and behaviors among youth and adults with ADHD. However, a number of questions remain unaddressed about the association between ADHD and ED, such as the portion of individuals with ADHD who experience ED, the extent to which ED is associated with the above impairments and behaviors, and whether or not ED is malleable. To begin addressing these questions, we summarize and critically evaluate the literature on the association between ADHD and ED and make recommendations for future basic, translational, and treatment outcome research

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CNS Drugs. 2015;29:865-77.
Safety of Methylphenidate and Atomoxetine in Children with Attention-Deficit/Hyperactivity Disorder (ADHD): Data from the Italian National ADHD Registry.
Cortese S, Panei P, Arcieri R, et al.
OBJECTIVE: The aim of this study was to assess the type and frequency of adverse events (AEs) in children with attention-deficit/hyperactivity disorder (ADHD) treated with methylphenidate or atomoxetine over a 5-year period in a large naturalistic study.

METHODS: We draw on data from the Italian ADHD Registry, a national database for postmarketing phase IV pharmacovigilance of ADHD medications across 90 centers. AEs were defined as severe or mild as per the classification of the Italian Medicines Agency. AE frequency in the two treatment groups was compared using incidence rates per 100 person-years (IR100PY) and incidence rate ratios (IRRs). Mantel-Haenszel adjusted IRRs were calculated to control for psychiatric comorbidity.
RESULTS: A total of 1350 and 753 participants (aged 6-18 years, mean age 10.7 ± 2.8) were treated with methylphenidate and atomoxetine, respectively, from 2007 to 2012. Ninety participants (7 %) were switched from methylphenidate to atomoxetine, and 138 (18 %) from atomoxetine to methylphenidate. Thirty-seven children treated with atomoxetine and 12 with methylphenidate had their medication withdrawn. Overall, 645 patients (26.8 %) experienced at least one mild AE (including decreased appetite and irritability, for both drugs) and 95 patients (3.9 %) experienced at least one severe AE (including severe gastrointestinal events). IR100PY were significantly higher in the atomoxetine-treated group compared with the methylphenidate-treated group for a number of mild and severe AEs and for any severe or mild AEs. After controlling for comorbidities, IRR was still significantly higher in the atomoxetine group compared with the methylphenidate group for a number of mild (decreased appetite, weight loss, abdominal pain, dyspepsia, stomach ache, irritability, mood disorder and dizziness) and severe (gastrointestinal, neuropsychiatric, and cardiovascular) AEs.
CONCLUSIONS: In this naturalistic study, methylphenidate had a better safety profile than atomoxetine

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Drug Ther Bull. 2015;53:117-20.

MELATONIN FOR SLEEP PROBLEMS IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.

Children with neurodevelopmental disorders are at risk of sleep problems, typically difficulty getting to sleep, sleep/wake rhythm disturbances and reduced duration of sleep (insomnia).1,2 This may be associated with abnormally timed or inadequate secretion of melatonin, a naturally-occurring hormone involved in coordinating the body's sleep-wake cycle.1,3 Previously, we reviewed the use of a melatonin product licensed for primary insomnia in adults aged over 55 years.4 Here we review off-label and unlicensed use of melatonin in children with attention-deficit hyperactivity disorder (ADHD) or autism spectrum disorder or related neurodevelopmental disorders

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Early Hum Dev. 2015.

LONGITUDINAL STUDY OF VERY LOW BIRTH WEIGHT INFANTS UNTIL 9YEARS OF AGE; ATTENTION DEFICIT HYPERACTIVITY AND AUTISTIC FEATURES ARE CORRELATED WITH THEIR COGNITIVE FUNCTIONS .

Ochiai M, Ichiyama M, Iwayama M, et al.

Background: Increasing attention has been given to neuro-developmental problems of very low birth weight infants (VLBWIs) at school age. However, it remains unknown whether their neuro-cognitive function and psychiatric symptoms are mutually associated.
Aim: The aim of this study was to investigate the characteristics of neuro-cognitive functions in VLBWIs and their relationship with psychiatric symptoms.
Methods: A total of 160 VLBWIs who were born at our institute between 2001 and 2005 were recruited consecutively and followed up until nine years of age. The developmental profiles were obtained from 77 children (45 males and 32 females) at six to nine years of age using the ADHD Rating Scale-Fourth edition (ADHD-RS), Autism Screening Questionnaire-Japanese version (ASQ-J) and the Wechsler Intelligence Scale for Children-Third edition (WISC-III).
Results: The full-scale intelligence quotient did not significantly differ between the male and female VLBWIs (median: 91 vs. 99, p= 0.17). The males had higher total scores (median: 13 vs. 4, p. <. 0.01) and higher scores on the subscales of Inattention (8 vs. 2, p. <. 0.01) and Hyperactivity-Impulsivity (5 vs. 1, p. <. 0.01) of the ADHD-RS compared with the females. The Verbal Comprehension Index (VCI) of the WISC-III was inversely correlated with the total scores of the ASQ-J for all VLBWIs (n= 77, rc: - 0.32, 95% CI: - 0.19 to - 0.01, p= 0.04). We also observed that the Freedom from Distractibility Index (FDI) of the WISC-III was

significantly correlated with the Inattentive scores of the ADHD-RS (n= 45, rc: - 0.18, 95% CI: - 0.35 to - 0.02, p= 0.03) in male, but not female VLBWIs.
Conclusions: We herein report that the VCI and FDI of the WISC-III were correlated with the autism spectrum disorder and attention deficit hyperactivity disorder symptoms, respectively, in male VLBWIs

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Epilepsy Res. 2015;117:58-62.
CHILDREN (10-12 YEARS AGE) OF WOMEN WITH EPILEPSY HAVE LOWER INTELLIGENCE, ATTENTION AND MEMORY: OBSERVATIONS FROM A PROSPECTIVE COHORT CASE CONTROL STUDY.
Gopinath N, Muneer AK, Unnikrishnan S, et al.
OBJECTIVE: To compare the cognitive outcome of children of women with epilepsy (CWE) with matched controls (CWO).
METHODS: CWE (10-12 years) under follow up in Kerala Registry of Epilepsy and Pregnancy (n=190) were evaluated with WISC-IV, Trail Making Test (TMT), Rey Auditory Verbal Learning Test (RAVLT) and compared with age and sex matched children of women without epilepsy - CWO (n=149) drawn from schools in the same region. The dosage was expressed as prescribed daily dose/daily-defined dose (PDD/DDD) ratio in order to make comparisons.
RESULTS: The Full Scale IQ of CWE (77.9±14.6) was 8.5 points lower than that of CWO (86.4±13.4), which was statistically significant (p=0.001). They performed lower on TMT Part A & B and RAVLT. The FSIQ mean±SD; PDD/DDD ratio and number of monotherapy exposure for different anti-epileptic drugs were phenobarbital: (74.5±14; 1.1±0.8; 22), valproate: (82.8±12.4; 0.3±0.1; 36), carbamazepine: (82.2±13.9; 0.6±0.3; 41), phenytoin: (82.6±13.5; 0.8±0.3; 11). The FSIQ for those exposed to phenobarbital was significantly (p=0.01) lower than others. The significant predictors of FSIQ differed at lower and higher ends of its spectrum. These predictors were low body mass index and low maternal education for FSIQ<80 and low maternal education, low maternal IQ and high anti-epileptic drug dosage for FSIQ<86. High anti-epileptic drug dosage, low maternal IQ, and low paternal education were the predictors for FSIQ<92.
SIGNIFICANCE: The IQ, attention and memory were significantly lower for 10-12 year old CWE when compared to CWO. The important predictors of low FSIQ were antiepileptic drug dosage, maternal IQ, and parental education.

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Eur Child Adolesc Psychiatry. 2015;24:1497-507.
IDENTIFICATION OF NEUROMOTOR DEFICITS COMMON TO AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER, AND IMITATION DEFICITS SPECIFIC TO AUTISM SPECTRUM DISORDER.
Biscaldi M, Rauh R, Müller C, Irion L, et al.
Deficits in motor and imitation abilities are a core finding in autism spectrum disorders (ASD), but impaired motor functions are also found in attention deficit/hyperactivity disorder (ADHD). Given recent theorising about potential aetiological overlap between the two disorders, the present study aimed to assess difficulties in motor performance and imitation of facial movements and meaningless gestures in a sample of 24 ADHD patients, 22 patients with ASD, and 20 typically developing children, matched for age (6-13 years) and similar in IQ (>80). Furthermore, we explored the impact of comorbid ADHD symptoms on motor and imitation performance in the ASD sample and the interrelationships between the two groups of variables in the clinical groups separately. The results show motor dysfunction was common to both disorders, but imitation deficits were specific to ASD. Together with the pattern of interrelated motor and imitation abilities, which we found exclusively in the ASD group, our findings suggest complex phenotypic, and possibly aetiological, relationships between the two neurodevelopmental conditions.

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Eur Child Adolesc Psychiatry. 2015;24:1349-59.

AFFECTIVE PROCESSING BIAS IN YOUTH WITH PRIMARY BIPOLAR DISORDER OR PRIMARY ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Seymour KE, Kim KL, Cushman GK, et al.

High rates of comorbidity and overlapping diagnostic criteria between pediatric bipolar disorder (BD) and attention-deficit/hyperactivity disorder (ADHD) contribute to diagnostic and treatment confusion. To advance what is known about both disorders, we compared effect of emotional stimuli on response control in children with primary BD, primary ADHD and typically developing controls (TDC). Participants included 7-17 year olds with either "narrow-phenotype" pediatric BD (n = 25), ADHD (n = 25) or TDC (n = 25). Groups were matched on participant age and FSIQ. The effect of emotional stimuli on response control was assessed using the Cambridge Neuropsychological Test Automated Battery Affective Go/No-Go task (CANTAB AGN). We found a group by target valence interaction on commission errors [$F(2,71) = 5.34$, $p < 0.01$, $\eta p (2) = 0.13$] whereby ADHD, but not TDC participants, made more errors on negative than positive words [$t(24) = -2.58$, $p < 0.05$, $r = 0.47$]. In contrast, there was a nonsignificant trend for BD participants to make fewer errors on negative versus positive words compared to ADHD and TDC participants. Between-subjects effects showed that ADHD participants made more errors than TDC, but not BD participants. Our main finding advances what is known about the effect of emotional stimuli on response control in children with ADHD. Our results suggesting a positive affective processing bias in children with ADHD compliment emerging literature show that difficulties with emotional processing and regulation may be core features of ADHD. Further, given the observed pattern of results in children with ADHD compared to BD children, our behavioral results suggest the importance of examining differences in the brain-behavior mechanisms involved in affective processing in children with ADHD compared to BD children

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Eur Child Adolesc Psychiatry. 2015;24:1325-37.

ARE ALL THE 18 DSM-IV AND DSM-5 CRITERIA EQUALLY USEFUL FOR DIAGNOSING ADHD AND PREDICTING COMORBID CONDUCT PROBLEMS?

Garcia RA, Vitoratou S, Banaschewski T, et al.

In view of ICD-11 revision, we evaluate whether the 18 DSM-IV diagnostic items retained by DSM-5 could be further improved (i) in predicting ADHD 'caseness' and 'impairment' and (ii) discriminating ADHD without CD (ADHD - CD) cases from ADHD with CD (ADHD + CD) cases. In a multi-centre study sample consisting of 1497 ADHD probands and 291 unaffected subjects, 18 diagnostic items were examined for redundancy; then each item was evaluated for association with caseness, impairment and CD status using Classical Test Theory, Item-Response Theory and logistic regression methods. First, all 18 DSM-IV items contributed significantly and independently to the clinical diagnosis of ADHD. Second, not all the DSM-IV items carried equal weighting. "Often loses things", "forgetfulness" and "difficulty sustaining attention" mark severity for Inattentiveness (IA) items and "often unduly noisy", "exhibits a persistent pattern of restlessness", "leaves seat in class" and "often blurts out answers" for Hyperactivity/Impulsivity (HI) items. "Easily distracted", "inattentive to careless mistakes", "often interrupts" and "often fidgets" are associated with milder presentations. In the IA domain, "distracted" yields most information in the low-severity range of the latent trait, "careless" in the mid-severity range and "loses" in the high-severity range. In the HI domains, "interrupts" yields most information in the low-severity range and "motor" in the high-severity range. Third, all 18 items predicted impairment. Fourth, specific ADHD items are associated with ADHD + CD status. The DSM-IV diagnostic items were valid and not redundant; however, some carried more weight than others. All items were associated with impairment

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Eur Child Adolesc Psychiatry. 2015.

THE INFLUENCE OF COMORBID OPPOSITIONAL DEFIANT DISORDER ON WHITE MATTER MICROSTRUCTURE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

van EH, Noordermeer SDS, Heslenfeld DJ, et al.

Attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) are highly comorbid disorders. ADHD has been associated with altered white matter (WM) microstructure, though the literature is inconsistent, which may be due to differences in the in- or exclusion of participants with comorbid ODD. WM abnormalities in ODD are still poorly understood, and it is unclear whether comorbid ODD in ADHD may have confounded the current ADHD literature. Diffusion Tensor Imaging (DTI) was used to compare fractional anisotropy (FA) and mean diffusivity (MD) between ADHD patients with (n=42) and without (n=117) comorbid ODD. All participants were between 8ΓÇô25 years and groups did not differ in mean age or gender. Follow-up analyses were conducted to examine the role of antisocial behaviour (conduct problems) on FA and MD values in both groups. Comorbid ODD in ADHD was associated with lower FA in left frontotemporal WM, which appeared independent of ADHD symptoms. FA was negatively associated with antisocial behaviour in ADHD + ODD, but not in ADHD-only. Comorbid ODD is associated with WM abnormalities in individuals with ADHD, which appears to be independent of ADHD symptoms. Altered WM microstructure in comorbid ODD may play a role in inconsistencies in the current DTI literature in ADHD. Altered development of these tracts may contribute to social-emotional and cognitive problems in children with oppositional and antisocial behaviour

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Eur J Clin Pharmacol. 2015 Nov.

THERAPEUTIC DRUG MONITORING OF SECOND-GENERATION ANTIPSYCHOTICS IN PEDIATRIC PATIENTS: AN OBSERVATIONAL STUDY IN REAL-LIFE SETTINGS.

Pozzi M, Cattaneo D, Baldelli S, et al.

PURPOSE: Available guidelines on therapeutic drug monitoring of second-generation antipsychotics were designed for adults; therefore, they cannot be transferred as such in pediatric patients, who may have different drug absorption, distribution, metabolism, and elimination. Moreover, available tools that guide dosing in neuropsychiatric pediatric patients are scant, leading to the possibility of reduced efficacy and/or increased risks of toxicity. Here we describe the results of observational therapeutic drug monitoring conducted in three pediatric neuropsychiatry units across Italy in 2012-2014, with the following aims: (1) to describe the distribution of plasma concentrations of second-generation antipsychotics in our pediatric patients and (2) to identify clinical covariates associated with plasma drug levels.

METHODS: Five hundred fifty-six plasma trough concentrations of the second-generation antipsychotics risperidone (plus 9-hydroxy-risperidone), aripiprazole, olanzapine, and quetiapine were measured from 172 pediatric outpatients overall. The distribution of drug concentrations was described and correlated with drug doses and clinical variables.

RESULTS: Risperidone plasma levels were lower than in adults (median 13.6 ng/ml), with a high inter-patient (78.9 %) but lower intra-patient (34.2 %) variability. In multiple regression analyses, risperidone plasma levels depended only on drug dose ($p < 0.001$). Aripiprazole plasma levels were similar to those described in adults (median 165.8 ng/ml) and were widely distributed, with an inter-patient variability of 81.1 %, while the intra-patient variability was much lower (29.3 %). Multiple regression analyses indicated that aripiprazole plasma levels were influenced by the daily doses ($p < 0.001$) and by the number of concomitant drugs ($p < 0.01$).

CONCLUSION: Our study described the distribution of plasma levels of SGAs in a real-life setting involving pediatric patients, significantly increasing the amount of available data for this fragile population. If confirmed in larger dataset, these data may contribute to the definition of optimal therapeutic window for risperidone and aripiprazole plasma levels in pediatric patients

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Front Psychiatry. 2015;6.

FACE SCANNING IN AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER: HUMAN VERSUS DOG FACE SCANNING.

Muszkat M, de Mello CB, Muñoz Pde O, et al.

This study used eye tracking to explore attention allocation to human and dog faces in children and adolescents with autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), and typical development (TD). Significant differences were found among the three groups. TD participants looked longer at the eyes than ASD and ADHD ones, irrespective of the faces presented. In spite of this difference, groups were similar in that they looked more to the eyes than to the mouth areas of interest. The ADHD group gazed longer at the mouth region than the other groups. Furthermore, groups were also similar in that they looked more to the dog than to the human faces. The eye-tracking technology proved to be useful for behavioral investigation in different neurodevelopmental disorders

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Front Psychiatry. 2015;6.

MUSIC AND SOUND IN TIME PROCESSING OF CHILDREN WITH ADHD.

Carrer LRJ.

ADHD involves cognitive and behavioral aspects with impairments in many environments of children and their families' lives. Music, with its playful, spontaneous, affective, motivational, temporal, and rhythmic dimensions can be of great help for studying the aspects of time processing in ADHD. In this article, we studied time processing with simple sounds and music in children with ADHD with the hypothesis that children with ADHD have a different performance when compared with children with normal development in tasks of time estimation and production. The main objective was to develop sound and musical tasks to evaluate and correlate the performance of children with ADHD, with and without methylphenidate, compared to a control group with typical development. The study involved 36 participants of age 6-14 years, recruited at NANI-UNIFESP/SP, subdivided into three groups with 12 children in each. Data was collected through a musical keyboard using Logic Audio Software 9.0 on the computer that recorded the participant's performance in the tasks. Tasks were divided into sections: spontaneous time production, time estimation with simple sounds, and time estimation with music.

Results: (1) performance of ADHD groups in temporal estimation of simple sounds in short time intervals (30 ms) were statistically lower than that of control group ($p < 0.05$); (2) in the task comparing musical excerpts of the same duration (7 s), ADHD groups considered the tracks longer when the musical notes had longer durations, while in the control group, the duration was related to the density of musical notes in the track. The positive average performance observed in the three groups in most tasks perhaps indicates the possibility that music can, in some way, positively modulate the symptoms of inattention in ADHD

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Front Psychiatry. 2015;6.

A 4-YEAR FOLLOW-UP STUDY OF ATTENTION-DEFICIT HYPERACTIVITY SYMPTOMS, COMORBIDITIES, AND PSYCHOSTIMULANT USE IN A BRAZILIAN SAMPLE OF CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Palma SMM, Natale ACMP, Calil HM.

The aim of this study was to evaluate symptom persistence in attention-deficit/hyperactivity disorder (ADHD), the development of comorbidities, and psychostimulant usage patterns. Follow-up studies were conducted in 37 patients with ADHD and 22 healthy controls, aged 10 and 18, 4 years after their first assessment. The ADHD was rated as persistent if participants met all DSM-IV criteria for syndromic or sub-threshold persistence, or had functional impairments (functional persistence). Of the 37 ADHD patients we reevaluated, 75% had persistent symptoms, and psychiatric comorbidities with additional functional impairments and academic problems were more common than in controls. These follow-up findings show a high comorbidity

associated with ADHD and support the importance of evaluation and treatment for ADHD and comorbidities throughout life

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Front Psychiatry. 2015;6.

ATTENTIONAL PROFILES AND WHITE MATTER CORRELATES IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER PREDOMINANTLY INATTENTIVE TYPE.

Rossi ASU, de Moura LM, De Mello CB, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a widely studied neurodevelopmental disorder. It is a highly heterogeneous condition, encompassing different types of expression. The predominantly inattentive type is the most prevalent and the most stable over the lifetime, yet it is the least-studied presentation. To increase understanding of its cognitive profile, 29 children with attention-deficit/hyperactivity disorder of predominantly inattentive type (ADHD-I) and 29 matched controls, aged 7-15 years, had their attentional abilities assessed through the Conners' continuous performance test. Diffusion tensor imaging data were collected for all of the participants using a 3.0-T MRI system. Fractional anisotropy (FA) values were obtained for 20 fiber tracts, and brain-behavior correlations were calculated for 42 of the children. The ADHD-I children differed significantly from the typically developing (TD) children with respect to attentional measures, such as the ability to maintain response-time consistency throughout the task (Hit RT SE and Variability), vigilance (Hit RT ISI and Hit RT ISI SE), processing speed (Hit RT), selective attention (Omissions), sustained attention (Hit RT Block Change), error profile (Response Style), and inhibitory control (Perseverations). Evidence of significant differences between the ADHD-I and the TD participants was not found with respect to the mean FA values in the fiber tracts analyzed. Moderate and strong correlations between performance on the attention indicators and the tract-average FA values were found for the ADHD-I group. Our results contribute to a better characterization of the attentional profile of ADHD-I individuals and suggest that in children and adolescents with ADHD-I, attentional performance is mainly associated with the white matter structure of the long associative fibers that connect anterior-posterior brain areas

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Geneesmiddelenbulletin. 2015;49:104-05.

NHG STANDARD 'ADHD IN CHILDREN'.

Damen-Van BZ.

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Genes Brain Behav. 2014 Nov;13:841-49.

A CASE-CONTROL STUDY OF BRAIN STRUCTURE AND BEHAVIORAL CHARACTERISTICS IN 47,XXX SYNDROME.

Lenroot RK, Blumenthal JD, Wallace GL, et al.

Trisomy X, the presence of an extra X chromosome in females (47,XXX), is a relatively common but under-recognized chromosomal disorder associated with characteristic cognitive and behavioral features of varying severity. The objective of this study was to determine whether there were neuroanatomical differences in girls with Trisomy X that could relate to cognitive and behavioral differences characteristic of the disorder during childhood and adolescence. MRI scans were obtained on 35 girls with Trisomy X (mean age 11.4, SD 5.5) and 70 age- and sex-matched healthy controls. Cognitive and behavioral testing was also performed. Trisomy X girls underwent a semi-structured psychiatric interview. Regional brain volumes and cortical thickness were compared between the two groups. Total brain volume was significantly decreased in subjects with Trisomy X, as were all regional volumes with the exception of parietal gray matter. Differences in cortical thickness had a mixed pattern. The subjects with Trisomy X had thicker cortex in bilateral medial prefrontal cortex and right medial temporal lobe, but decreased cortical thickness in both lateral temporal lobes. The most common psychiatric disorders present in this sample of Trisomy X girls included anxiety disorders (40%), attention-deficit disorder (17%) and depressive disorders (11%). The most strongly affected brain regions are consistent with phenotypic characteristics such as language delay, poor executive function

and heightened anxiety previously described in population-based studies of Trisomy X and also found in our sample

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Horm Res Paediatr. 2015;84:311.

ATTENTION DEFICIT AND SLUGGISH COGNITIVE TEMPO SYMPTOMS IN CONGENITAL HYPOTHYROIDISM: RESULTS FROM A CASE-CONTROL STUDY.

Esposito A, D'Acunzo I, Di MR, et al.

Background: Despite neonatal screening, children with congenital hypothyroidism (CH) may still display behavioural problems such as inattention, distractibility, hyperactivity and restlessness.

Objective and hypotheses: The aim of present study was to evaluate attention and sluggish cognitive tempo (SCT) symptoms in 32 children with CH compared to 32 matched healthy controls.

Method: The study population consisted of 32 CH children aged 9-14 years. CH children were diagnosed by neonatal screening and treated at a mean age of 19.34±4.5 days with mean starting Levothyroxine (LT4) dose of 11.8±1.4 µg/kg/day per die (range 10-15 µg/kg/day). 32 healthy subjects, comparable for age, sex and socioeconomic status were enrolled as control. CH patients and controls underwent Child and Adolescent Disruptive Behaviour Inventory-Plus (CADBI-plus) to evaluate attention and SCT symptoms. Cooperation from both parents and from teacher of enrolled subject was required to enter the study. SCT is a newly defined childhood disorder associated with a slow cognitive processing, sluggishness, daydreaming, drowsiness, lethargy and under-activeness.

Results: CH children scored significantly higher than controls in: attention problems referred by both mothers (M) (5.29±5.01 vs 3.17-¦2.54; P 0.04), and teachers (T) (7.2±8.49 vs 2.69±3.28, P<0.01) and SCT symptoms referred by both parents (F 9.61G7.04 vs 5.41G4.77, P<0.01; M 10.63±9.57 vs 4.9±4.68, P<0.01) and teachers (T 13.2±13.01 vs 4.28±5.63, P<0.01). No significant differences were found in hyperactivity or oppositional behaviors. Concerning academic performance, teachers report lower scores in mathematics in CH children compared to controls (6.25±2.13 vs 7.1±1.13, P 0.05).

Conclusion: The results of our study suggest that CH children may have ADs, SCT symptoms and impaired mathematical abilities, despite early replacement therapy and high starting LT4 doses

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Horm Res Paediatr. 2015;84:171.

THE ASSOCIATION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDERS WITH THE MEAN PLATELET VOLUME AND VITAMIN D.

Bala KA, Do-çan M, Mutluer T, et al.

Purpose: The purpose of this study was to assess the values of the mean platelet volume (MPV), a predictor of cardiovascular disease, in paediatric patients with attention deficit hyperactivity disorder (ADHD) and with autism spectrum disorders (ASD), in addition to healthy controls, to determine the risk of cardiovascular disease in these two disorder groups.

Material and method: The study included a total of 79 patients aged 3-18 with ADHD (36 patients) and with ASD (18) and controls (25) in the Van Region of Turkey. The control group included subjects of matching age and gender with no ADHD, ASD, and chronic disease and taking no vitamins. After measuring the weight and height of the patients in the groups, blood samples were obtained. The haematological parameters of the patients including MPV, vitamin B12, and vitamin D were assessed.

Results: The study included a total of 79 children and adolescents aged 2-18 (32 females and 47 males). Of the patients, 36 were in the ADHD group, 18 in the ASD group, and 25 in the control group. There was no statistically significant difference in haematological parameters between the groups, but there were significant differences in terms of vitamin D and vitamin B12. The patient groups showed lower levels of vitamin B12 and vitamin D when compared to the control group. In the ADHD group, there was a negative correlation between both vitamins and MPV (P<0.05). The partial correlation analysis of the ADHD group showed that in particular, MPV was negatively correlated to vitamin D, and not to vitamin B12 (P: 0.03).

Conclusion: The difference in MPV between the patient groups and the control group may be due to the limited number of patients studied. The vitamin D deficit particularly in the ADHD group may contribute to the elevated MPV value found by Yoruk and coworkers

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Horm Res Paediatr. 2015;84:526.

HORMONE DISORDER AND VITAMIN DEFICIENCY IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND AUTISM SPECTRUM DISORDERS (ASD).

Do-çan M, Bala KA, Mutluer T, et al.

Objective: To evaluate thyroid hormones and antibodies, vitamins B12 and D levels, ferritin levels, adrenal and gonadal steroid levels in children diagnosed with ADHD and ASD.

Material method: Patients between the ages of 2-18 years followed-up with the diagnosis of ADHD and ASD in the Van region were included in this study. The weights and heights of the patients were recorded and then the blood samples were obtained between 0800 and 0900 h. in the morning due to the diurnal variation of the hormone. 27 cases compatible with the patient group in terms of age and gender and who did not have the diagnostic criteria of ADHD and ASD were taken as the control group.

Findings: While there was no significant difference between the groups for thyroid hormone levels statistically, there was a significant difference in terms of vitamins B12 and D and ferritin statistically. While the highest ferritin and lowest vitamin M12 and vitamin D levels were found in the ASD group, the vitamin D level in the ADHD group was significantly lower than that of the controls, too. There was no statistically significant difference between the groups in terms of adrenal and gonadal hormone levels.

Conclusion: Our study is unique in the literature in terms of including and evaluating ADHD and ASD and the risk factors vitamin B12, ferritin, vitamin D, adrenal androgens, celiac disease and subclinical hypothyroidism. Besides, with the current study, we want to screen the levels and importance of supplementation of vitamin B12 and D in ASD and ADHD group patients and to especially emphasize the informing of the population about vitamin B12 and D deficiency in terms of prevention of these diseases and necessity of stimulation of the health workers in order to take the measures such as diet relieving the deficiency and supplementation

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Infancia y Aprendizaje / Journal for the Study of Education and Development. 2015 Oct;38:775-807.

LEARNING AND BEHAVIOUR OF THREE- TO FIVE-YEAR-OLD CHILDREN WITH ADHD.

García JV, Grau C, Garcés J.

Early childhood education is a developmental period in which early symptoms of attention deficit hyperactivity disorder (ADHD) can be observed. This work examines the educational background of 206 children, from the ages of three to five years (109 of them with an ADHD diagnosis and 97 without a clinical diagnosis), by analysing 306 reports from their teachers. The aim of this study is to discover if these educational reports reflect differences in academic performance and behaviour between both groups. The 123 educational goals analysed in the reports have been classified into 15 categories. A nonparametric analysis (Chi square) was performed on each variable to compare ADHD/control groups. Our results claim that ADHD children show more difficulties in different curricular and behavioural aspects like attention, self-regulation, independence, motivation, basic learning, social relationships, motor skills and communication. These reports are useful in identifying children who are at risk of developing the disorder and in establishing intervention goals that decrease negative effects in children's development.

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International Journal of Clinical and Experimental Medicine. 2015;8:13969-75.

DIAGNOSIS OF CHILDREN□ÇÖS ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND ITS ASSOCIATION WITH CYTOMEGALOVIRUS INFECTION WITH ADHD: A HISTORICAL REVIEW.

Zhou R, Xia Q, Shen H, et al.

As the most common mental disorder identified in children and teenagers, attention deficit hyperactivity disorder (ADHD) affects millions of children and their families, making it a critical health issue worldwide. This article reviewed the historical opinions about the diagnosis of ADHD and defined different subtypes of this disorder. It also summarized the current diagnostic criteria and available medications. After re-visiting the etiology of ADHD in the sense of both genetic and environment factors, it was further hypothesized that viral infection might be involved in ADHD pathogenesis. Human cytomegalovirus (HCMV) infection may be associated with ADHD, although both clinical observations and animal studies need to be performed for validation

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International Journal of Clinical and Health Psychology. 2015 Sep;15:217-25.

NEUROFEEDBACK, PHARMACOLOGICAL TREATMENT AND BEHAVIORAL THERAPY IN HYPERACTIVITY: MULTILEVEL ANALYSIS OF TREATMENT EFFECTS ON ELECTROENCEPHALOGRAPHY.

Moreno-García I, Delgado-Pardoa G, de Reya CC-V, et al.

The purpose of this study was to investigate the efficacy of neurofeedback, pharmacological treatment and behavioral therapy in Attention Deficit Hyperactivity Disorder (ADHD) through a controlled, randomized, multigroup design, with pre-, post- and follow-up treatment phases. The objectives of this study are: a) to analyze individual trajectories over time of each child in treatment, from specific measures of EEG (theta/beta ratio/TBR) considering age and sex and b) to determine the therapeutic effect on attentional and behavioral variables evaluated through the Integrated Visual and Auditory Continuous Performance Test. A total of 57 children (7-14 years) diagnosed with ADHD, were randomly assigned to one of the following experimental conditions: 1) 30 Theta/Beta training sessions, 2) Methylphenidate treatment and, 3) Behavior therapy administered according to a cognitive-behavioral protocol based on manuals. Data were analyzed using a Multilevel Longitudinal Regression Model. Results show that administered treatments are effective and cause similar effects on TBR variable, with no differences between them. However, significant differences were observed in the global attention (p = .002), auditory attention (p = .017) and visual attention (p = .028).

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Iran J Pediatr. 2015;25.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN A PATIENT WITH CONGENITAL MIRROR MOVEMENT DISORDER AND COLPOCEPHALY.

Yaroglu KS.

Introduction: Congenital mirror movement disorder designates involuntary movements on one side of the body that occur as mirror of the intentional movements on the contralateral side. Colpocephaly is described as persistence of fetal configuration of lateral ventricles.

Case Presentation: A two-month old male infant was brought to the hospital due to bilateral identical movements of the hands. Except for bilateral involuntary synkinetic imitative movements in hands, neurological and physical examination was normal. Cranial MRI showed corpus callosum dysgenesis, hypogenesis and dilation of bilateral lateral ventricular posterior horns (colpocephaly). At the age of 7 years, he was started to use metylphenydate to mitigate attention deficit and hyperactivity disorder. The mirror movements were decreasing in amplitude by years and were not so serious to affect normal life activities.

Conclusions: Mirror movements, diagnosed usually during childhood, may be congenital or secondary to neurological diseases. Although they generally do not affect normal life activities, in some cases severity of mirror movements causes a real debilitating disease. In our case the patient was diagnosed at the age of 2 months and on follow-up no debilitating problems were observed. This is the first case to describe the association of colpocephaly and mirror movements. The exact mechanism of this association is not known. Although it is known that mirror movements may be in relation with some pychiatric pathologies, this is the

first report of attention deficit and hyperactivity disorder in conjunction with mirror movements and/or colpocephaly. Managing comorbidities, either physical or psyhchological, will help the patient to live in good health without trying to cope with other pathological diseases

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J Abnorm Child Psychol. 2013 Jul;41:691-703.

EARLY FATHERING AS A PREDICTOR OF LATER PSYCHOSOCIAL FUNCTIONING AMONG PRESCHOOL CHILDREN WITH BEHAVIOR PROBLEMS.

Herbert SD, Harvey EA, Lugo-Candelas CI, et al.

The present study examined the role of early fathering in subsequent trajectories of social emotional and academic functioning of preschool children with behavior problems. Participants were 128 preschool-aged children (73 boys, 55 girls) with behavior problems whose biological fathers took part in a longitudinal study. Children were 3 years of age at the beginning of the study and were assessed annually for 3 years. Early paternal depressive symptoms predicted many aspects of children's outcome 3 years later, including externalizing and internalizing problems, social skills deficits, and lower cognitive and academic functioning, and predicted changes in children's externalizing, internalizing, and social problems across the preschool years. Paternal socioeconomic status (SES) also consistently predicted children's later functioning across these domains. Furthermore, self-reported paternal attention-deficit hyperactivity disorder (ADHD) symptoms and laxness, as well as observed frequent commands were associated with later externalizing problems in children. Paternal depressive symptoms and laxness mediated the relation between paternal ADHD symptoms and child functioning. Results suggest that aspects of early father functioning play an important role in the psychosocial, cognitive, and academic development of preschool-aged children with behavior problems

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J Abnorm Child Psychol. 2015 Nov;43:1573-83.

VARIATION IN PARASYMPATHETIC DYSREGULATION MODERATES SHORT-TERM MEMORY PROBLEMS IN CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ward AR, Alarcón G, Nigg JT, et al.

[Correction Notice: An Erratum for this article was reported in Vol 43(8) of Journal of Abnormal Child Psychology (see record [rid]2015-47956-001[/rid]). In the reference section of the original article, an incorrect reference was used. This reference was mistakenly cited in the article in the Participants and Discussion sections. The correct citation is provided in the erratum.] Although attention deficit/hyperactivity disorder (ADHD) is associated with impairment in working memory and short-term memory, up to half of individual children with ADHD perform within a normative range. Heterogeneity in other ADHD-related mechanisms, which may compensate for or combine with cognitive weaknesses, is a likely explanation. One candidate is the robustness of parasympathetic regulation (as indexed by respiratory sinus arrhythmia; RSA). Theory and data suggest that a common neural network is likely tied to both heart-rate regulation and certain cognitive functions (including aspects of working and short-term memory). Cardiac-derived indices of parasympathetic reactivity were collected during short-term memory (STM) storage and rehearsal tasks from 243 children (116 ADHD, 127 controls). ADHD was associated with lower STM performance, replicating previous work. In addition, RSA reactivity moderated the association between STM and ADHD – both as a category and a dimension – independent of comorbidity. Specifically, conditional effects revealed that high levels of withdrawal interacted with weakened STM but high levels of augmentation moderated a positive association predicting ADHD. Thus, variations in parasympathetic reactivity may help explain neuropsychological heterogeneity in ADHD.

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Journal of Attention Disorders. 2015 Sep;19:779-93.

EMOTIONAL IMPULSIVITY AND EMOTIONAL AND BEHAVIORAL DIFFICULTIES AMONG CHILDREN WITH ADHD: AN ECOLOGICAL MOMENTARY ASSESSMENT STUDY.

Rosen PJ, Factor PI.

Objective: Children with ADHD often demonstrate impulsive shifts in emotion, characterized by sudden and intense shifts in affect. This study examined the effects of emotional impulsivity over time on the emotional and behavioral functioning of children with ADHD using ecological momentary assessment (EMA).

Method: Twenty-seven 8- to 12-year-old children with ADHD, and their parents, completed baseline measures of the children's emotional and behavioral functioning. Parents and children then completed an EMA protocol, whereby they each rated the child's affect three times daily for 28 days.

Results: Hierarchical regression analyses strongly supported the relation of greater EMA-derived emotional impulsivity to children's increased emotional and behavioral difficulties. These effects were evident across reporters and were maintained after controlling for baseline emotion dysregulation.

Conclusion: Overall, this study demonstrated the utility of EMA-based assessments and suggested that emotional impulsivity may play an important role in the emotional and behavioral functioning of children with ADHD.

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Journal of Attention Disorders. 2015 Sep;19:741-54.

THE PREVALENCE OF ADHD IN A POPULATION-BASED SAMPLE.

Rowland AS, Skipper BJ, Umbach DM, et al.

Objective: Few studies of ADHD prevalence have used population-based samples, multiple informants, and Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) criteria. Moreover, children who are asymptomatic while receiving ADHD medication often have been misclassified. Therefore, we conducted a population-based study to estimate the prevalence of ADHD in elementary school children using DSM-IV criteria.

Method: We screened 7,587 children for ADHD. Teachers of 81% of the children completed a DSM-IV checklist. We then interviewed parents using a structured interview (DISC). Of these, 72% participated. Parent and teacher ratings were combined to determine ADHD status. We also estimated the proportion of cases attributable to other conditions.

Results: Overall, 15.5% of our sample met DSM- (4th ed.; text rev., DSM-IV-TR) criteria for ADHD (95% CI [14.6%, 16.4%]); 42% of cases reported no previous diagnosis. With additional information, other conditions explained 9% of cases.

Conclusion: The prevalence of ADHD in this population-based sample was considerably higher than 3% to 7%. To compare study results, the DSM criteria need standardization.

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Journal of Attention Disorders. 2015 Sep;19:755-63.

ADJUSTMENT OF TIME PERCEPTION IN THE RANGE OF SECONDS AND MILLISECONDS: THE NATURE OF TIME-PROCESSING ALTERATIONS IN CHILDREN WITH ADHD.

Walg M, Oepen J, Prior H.

Objective: The nature of time-processing alterations in ADHD was assessed by means of duration judgments and temporal set-shifting tasks lasting several seconds and milliseconds.

Method: After training with visual sample stimuli for long and short durations, 31 children with ADHD and 29 controls estimated the durations of test stimuli. During testing, the temporal context was systematically varied by shifting the duration of stimulus sets to longer or shorter intervals.

Results: Children with ADHD generally overestimated the durations of stimuli on the seconds scale. Their assessment of stimuli on the milliseconds scale can be characterized as less-efficient adaptations to new temporal sets alongside otherwise normal discrimination performance.

Conclusion: Findings support a pure time perception alteration in ADHD. In addition, results provide first evidence that difficulties in mental set-shifting, which have been reported for other tasks, extend to temporal processing in children with ADHD

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Journal of Attention Disorders. 2015 Sep;19:771-78.

ADHD: AUDITORY AND VISUAL STIMULI IN AUTOMATIC AND CONTROLLED PROCESSES.

Fabio RA, Castriciano C, Rondanini A.

Objective: Deficits in ADHD executive function (EF) task have been widely documented in a number of different studies. The aim of this work is to analyze the characteristics of auditory vigilance in ADHD and control subjects in two conditions: with and without interference.

Method: in the first study the Merrill's (1992) procedure on automaticity with the dual-task interference paradigm was used; in the second study the auditory test with automatic procedure was used.

Results: The results of the study confirm that people with ADHD show deficits in auditory vigilance tests and become less careful when interference is introduced.

Conclusion: Results were discussed in terms of a deficit in automaticity process.

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Journal of Attention Disorders. 2015 Sep;19:764-70.

SEX DIFFERENCES IN ATTENTIONAL PERFORMANCE IN A CLINICAL SAMPLE WITH ADHD OF THE COMBINED SUBTYPE.

Günther T, Knospe EL, Herpertz-Dahlmann B, et al.

Objective: The goal of the present study was to assess whether girls with ADHD express similar deficits in various attention tasks to those described in boys.

Method: A total of 175 children with the combined subtype of ADHD (89 females) and 132 normal controls (60 females) aged 8 to 14 years participated.

Five different tests were conducted: alertness, sustained attention, focused attention, divided attention, and a set-shifting task.

Results: The children with ADHD performed worse on all aspects of attention compared with healthy control participants. Several overall general sex differences could be detected, with boys exhibiting faster reaction times and greater response variability. Controlling for ADHD symptom severity and psychiatric comorbidities, no Sex × Diagnosis interaction was found, suggesting that males and females with ADHD experience comparable attentional deficits.

Conclusion: These results indicate that deficits in various attentional domains are a robust component of ADHD in males and females

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Journal of Attention Disorders. 2015 Sep;19:794-804.

JITTER REDUCES RESPONSE-TIME VARIABILITY IN ADHD: AN EX-GAUSSIAN ANALYSIS.

Lee RWY, Jacobson LA, Pritchard AE, et al.

Objective: "Jitter" involves randomization of intervals between stimulus events. Compared with controls, individuals with ADHD demonstrate greater intrasubject variability (ISV) performing tasks with fixed interstimulus intervals (ISIs). Because Gaussian curves mask the effect of extremely slow or fast response times (RTs), ex-Gaussian approaches have been applied to study ISV.

Method: This study applied ex-Gaussian analysis to examine the effects of jitter on RT variability in children with and without ADHD. A total of 75 children, aged 9 to 14 years (44 ADHD, 31 controls), completed a go/no-go test with two conditions: fixed ISI and jittered ISI.

Results: ADHD children showed greater variability, driven by elevations in exponential (tau), but not normal (sigma) components of the RT distribution. Jitter decreased tau in ADHD to levels not statistically different than controls, reducing lapses in performance characteristic of impaired response control.

Conclusion: Jitter may provide a nonpharmacologic mechanism to facilitate readiness to respond and reduce lapses from sustained (controlled) performance.

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J Child Adolesc Psychopharmacol. 2015;25:625-32.

VARIANTS OF DOPAMINE BETA HYDROXYLASE GENE MODERATE ATOMOXETINE RESPONSE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Fang Y, Ji N, Cao Q, et al.

Objective: Atomoxetine is the most widely used nonstimulant for the treatment of attention-deficit/hyperactivity disorder (ADHD). It selectively acts on the norepinephrine (NE) system. Dopamine beta hydroxylase (DBH) regulates the synthesis of NE. This study aimed to investigate whether variants in the DBH gene have an effect on the differential response to atomoxetine.

Methods: Children and adolescents with ADHD were enrolled in a prospective, open-label study of atomoxetine for 8-12 weeks. The dose was titrated to 1.2-1.4mg/kg per day and maintained for at least 4 weeks. The primary efficacy measure was the investigator-rated ADHD Rating Scale-IV (ADHD-RS-IV). Three categorical evaluations of treatment effects (defined as response, robust response, and remission) were used. We used a candidate gene approach. Eight single nucleotide polymorphisms (SNPs) in DBH were selected and genotyped based on the functional annotation in literature. Their association with response or remission status was analyzed.

Results: Four SNPs were found nominally associated with response status (rs1076150, p=0.0484; rs2873804, p=0.0348; rs1548364, p=0.0383; and rs2519154, p=0.0097), two were associated with robust response (rs1076150, p=0.0349; and rs2519154, p=0.0047), and one was associated with remission (rs2519154, p=0.0479). The association between rs2519154 and robust response was significant after correction of multiple comparison (p=0.0384). Two haplotypes of linkage disequilibrium (LD) block1 (constituted by rs1108580, rs2873804, rs1548364, and rs2519154) were nominally associated with response and robust response status (CTAC: p=0.0301 for response, p=0.0374 for robust response; TCGT: p=0.0317 for response, p=0.021 for robust response), whereas one haplotype (GC) of LD block2 (constituted by rs2073837 and rs129882) was associated with robust response and remission status (p=0.0377 for robust response; p=0.0321 for remission), although none achieved significant threshold after multiple comparison.

Conclusions: Variants in DBH genes were associated with atomoxetine response in the treatment of ADHD. Further replication in larger samples would be warranted

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J Child Adolesc Psychopharmacol. 2015;25:633-40.

ASSOCIATION BETWEEN 5-HTTLPR POLYMORPHISM AND TICS AFTER TREATMENT WITH METHYLPHENIDATE IN KOREAN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Park SY, Kim EJ, Cheon K-A.

Objectives: The purpose of this study is to examine the relationship between 5-HTTLPR polymorphism (44-bp insertion/deletion polymorphism of serotonin transporter gene) and methylphenidate (MPH) treatment response, as well as the association between the adverse events of MPH treatment and 5-HTTLPR polymorphism in children with attention-deficit/hyperactivity disorder (ADHD).

Methods: A total of 114 children with ADHD (mean age 9.08-¦1.94 years) were recruited from the child psychiatric clinic in a hospital in South Korea. We have extracted the genomic DNA of the subjects from their blood lymphocytes and analyzed 5-HTTLPR polymorphism of the SLC6A4 gene. All children were treated with MPH for 8 weeks, with clinicians monitoring both the improvement of ADHD symptoms and the side effects. We compared the response to MPH treatment and adverse events among those with the genotype of 5-HRRLPR polymorphism.

Results: There was no significant association between the 5-HTTLPR genotype and the response to MPH treatment in children with ADHD. Subjects with the S/L+L/L genotype tended to have tics and nail biting (respectively, p<0.001, p=0.017).

Conclusions: The results of this study do not support the association between the 5-HTTLPR polymorphism and treatment response with MPH in ADHD. However, our findings suggest the association between 5-HTTLPR polymorphism and the occurrence of tics and nail-biting as an adverse event of methylphenidate. This may aid in our understanding of the genetic contribution and genetic susceptibility of a particular allele in those ADHD patients with tics or nail biting

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J Child Adolesc Psychopharmacol. 2015;25:649-52.

NONMEDICAL USE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MEDICATION AMONG SECONDARY SCHOOL STUDENTS IN THE NETHERLANDS.

Koster ES, De HL, Bouvy ML, et al.

Objective: No studies in Europe have assessed the extent of nonmedical attention-deficit/hyperactivitiy disorder (ADHD) medication use among adolescents, while also, in Europe, prescribing of these medicines has increased. Our objective was to study the prevalence and motives for nonmedical ADHD medication use among secondary school students in the Netherlands.

Methods: Adolescent students 10-19 years of age from six secondary schools were invited to complete an online survey on use of ADHD medication, tobacco, alcohol, and drugs. Nonmedical ADHD medication use was defined as self-reported use without a prescription during the previous 12 months.

Results: Survey data were available for 777 students (15% response rate). The overall proportion of students self-reporting nonmedical ADHD medication use was 1.2% (n=9), which represented almost 20% of the adolescents who reported ADHD medication use (n=49). Most adolescents reported self-medication or enhancing study performance as motives for ADHD medication use.

Conclusions: The proportion of the study sample reporting nonmedical ADHD medication use in our study is lower compared with that in previous research conducted in the United States and Canada; however, on a population-based level, there might be a considerable proportion of recreational users

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J Child Adolesc Psychopharmacol. 2015 Sep;25:566-73.

AN OPEN-LABEL, RANDOMIZED TRIAL OF METHYLPHENIDATE AND ATOMOXETINE TREATMENT IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shang CY, Pan YL, Lin HY, et al.

Objective: The efficacy of both methylphenidate and atomoxetine has been established in placebo-controlled trials. The present study aimed to directly compare the efficacy of methylphenidate and atomoxetine in improving symptoms among children with attention-deficit/hyperactivity disorder (ADHD).

Methods: The study sample included 160 drug-naïve children and adolescents 7–16 years of age, with DSM-IV-defined ADHD, randomly assigned to osmotic-release oral system methylphenidate (OROS-methylphenidate) (n = 80) and atomoxetine (n = 80) in a 24 week, open-label, head-to-head clinical trial. The primary efficacy measure was the score of the ADHD Rating Scale-IV Parents Version: Investigator Administered and Scored (ADHD-RS-IV). The secondary efficacy measures included the Clinical Global Impressions–ADHD–Severity (CGI-ADHD-S) and Chinese Swanson, Nolan, and Pelham IV scale (SNAP-IV), based on the ratings of investigators, parents, teachers, and subjects.

Results: At week 24, mean changes in ADHD-RS-IV Inattention scores were 13.58 points (Cohen's d, -3.08) for OROS-methylphenidate and 12.65 points (Cohen's d, -3.05) for atomoxetine; and mean changes in ADHD-RS-IV Hyperactivity- Impulsivity scores were 10.16 points (Cohen's d, -1.75) for OROS-methylphenidate and 10.68 points (Cohen's d, -1.87) for atomoxetine. In terms of parent-, teacher-, and self-ratings on behavioral symptoms, both of the two treatment groups significantly decreased on the SNAP-IV scores at the end-point, with effect sizes ranging from 0.9 to 0.96 on the Inattention subscale and from 0.61 to 0.8 on the Hyperactivity/Impulsivity subscale for OROS-methylphenidate; and from 0.51 to 0.88 on the Inattention subscale and from 0.29 to 0.57 on the Hyperactivity/Impulsivity subscale for atomoxetine. No statistically significant differences between treatment groups were observed on the outcome measures. Vomiting, somnolence, and dizziness were reported more often for atomoxetine than for OROS-

methylphenidate, whereas insomnia was reported more often for OROS-methylphenidate than for atomoxetine.
Conclusions: After 24 weeks of treatment, OROS-methylphenidate and atomoxetine had comparable efficacy in reducing core ADHD symptoms in drug-naïve children and adolescents with ADHD.

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J Child Adolesc Psychopharmacol. 2015 Sep;25:558-65.
EARLY MORNING FUNCTIONING IN STIMULANT-TREATED CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, AND ITS IMPACT ON CAREGIVERS.
Sallee FR.
Objective: The purpose of this study was to examine the temporal occurrence and severity of inadequate attention-deficit/ hyperactivity disorder (ADHD) symptom control throughout the day, and, more specifically, the frequency and severity of associated functional impairments and their apparent emotional impact on parents and caregivers during the early morning routine before school, in children and adolescents with ADHD currently treated with stable doses of stimulant medications.
Methods: Information was obtained from 201 primary caregivers of children and adolescents with ADHD using a self-administered, on-line quantitative research survey.
Results: Inadequately controlled ADHD symptoms were rated as most severe during the evening homework time and the early morning routine. The majority of caregivers reported early morning ADHD symptoms and impairment of early morning functioning (EMF) as moderate to severe. Caregiver reactions to their child's early morning ADHD symptoms and unwanted behaviors included feeling overwhelmed, exhausted, and constantly stressed.
Conclusions: Control of EMF impairments from inadequately controlled ADHD symptoms is a significant unmet need in children and adolescents with ADHD treated with stable morning doses of stimulant medications. Current orally administered stimulant treatment options have not addressed this challenge.

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J Child Adolesc Psychopharmacol. 2015;25:611-17.
META-ANALYSIS: REDUCED RISK OF ANXIETY WITH PSYCHOSTIMULANT TREATMENT IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Coughlin CG, Cohen SC, Mulqueen JM, et al.
OBJECTIVE: Anxiety is a commonly reported side-effect of psychostimulant treatment. Our goal was to quantify the risk of anxiety as a side effect of psychostimulant treatment for attention-deficit/hyperactivity disorder (ADHD).
METHODS: We conducted a PubMed search to identify all double-blind, randomized, placebo-controlled trials examining the efficacy of psychostimulant medications in the treatment of children with ADHD. We used a fixed-effects meta-analysis to examine the risk ratio of anxiety reported as a side effect in children treated with psychostimulants compared with those treated with placebo. We used stratified subgroup analysis and meta-regression to examine the effects of stimulant type, dosage, duration of use, and trial design on the measured risk of anxiety.
RESULTS: We identified 23 studies involving 2959 children with ADHD for inclusion in our meta-analysis. The risk of anxiety associated with psychostimulant treatment was significantly lower than that experienced with placebo (relative risk [RR] = 0.86 [95% CI: 0.77, 0.95], $z = -2.90$, $p < 0.05$). Higher doses of psychostimulants were associated with a reduced measured risk of anxiety of psychostimulants when compared with placebo ($\beta = -0.0039$ [95% CI: -0.00718, -0.00064], $z = -2.34$, $p = 0.019$).
CONCLUSIONS: Meta-analysis suggests that treatment with psychostimulants significantly reduced the risk of anxiety when compared with placebo. This finding does not rule out the possibility that some children experience increased anxiety when treated with psychostimulants, but suggests that those risks are outweighed by the number of children who experience improvement in anxiety symptoms (possibly as a secondary effect of improved control of ADHD symptoms). Clinicians should consider rechallenging children

with ADHD who report new-onset or worsening anxiety with psychostimulants, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants

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J Child Adolesc Psychopharmacol. 2015 Sep;25:589-92.

METFORMIN IN AN ADOLESCENT WITH SIGNIFICANT WEIGHT GAIN.

Salau M, Adam B, Coffey BJ.

Presents a case report of A. 13 year old boy who referred for irritability and aggression in the context of ASD, ADHD, anxiety, and ODD. Notable was his early history of difficulty with social reciprocity, use of social language, and making and sustaining peer relationships. Irritability and aggression were impairing his academic progress and social interactions. Longstanding hyperactivity,inattentiveness, and impulsivity intensified his social and academic problems. From a biopsychosocial perspective, A. was the product of a pregnancy complicated by maternal gestational asthma and steroid treatment; a family history of neurodevelopmental and psychiatric disorders was significant. Developmental progress was impeded by his anxiety and ADHD symptoms despite an adaptive educational environment. A. had several important strengths including normal IQ, a supportive family structure, and adherence to pharmacological treatment. Irritability and aggressive behavior were reduced by treatment with aripiprazole, but resulted in excessive weight gain and the development of metabolic syndrome. Metformin slowed but did not reverse the weight gain. Longer-term follow up was notable for successful taper and discontinuation of aripiprazole and metformin, fortunately followed by a period of weight loss without increase in irritability and aggression.

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Journal of Clinical Child and Adolescent Psychology. 2015 Nov;44:1015-29.

DIFFERENTIATING ANXIETY AND DEPRESSION IN RELATION TO THE SOCIAL FUNCTIONING OF YOUNG ADOLESCENTS WITH ADHD.

Becker SP, Langberg JM, Evans SW, et al.

The present study examined anxiety and depressive symptoms in relation to the social functioning of young adolescents with attention-deficit/hyperactivity disorder (ADHD) and builds upon prior work by incorporating youths' self-reports of internalizing symptoms and examining distinct anxiety and depression dimensions to increase specificity. Participants were 310 young adolescents (ages 10–14; 71% male, 78% Caucasian) diagnosed with ADHD. Youth provided ratings of anxiety/depression, and parents provided ratings of their own depression. Parents and youth both reported on youths' social skills and perceived social acceptance. Path analyses indicated that above and beyond child demographics, ADHD and oppositional defiant disorder symptom severity, and parents' own depression, self-reported social anxiety and anhedonia were both associated with lower youth-reported social skills and both parent- and youth-reported social acceptance. Negative self-evaluation was associated with poorer parent-reported social skills. Finally, harm avoidance was positively associated with both youth- and parent-reported social skills. A path analysis using comorbid diagnoses (rather than symptom dimensions) indicated that that having a comorbid disruptive behavior disorder or depression diagnosis (but not a comorbid anxiety diagnosis) was associated with poorer parent-reported social functioning. Results demonstrate that the relation between internalizing symptoms and social functioning among young adolescents with ADHD is nuanced, with social anxiety and anhedonia symptoms associated with lower social skills and social acceptance in contrast to harm avoidance being associated with higher ratings of social skills (and unrelated to social acceptance). In terms of comorbid diagnoses, depression is more clearly related than anxiety to poorer social functioning among young adolescents with ADHD. These results point to the importance of attending to specific facets of anxiety and depression in clinical care and future research.

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Journal of Clinical Child and Adolescent Psychology. 2015 Nov;44:985-91.

TREATMENT OUTCOMES IN ANXIOUS YOUTH WITH AND WITHOUT COMORBID ADHD IN THE CAMS.

Halldorsdottir T, Ollendick TH, Ginsburg G, et al.

The purpose of this study is to examine the influence of Attention-Deficit/Hyperactivity Disorder (ADHD), independent of Oppositional Defiant Disorder (ODD), on acute treatment response, remission rates and maintenance of gains at 6-month follow-up in anxious youth (ages 7–17, 76% Caucasian, 52% female) who received cognitive-behavioral therapy (CBT) alone, pharmacotherapy alone, the combination of CBT and pharmacotherapy or placebo pill in the Child/Adolescent Multimodal Study. Treatment response was defined as independent evaluator rated meaningful improvement in anxiety. Remission was operationalized as the absence of targeted anxiety disorders. ADHD and ODD were examined as moderators of outcomes at a diagnostic level. In the CBT group only, an ADHD diagnosis predicted poorer immediate treatment response and remission rates. However, these associations were not obtained for the pharmacotherapy groups. Participants with comorbid ODD were not less likely to achieve acute treatment response and remission rates than their counterparts across treatment conditions. Due to small sample size of the comorbid subgroups, our analyses must be considered preliminary. Nevertheless, our initial findings suggest further exploration of the separate roles of ADHD and ODD are worth pursuing, as they may be differentially associated with treatment outcomes in anxious youth treated with CBT but not youth treated with pharmacotherapy. If confirmed, findings may indicate that anxious youth with comorbid ADHD are less likely to benefit from CBT strategies alone and raise the possibility that these youth need adjunctive pharmacotherapy or psychosocial interventions

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J Clin Psychopharmacol. 2015 Oct;35:525-34.

REMISSION RATE AND FUNCTIONAL OUTCOMES DURING A 6-MONTH TREATMENT WITH OSMOTIC-RELEASE ORAL-SYSTEM METHYLPHENIDATE IN CHILDREN WITH ATTENTION- DEFICIT/HYPERACTIVITY DISORDER.

Su Y, Li H, Chen Y, et al.

Many definitions have been used to evaluate remission in patients with attention-deficit/hyperactivity disorder (ADHD) in different studies resulting with varied remission rates. This open-label, multicenter study investigated the remission rate in Chinese children (n = 239; aged 6–16 years) with a diagnosis of ADHD (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), treated with osmotic-release oralsystemmethylphenidate at doses of 18, 36, and 54 mg, once daily. Two definitions of remission were used: (1) (primary end point): average scores of SNAP-IV (Swanson, Nolan, and Pelham, Fourth Edition) items of 1 or less (0–3 rating scale for each item) according to the subtype of ADHD (inattentive [1–9], hyperactive-impulsive [10–18], and combined type [1–18]), and (2) total score of SNAP-IV items 1 to 18 of 18 or less, at week 8. The study consisted of screening/baseline, titration/open-label treatment (8 weeks), and extended observation (up to 24 weeks) phases. Secondary efficacy assessments were Clinical Global Impression–Improvement (clinical efficacy), Behavior Rating Inventory of Executive Function Scale (BRIEF; executive function behaviors), and Weiss Functional Impairment Rating Scale (social function). Validity of remission was assessed by comparing the function measures (BRIEF and Weiss's) between patients who achieved remission and those who did not. At week 8, 69.3% (151/218) of patients achieved remission by definition 1, and 73.2% (161/220) by definition 2. At weeks 8 and 24, the remission group had significantly lower BRIEF, Weiss's, and Clinical Global Impression–Improvement scores ($P < 0.001$ for all) compared with the nonremission group. Overall, treatment with osmotic-release oral-system methylphenidate was well tolerated, with increased remission rates in children with ADHD

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J Clin Psychopharmacol. 2015;35:739-41.

STUTTERING ASSOCIATED WITH THE USE OF SHORT-ACTING ORAL METHYLPHENIDATE.

Alpaslan AH, Coşkun KŞ, Kocak U, Gorücü Y.

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J Consult Clin Psychol. 2015.

EVALUATION OF A SCHOOL-BASED TREATMENT PROGRAM FOR YOUNG ADOLESCENTS WITH ADHD.

Evans SW, Langberg JM, Schultz BK, et al.

Objective: This study compared 2 school-based training interventions for adolescents with attention deficit-hyperactivity disorder (ADHD): the Challenging Horizons Program-after school version (CHP-AS) and Challenging Horizons Program-mentoring version (CHP-M) with each other and with a community care (CC) condition.

Method: Participants were 326 students (sixth through eighth grade) diagnosed with ADHD. Interventions were conducted for 1 academic year. CHP-AS occurred twice weekly and included organization, social functioning, and academic study skills interventions. In CHP-M, students were paired with a mentor (e.g., teacher) who was trained by a consultant and delivered a subset of the CHP-AS interventions during school. No direct intervention was provided in CC. Participants were assessed at pretreatment, 4 occasions during the intervention year, posttreatment, and at a 6-month follow-up.

Results: Intent-to-treatment analyses using hierarchical linear modeling to compare outcomes between the 3 conditions indicate participation in the CHP-AS intervention is associated with moderate effect size improvements in parent-rated organization and time-management skills, homework problems, and ADHD symptoms of inattention, and with small improvements in overall academic functioning and grade point average (GPA). These improvements were in comparison to CC and to CHP-M. Gains were sustained into the next school year and even increased in magnitude for several of the measures.

Conclusions: The CHP-AS program leads to significant benefits for adolescents with ADHD compared with the services provided in the CHP-M and CC. The persistence of improvements over time supports the use of training interventions that teach skills for adolescents

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J Headache Pain. 2015;16.

P046. ADHD AND HEADACHE: OBSERVATIONAL STUDY OF CASE SERIES.

De CD, De RnG, Ronchese M, et al.

Background: Attention deficit and hyperactivity disorder (ADHD) and headache are two very common diseases in childhood and both of them have an important impact on quality of life and academic performance [1]. In the literature there are many studies on psychopathology in headache, but the relationship between headache and ADHD is considered in few of them [2]. Recent studies have reported possible neural pathways and pathophysiological mechanisms that may underlie this relationship [3].

Aim: Analysis of comorbility between ADHD and headache searching for the presence of ADHD trait in a population of headache patients.

Subjects and methods: Observational study of case series based on collection of clinical-anamnestic data and on the administering of a standardized questionnaire (Strengths and Difficulties Questionnaire, SDQ) to evaluate the presence of ADHD traits in all the patients consecutively referred to the Juvenile Headache Centre of Padua (December 2014-May 2015).

Inclusion criteria: age 5-18 years; diagnosis of primary headache, using the International Classification of Headache Disorders III, 2013 [4]: migraine without aura (MO) or with aura (MA), chronic migraine (CM), episodic (ETTH) or chronic tension-type headache (CTTH).

Results: Total sample of 180 cases (81 M, 99 F) with mean age at interview of 11.8 years (8-18 years).

Headache types: 120 migraine (M) (66.7%), 49 tension-type headache (TTH) (27.2%), 5 headaches with mixed pattern (M + TTH) (2.8%) and 6 other headaches (3.3%). M patients were divided into 107 MO (89.2%), 13 MA (10.8%); TTH were divided into 45 ETTH (91.8%) and 4 CTTH (8.2%). Family history for headache was present in 122/180 patients (71.8%), family history for M in 50/122 (41.0%). Prevalence of ADHD traits was 19.4% in SDQ questionnaires completed by parents and 21.3% in self-assessment SDQ questionnaires from children/adolescents. There was a low level of agreement between parents and children, reflecting heterogeneity symmetrical judgment between the two groups (p 0.53, K 0.53). There were no correlations with the diagnosis of headache or with other clinical features (sex, age of patients, age of onset, duration of illness, family history for headache); statistically significant relationships were found with the worsening of academic performance (p 0.001) and marginally with school absences (p 0.08).

Conclusions: This study confirms most literature studies on the possible relationship between headache and ADHD, especially concerning the important impact on quality of life and academic performance [1-3]. It confirms the remarkable role of ADHD traits in the personal and family history of the juvenile patients affected by primary headaches

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Journal of Health and Social Behavior. 2015 Sep;56:398-414.

THE EFFECT OF MEDICAL TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) ON FOSTER CARE CASELOADS: EVIDENCE FROM DANISH REGISTRY DATA.

Fallesen P, Wildeman C.

Since the early 2000s, foster care caseloads have decreased in many wealthy democracies, yet the causes of these declines remain, for the most part, a mystery. This article uses administrative data on all Danish municipalities (N = 277) and a 10% randomly drawn sample of all Danish children (N = 157,938) in the period from 1998 to 2010 to show that increasing medical treatment of attention deficit hyperactivity disorder (ADHD) accounts for a substantial share of the decrease in foster care caseloads. According to our estimates, the decline in foster care caseloads during this period would have been 45% smaller absent increases in medical treatment of ADHD. These findings are especially provocative in light of recent research showing ambiguous effects of medical treatment of ADHD. Future research should be attentive to how medical treatment aimed at addressing children's acute behavioral problems could also have a powerful effect on foster care caseloads.

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J Intellect Disabil Res. 2015;59:104.

DRUG THERAPY FOR ADHD IN PEOPLE WITH INTELLECTUAL DISABILITIES.

Courtenay K.

Objectives: Attention Deficit Hyperactivity Disorder (ADHD) is more prevalent in people with intellectual disabilities (ID). Drug therapy is the primary treatment for ADHD targeting the core signs of inattention, impulsivity, and hyperactivity. Knowledge on ADHD is gained from studies in children with some people with ID. People with ID have co-morbid disorders for example Autism and epilepsy that can complicate the assessment and treatment of ADHD. Therefore, knowledge of the effects of treatment is essential in managing ADHD in people with ID. The objective is to describe the current evidence on the application of drug therapy for ADHD in ID.

Methods: A literature review of publications in English and German languages was undertaken searching Medline, Psychinfo, and Google Scholar databases.

Results: Medication for ADHD is effective in treating the signs of ADHD in people with ID. The response rates in people with ID to drug therapy for ADHD approximates to 55% that is lower than in the general population. People with ID experience more side effects from medication that can lead to withdrawal from treatment. Guidelines exist internationally on the appropriate prescribing of medication. Methylphenidate, a psycho-stimulant drug is the drug of first choice. Atomoxetine, a non-stimulant drug, is effective in people with ID.

Conclusions: ADHD in people with ID is treatable but clinicians need to be knowledgeable and skilled in managing the disorder in people with ID. Newer drugs could offer more because of their different profile of more tolerable side effects

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Journal of Krishna Institute of Medical Sciences University. 2015;4:10-17.

BRAIN-DERIVED NEUROTROPHIC FACTOR AS A BIOMARKER IN CHILDREN WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Saadat F, Kosha M, Amiry A, et al.

Background: Evidence suggests that Brain-Derived Neurotrophic Factor (BDNF) is involved in the pathogenesis of Attention-Deficit Hyperactivity Disorder (ADHD), although experimental data regarding the contribution of BDNF concentration to this psychiatric disorder are controversial.
Aim: To evaluate the plasma levels of BDNF in patients with ADHD.
Material and Methods: In this cross sectional study, ADHD and controls were recruited from the outpatient clinic of the Shafa Hospital, Rasht; between March 2012 and April 2013. Clinical data concerning ADHD diagnosis and blood samples for patients were collected before treatment. Medical, neurological and psychiatric co-morbidities were excluded. The mean of BDNF concentration measured and compared with healthy controls. BDNF assay was determined using ELISA kits according to manufacturer's instructions. Descriptive statistical analysis was used with analysis of variance to find the significance of data.
Results: Statistical analyses showed that the mean BDNF levels were significantly lower in ADHD patients and its subgroups as compared with normal control subjects ($p<0.001$).
Conclusion: This study showed a dramatically lower BDNF plasma levels in untreated patients with ADHD, which might be useful adjunct method for diagnosis of ADHD in society

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Journal of Learning Disabilities. 2015 Nov;48:563-76.

OBESITY, PHYSICAL ACTIVITY, AND SEDENTARY BEHAVIOR OF YOUTH WITH LEARNING DISABILITIES AND ADHD.

Cook BG, Li D, Heinrich KM.

Obesity, physical activity, and sedentary behavior in childhood are important indicators of present and future health and are associated with school-related outcomes such as academic achievement, behavior, peer relationships, and self-esteem. Using logistic regression models that controlled for gender, age, ethnicity/race, and socioeconomic status, we investigated the likelihood that youth with learning disabilities (LD) and attention-deficit/hyperactivity disorder (ADHD) are obese, physically active, and sedentary using a nationally representative sample of 45,897 youth in the United States from 10 to 17 years of age. Results indicated that youth with comorbid LD/ADHD were significantly more likely than peers without LD or ADHD to be obese; that youth with LD only, ADHD only, and comorbid LD/ADHD were significantly less likely to meet recommended levels of physical activity; and that youth with LD only were significantly more likely to exceed recommended levels of sedentary behavior. Medication status mediated outcomes for youth with ADHD. We offer school-based recommendations for improving health-related outcomes for students with LD and ADHD

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J Managed Care Pharm. 2015;21:793-802.

IMPACT OF A STEP THERAPY FOR GUANFACINE EXTENDED-RELEASE ON MEDICATION UTILIZATION AND HEALTH CARE EXPENDITURES AMONG INDIVIDUALS RECEIVING TREATMENT FOR ADHD.

Suehs BT, Sikirica V, Mudumby P, et al.

BACKGROUND: While step therapy (ST) policies are generally effective at reducing cost through the managed utilization of targeted medications, the clinical implications of ST policies are not clear and may vary across therapeutic areas. Guanfacine extended-release (GXR) is approved by the FDA for the treatment of attention-deficit/hyperactivity disorder (ADHD) as both monotherapy and adjunctive to stimulant treatment. At the introduction of GXR to the market, Humana implemented an ST policy on GXR requiring the documentation of previous treatment, intolerance, or contraindication to generic clonidine or guanfacine.
OBJECTIVE: To examine the impact of a GXR ST coverage determination (i.e., approved vs. denied) on medication utilization and health care costs among members of a commercial health plan with an ST policy for GXR.

METHODS: This study was a retrospective cohort study of administrative claims data. Humana commercial members prescribed GXR who had an ST coverage determination review were identified. All members included in this analysis were required to be aged 6-17 years, have a diagnosis of ADHD or be receiving stimulant medication, have an ST coverage determination (index event) between September 1, 2009, and May 30, 2012, and have 6 months of pre- and post-index continuous enrollment. Members were assigned to either the approved or denied group based on the outcome of the ST coverage determination. Medical and pharmacy claims data were used to measure baseline demographic and clinical characteristics and to measure medication utilization and health care costs. Outcomes assessed during follow-up included ADHD medication use, proportion of days covered (PDC) with any ADHD medication treatment, time to first observed post-index ADHD treatment, and all-cause and mental health (MH)-related health care costs. Administrative costs associated with the coverage determination process were also estimated. Bivariate and multivariable adjusted analyses were conducted to compare medication utilization and health care costs between the approved and denied groups.
RESULTS: A total of 642 members were included in the analysis (denied group n = 395 [61.5%], approved group n = 247 [38.5%]). The approved and denied groups were similar in terms of baseline demographics, provider characteristics, and baseline MH diagnoses, with the exception of anxiety disorders being more prevalent in the approved group compared with the denied group (18.2% vs. 10.6%, P = 0.006). A denied GXR coverage determination was associated with a greater percentage of members receiving no ADHD treatment post-index (13.9% vs. 3.2%, P < 0.001), greater mean [SD] number of days between index and first observed post-index ADHD medication claim (44.5 [59.6] vs. 17.6 [33.4], P < 0.001), and lower mean [SD] PDC with any ADHD medication post-index (0.59 [0.33] vs. 0.75 [0.26], P < 0.001). These findings remained statistically significant in multivariable regression models. Unadjusted pre-index median total health care costs and MH-related costs were greater among the approved group compared with the denied group (total health care: $1,582 vs. $1,465, P = 0.033; MH-related: $993 vs. $981, P = 0.020). Likewise, post-index median total health care and MH-related costs were greater among the approved group compared with the denied group (total: $2,056 vs. $1,420, P < 0.001; MH-related: $1,543 vs. $946, P < 0.001). After adjustment for potentially confounding covariates including pre-index costs, there were no statistically significant differences between the approved and denied groups in all-cause total health care (P = 0.393) or MH-related health care costs (P = 0.054).
CONCLUSIONS: The current study found that GXR coverage denial was associated with lower rate of ADHD medication utilization, greater delay in receiving ADHD medication, and lower PDC with ADHD medication. There were no differences observed between the approved and denied group in terms of all-cause total health care or MH-related total health care costs after controlling for potentially confounding variables. Prior to implementation in the ADHD therapeutic area and others, payers should consider the potentially unintended consequences of ST policies, including delay in treatment and undertreatment

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J Nerv Ment Dis. 2015;203:813-19.

MILD TRAUMATIC BRAIN INJURY AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN YOUNG STUDENT ATHLETES.

Biederman J, Feinberg L, Chan J, et al.

A recent meta-analysis documented a significant statistical association between mild traumatic brain injury (mTBI) and attention deficit hyperactivity disorder (ADHD) (Adeyemo et al., 2014), but the direction of this effect was unclear. In this study, we hypothesized that ADHD would be an antecedent risk factor for mTBI. Participants were student athletes ages 12 to 25 who had sustained a mTBI and Controls of similar age and sex selected from studies of youth with and without ADHD. Subjects were assessed for symptoms of ADHD, concussion severity, and cognitive function. mTBI subjects had a significantly higher rate of ADHD than Controls, and in all cases the age of onset of ADHD was before mTBI onset. mTBI+ADHD subjects also had more severe concussion symptoms (fatigue and poor concentration) than mTBI-ADHD subjects. These results support ADHD as an antecedent risk factor for mTBI in student athletes and that its presence complicates the course of mTBI

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Journal of Neurophysiology. 2015;114:2625-36.

PREDICTIVE CODING IN AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Gonzalez-Gadea ML, Chennu S, Bekinschtein TA, et al.

Predictive coding has been proposed as a framework to understand neural processes in neuropsychiatric disorders. We used this approach to describe mechanisms responsible for attentional abnormalities in autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). We monitored brain dynamics of 59 children (8ΓÇô15 yr old) who had ASD or ADHD or who were control participants via high-density electroencephalography. We performed analysis at the scalp and source-space levels while participants listened to standard and deviant tone sequences. Through task instructions, we manipulated top-down expectation by presenting expected and unexpected deviant sequences. Children with ASD showed reduced superior frontal cortex (FC) responses to unexpected events but increased dorsolateral prefrontal cortex (PFC) activation to expected events. In contrast, children with ADHD exhibited reduced cortical responses in superior FC to expected events but strong PFC activation to unexpected events. Moreover, neural abnormalities were associated with specific control mechanisms, namely, inhibitory control in ASD and set-shifting in ADHD. Based on the predictive coding account, top-down expectation abnormalities could be attributed to a disproportionate reliance (precision) allocated to prior beliefs in ASD and to sensory input in ADHD

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JOURNAL OF PEDIATRIC ORTHOPAEDICS PART B. 2015.

FRACTURE RISK AND CORRELATING FACTORS OF A PEDIATRIC POPULATION WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A NATIONWIDE MATCHED STUDY.

Guo N-W, Lin C-L, Lin C-W, et al.

The aim of this study was to investigate the risk of fracture and the difference between sexes from a nationwide database of fracture risk among children aged 4-17 years with or without attention deficit hyperactivity disorder (ADHD, ICD-9-CD codes 314). The Longitudinal Health Insurance Database (LHID 2000) was used to analyze fracture characteristics of children from the National Health Insurance that covered 96.1% of the Taiwanese population (N=21.4 million). A total of 7200 ADHD children aged between 4 and 17 years whose diagnosis had been confirmed in at least three outpatient clinics between 1 January 2000 and 31 December 2009 were included, and a cohort of 36 000 children without ADHD matched for age, sex, and urbanization was recruited for analysis. The incidence rate of fractures in ADHD children was 21.0 (95% confidence interval=19.4-22.7) per 1000 person-years, significantly (P<0.001) higher than 15.0 (95% confidence interval=14.4-15.6) in non-ADHDs. After adjusting by age, sex, urbanization level, and geographic region, the statistically significant (P<0.001) hazard ratios (HR) of fracture for ADHD children compared with non-ADHD children included 1.62 in girls and 1.38 in boys, 1.53 in the skull, neck, and trunk (ICD-9-CM 800-809), 1.28 in the upper extremity (ICD-9-CM 810-819), and 1.84 in the lower extremity (ICD-9-CM 820-829). The HR also (P<0.001) increased significantly in all age groups, including 1.35 in 4-6, 1.37 in 7-9, and 1.54 in 10-17 years. ADHD should be listed among risk factors of children's fractures in each sex, all age groups, and all body areas that the parents, teachers, caregivers of ADHD children, and pediatric orthopedists should be aware of. Besides, ADHD girls were more affected than ADHD boys, especially after 10 years of age, whereas the adjusted HR was the highest in the lower extremities. Nationwide analysis matched for age and sex showed that ADHD should be considered the risk factor of children's fracture, especially for girls older than 10 years of age

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Journal of Psychiatry & Neuroscience. 2015 Sep;40:325-35.

ALTERED WHITE MATTER TRACT PROPERTY RELATED TO IMPAIRED FOCUSED ATTENTION, SUSTAINED ATTENTION, COGNITIVE IMPULSIVITY AND VIGILANCE IN ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER.

Chiang HL, Chen YJ, Lo YC, et al.

Background: The neural substrate for clinical symptoms and neuropsychological performance in individuals with attention-deficit/hyperactivity disorder (ADHD) has rarely been studied and has yielded inconsistent

results. We sought to compare the microstructural property of fibre tracts associated with the prefrontal cortex and its association with ADHD symptoms and a wide range of attention performance in youth with ADHD and healthy controls.
Methods: We assessed youths with ADHD and age-, sex-, handedness-, coil- and intelligence-matched controls using the Conners' Continuous Performance Test (CCPT) for attention performance and MRI. The 10 target tracts, including the bilateral frontostriatal tracts (caudate to dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and orbitofrontal cortex), superior longitudinal fasciculus (SLF) and cingulum bundle were reconstructed using diffusion spectrum imaging tractography. We computed generalized fractional anisotropy (GFA) values to indicate tract-specific microstructural property.
Results: We included 50 youths with ADHD and 50 healthy controls in our study. Youths with ADHD had lower GFA in the left frontostriatal tracts, bilateral SLF and right cingulum bundle and performed worse in the CCPT than controls. Furthermore, alteration of the right SLF GFA was most significantly associated with the clinical symptom of inattention in youths with ADHD. Finally, youths with ADHD had differential association patterns of the 10 fibre tract GFA values with attention performance compared with controls.
Limitations: Ten of the youths with ADHD were treated with methylphenidate, which may have long-term effects on microstructural property.
Conclusion: Our study highlights the importance of the SLF, cingulum bundle and frontostriatal tracts for clinical symptoms and attention performance in youths with ADHD and demonstrates the involvement of different fibre tracts in attention performance in these individuals

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J Am Acad Child Adolesc Psychiatry. 2015;54:916-25.

A RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF GUANFACINE EXTENDED RELEASE IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wilens TE, Robertson B, Sikirica V, et al.

Objective Despite the continuity of attention-deficit/hyperactivity disorder (ADHD) into adolescence, little is known regarding use of nonstimulants to treat ADHD in adolescents. This phase 3 trial evaluated the safety and efficacy of guanfacine extended release (GXR) in adolescents with ADHD.
Method This 13-week, multicenter, randomized, double-blind, placebo-controlled trial evaluated once-daily GXR (1-7 mg per day) in adolescents with ADHD aged 13 to 17 years. The primary endpoint was the change from baseline in the ADHD Rating Scale-IV (ADHD-RS-IV) total score; key secondary endpoints included scores from the Clinical Global Impressions-Severity of Illness (CGI-S), and Learning and School domain and Family domain scores from the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) at week 13.
Results A total of 314 participants were randomized (GXR, n = 157; placebo, n = 157). The majority of participants received optimal doses of 3, 4, 5, or 6 mg (30 [22.9%], 26 [19.8%], 27 [20.6%], or 24 [18.3%] participants, respectively), with 46.5% of participants receiving an optimal dose above the currently approved maximum dose limit of 4 mg. Participants receiving GXR showed improvement in ADHD-RS-IV total score compared with placebo (least-squares mean score change, -24.55 [GXR] versus -18.53 [placebo]; effect size, 0.52; p <.001). More participants on GXR also showed significant improvement in CGI-S scores compared with placebo (50.6% versus 36.1%; p =.010). There was no statistically significant difference between treatments at week 13 in the 2 WFIRS-P domains. Most treatment-emergent adverse events were mild to moderate, with sedation-related events reported most commonly.
Conclusion GXR was associated with statistically significant improvements in ADHD symptoms in adolescents. GXR was well tolerated, with no new safety signals reported.
Clinical Trial Registration Information - Dose-Optimization in Adolescents Aged 13-17 Diagnosed With Attention-Deficit/Hyperactivity Disorder (ADHD) Using Extended-Release Guanfacine HCl; http://ClinicalTrials.gov/; NCT01081132

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J Am Acad Child Adolesc Psychiatry. 2015;54:938-46.

SEX-BASED DISSOCIATION OF WHITE MATTER MICROSTRUCTURE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Jacobson LA, Peterson DJ, Rosch KS, et al.

Objective Sexual dimorphism is evident in attention-deficit/hyperactivity disorder (ADHD), including subtype prevalence, adverse outcomes, and neural phenotype. Neurobiological studies of ADHD suggest that boys show more abnormalities in motor and premotor structure and function, whereas girls differ from typically developing (TD) peers in prefrontal circuitry. We applied diffusion tensor imaging (DTI) to identify ADHD-related sex-specific differences in motor/premotor and prefrontal white matter (WM) microstructure in children.

Method DTI estimated differences in WM microstructure among 120 children 8 to 12 years of age, 60 with ADHD (30 boys and 30 girls) and 60 controls (30 boys and 30 girls), matched on age, IQ, and handedness. Effects of diagnosis and sex on fractional anisotropy (FA) were assessed in motor/premotor and prefrontal regions. Group differences in FA and associations with response control (e.g., reaction time variability [CVRT] and commission error rate) were examined separately within sex.

Results Sex-by-diagnosis interactions were observed for FA in primary motor (M1) and medial orbitofrontal (MOFC) cortex. Post hoc tests revealed that boys with ADHD showed bilateral reductions in FA within M1, compared with TD peers; in contrast, girls with ADHD showed higher FA bilaterally within MOFC. Decreased M1 FA was associated with higher CVRT in boys and higher commission error rates in girls. For MOFC, lower FA was associated with greater CVRT and commission error rates across all participants with ADHD.

Conclusion ADHD affects the white matter of boys and girls differently; boys appear to be more affected in regions responsible for control of basic actions, whereas girls show more abnormalities in regions responsible for higher-level, top-down control

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J Am Acad Child Adolesc Psychiatry. 2015;54:905-15.

ATOMOXETINE, PARENT TRAINING, AND THEIR COMBINATION IN CHILDREN WITH AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Handen BL, Aman MG, Arnold LE, et al.

OBJECTIVE: Impairments associated with attention-deficit/hyperactivity disorder (ADHD) and noncompliance are prevalent in children with autism spectrum disorder (ASD). However, ADHD response to stimulants is well below rates in typically developing children, with frequent side effects. Group studies of treatments for noncompliance are rare in ASD. We examined individual and combined-effectiveness of atomoxetine (ATX) and parent training (PT) for ADHD symptoms and noncompliance.

METHOD: In a 3-site, 10-week, double-blind, 2 × 2 trial of ATX and PT, 128 children (ages 5-14 years) with ASD and ADHD symptoms were randomized to ATX, ATX+PT, placebo+PT, or placebo. ATX was adjusted to optimal dose (capped at 1.8 mg/kg/day) over 6 weeks and maintained for 4 additional weeks. Nine PT sessions were provided. Primary outcome measures were the parent-rated DSM ADHD symptoms on the Swanson, Nolan and Pelham (SNAP) scale and Home Situations Questionnaire (HSQ).

RESULTS: On the SNAP, ATX, ATX+PT and placebo+PT were each superior to placebo (effect sizes 0.57-0.98; p values of .0005, .0004, and .025, respectively). For noncompliance, ATX and ATX+PT were superior to placebo (effect sizes 0.47-0.64; p values .03 and .0028, respectively). ATX was associated with decreased appetite but was otherwise well tolerated.

CONCLUSION: Both ATX and PT resulted in significant improvement on ADHD symptoms, whereas ATX (both alone and combined with PT) was associated with significant decreases on measures of noncompliance. ATX appears to have a better side effects profile than psychostimulants in the population with ASD.

CLINICAL TRIAL REGISTRATION INFORMATION: Atomoxetine, Placebo and Parent Management Training in Autism; http://clinicaltrials.gov/; NCT00844753.

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Journal of the Canadian Academy of Child and Adolescent Psychiatry / Journal de l'Académie canadienne de psychiatrie de l'enfant et de l'adolescent. 2015;24:100-08.

MENTAL HEALTH IMPLICATIONS OF TRAUMATIC BRAIN INJURY (TBI) IN CHILDREN AND YOUTH.

Schachar RJ, Park LS, Dennis M.

Objective: Traumatic brain injury (TBI) is the most common cause of death and disability in children and adolescents. Psychopathology is an established risk factor for, and a frequent consequence of, TBI. This paper reviews the literature relating psychopathology and TBI.

Method: Selective literature review.

Results: The risk of sustaining a TBI is increased by pre-existing psychopathology (particularly ADHD and aggression) and psychosocial adversity. Even among individuals with no psychopathology prior to the injury, TBI is frequently followed by mental illness especially ADHD, personality change, conduct disorder and, less frequently, by post-traumatic stress and anxiety disorders. The outcome of TBI can be partially predicted by pre-injury adjustment and injury severity, but less well by age at injury. Few individuals receive treatment for mental illness following TBI.

Conclusion: TBI has substantial relevance to mental health professionals and their clinical practice. Available evidence, while limited, indicates that the risk for TBI in children and adolescents is increased in the presence of several, potentially treatable mental health conditions and that the outcome of TBI involves a range of mental health problems, many of which are treatable. Prevention and management efforts targeting psychiatric risks and outcomes are an urgent priority. Child and adolescent mental health professionals can play a critical role in the prevention and treatment of TBI through advocacy, education, policy development and clinical practice

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Journal of the Canadian Academy of Child and Adolescent Psychiatry / Journal de l'Académie canadienne de psychiatrie de l'enfant et de l'adolescent. 2015;24:109-15.

INCREASED RISK OF ASTHMA IN CHILDREN WITH ADHD: ROLE OF PREMATURITY AND MATERNAL STRESS DURING PREGNANCY.

Grizenko N, Osmanlliu E, Fortier MÈ, et al.

OBJECTIVE: ADHD and asthma are prevalent conditions in childhood, with complex pathophysiology involving genetic-environmental interplay. The study objective is to examine the prevalence of asthma in our ADHD population and explore factors that may increase the risk of developing asthma in children with ADHD.

METHODS: We retrospectively analyzed the presence of maternal stress during pregnancy and history of asthma in 201 children diagnosed with ADHD.

RESULTS: Chi-square analysis indicated significant higher presence of asthma in our ADHD sample compared to Quebec children, $\chi(2)(1, N = 201) = 15.37$, $P<0.001$. Only prematurity and stress during pregnancy significantly predicted asthma in a logistic regression model, $\chi(2)(2)=23.70$, $P<0.001$, with odds ratios of 10.6 (95% CI: 2.8-39.5) and 3.2 (95% CI: 1.4-7.3), respectively.

CONCLUSION: Children with ADHD have a higher prevalence of asthma than the general Quebec pediatric population. Children with ADHD born prematurely and/or those whose mothers experienced stress during pregnancy have a significantly increased risk of developing asthma. The study highlights the importance of potentially offering social and psychological support to mothers who experienced stress during pregnancy and/or are at risk of delivering prematurely

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Journal of the Canadian Academy of Child and Adolescent Psychiatry / Journal de l'Académie canadienne de psychiatrie de l'enfant et de l'adolescent. 2015;24:92-99.

THE EFFECT OF MATERNAL STRESS DURING PREGNANCY ON IQ AND ADHD SYMPTOMATOLOGY.

Grizenko N, Fortier MÈ, Gaudreau-Simard M, et al.

Objective: Maternal stress during pregnancy (MSDP) has been linked to a decrease in Intelligence Quotient (IQ) in the general population. The purpose of this study is to first examine the association between MSDP

and IQ in children with Attention-Deficit/Hyperactivity Disorder (ADHD) and second, to confirm, in a large sample, the link between MSDP and ADHD behavioral symptomatology.
Methods: Four hundred ten children diagnosed with ADHD, ages six to 12, were consecutively recruited from the ADHD clinic and day hospital at the Douglas Institute from 1999 to 2013. IQ was assessed using the WISC III and IV. Symptom severity was evaluated using the Child Behavior Checklist (CBCL) and Connor's Global Index for Parents (CGI-P) and Teachers (CGI-T).
Results: No significant effect of MSDP on full scale IQ was observed, but MSDP had a significant effect on CBCL and CGI scores. Elevated MSDP was significantly associated with increased CBCL internalizing scores (ß = 4.2, p < .01), CBCL externalizing scores (ß = 1.9, p = .04), CGI-P restless-impulsive scores (ß = 2.6, p = .01), CGI-P emotional lability scores (ß = 3.1, p = .02), and CGI-T restless-impulsive (ß = 2.2, p = .05) and emotional lability (ß = 3.4, p = .04) scores. MSDP increased the variance explained of ADHD symptomatology even after controlling for various factors (i.e. familial income, parental education, smoking and drinking during pregnancy, gender and age).
Conclusion: The study demonstrates that in children with ADHD, MSDP does not have an impact on IQ but rather on ADHD symptomatology, highlighting the importance of potentially offering psychological and social support to mothers who experience stress during pregnancy

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J Int Neuropsychol Soc. 2015 Sep;21:584-95.

HOT AND COOL EXECUTIVE FUNCTIONS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND COMORBID OPPOSITIONAL DEFIANT DISORDER.

Antonini TN, Becker SP, Tamm L, et al.

While neuropsychological deficits in both "hot" and "cool" executive functions (EFs) have been documented among individuals with attention-deficit/hyperactivity disorder (ADHD), these EF deficits are not universal across all individuals with this diagnosis. One potential moderator of executive dysfunction may be the presence of comorbid oppositional defiant disorder (ODD). This study examined the association between "hot" and "cool" EFs and comorbid ODD in children with ADHD. Thirty-three children with ADHD and comorbid ODD (ADHD+ODD), 67 with ADHD without ODD (ADHD-ODD), and 30 typically developing controls participated. Children were 7–12 years of age. "Cool" EFs were assessed with a spatial span task and a card sorting test. "Hot" EFs were assessed using a delay discounting task and a gambling task. ADHD-ODD and ADHD+ODD groups performed more poorly on "cool" EF tasks than controls, but did not differ from each other. Furthermore, the number of ADHD symptoms, but not ODD symptoms, was associated with "cool" EF scores. The three groups did not differ on "hot" EF tasks and the number of ADHD or ODD symptoms was unrelated to "hot" EF scores. In sum, children with ADHD presented with "cool" EF deficits which appear to be unrelated to ODD comorbidity. However, "hot" EF deficits were not present among children with ADHD, irrespective of comorbid ODD status.

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Klin Psikofarmakol Bul. 2015;25:S119-S120.

PSYCHOTROPIC USE IN CHILDREN AGED UNDER 7: AN EVALUATION OF ADMISSIONS OF CHILDREN TO A TRAINING AND RESEARCH HOSPITAL.

Tunas SD, Uneri OS, Goker Z, et al.

Objective: This study aimed to evaluate the frequency of psychotropic medication use and their nature in children under the age of 7 and to determine the predictive variables of using medications.
Methods: Between June 2013 and December 2013, data of children recorded in the Child Psychiatry Department of Ankara Pediatric Hematology Training and Research Hospital was reviewed retrospectively and data of children under the age of 7 was evaluated. Statistical analysis was carried out with SPSS 17.0 (Chicago Inc., 2008). T-test, Chi-square, Fisher's exact test and binary logistical regression analysis were used where appropriate. p<0.05 was accepted as significant.
Results: Data for a total of 1433 of children aged under 7 was extracted from the 12,320 recorded data sets accumulated during the period of the study (11.6% of all sample). Mean age of children was 4.3±1.5 (1-6

years), the majority of the children was in the 4-6 age group (n=991, 69.2%) and male (n=939, %65.5). There were no psychiatric disorders in 11.9% (n=171) of the children, whereas 88.1% of the total (n=1262) had at least one psychiatric disorder. As far as the psychiatric disorders were concerned, by far the most prominent disorders were the following: “Communication disorders (n=354, 24.7%)”, “Mental Retardation (Full-Scale IQ score ≤69: n=248, 17.3%)” and “Attention deficit hyperactivity disorder (ADHD, n=205, 14.3%)”. The comorbid presence of any psychiatric disorders was found in 13.9% of all children (n=199), by far the most diagnosed one being “Disruptive behavior disorders (n=139, 9.7%)”. Psychotropic medication use was found in 15.7% (n=225) of the sample. Mean age of children who were medicated was 5.4-¦0.9 (2-6 years). Mean age differences between children who use medication (5.4±0.9), and those who do not (4.17±1.5) was found statistically significant (t=-12,018, p<0.001). The most used psychotropic medication was risperidone monotherapy (4.5%, n=64). Presence of ADHD (X2=7.991, p=0.005) and pervasive developmental disorder (PDD, X2=5.560, p=0.037) had an significant effect on starting medication. The presence of any comorbid psychiatric disorders in children with specific learning disorder (SLD) was found to be an indicator of psychotropic use (X2=22.069, p<0.001). Predictors of medication use were found as follows: age (4-6 age group; p<0.001, Beta=1.602 95% CI 1.250- 2.054); being male (p=0.006, Beta=0.595 95%CI 0.411-0.861); the presence of comorbid psychiatric disorders (p<0.001, Beta=0.071 95%CI 0.046-0.110); the presence of anxiety disorders (p<0.001, Beta=0.073 95%CI 0.047-0.114) and elimination disorders (p=0.005, Beta=0.240 95%CI 0.089-0.0.648).

Conclusion: Being male, in the 4-6 age group, the presence of comorbidity, the presence of anxiety disorders and elimination disorders are found as predictors for using medication in children aged under 7 who are admitted to the Child Psychiatry Department

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Klin Psikofarmakol Bul. 2015;25:S84-S85.

AN ONLINE SURVEY OF TURKISH PSYCHIATRISTS' ATTITUDES AND EXPERIENCES REGARDING ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CLINICAL PRACTICE.

Semerci B, Altin GE.

Objective: Adult attention deficit hyperactivity disorder (ADHD) can be an extremely debilitating neurodevelopmental disorder that often persists beyond childhood, affecting 2.5-5% of adults in the general population. Aim of this study was to provide data about the presentation of adult ADHD in clinical practice in Turkey and about treatment strategies of Turkish adult psychiatrists in different hospital settings.

Method: A cross-sectional online survey to be filled out by Turkish adult psychiatrists was designed in May 2014. The survey was administered through the Turkish Psychiatry Association (PAT) mail group which covers over 90% of the Turkish adult psychiatry population. It included 10 questions focusing on treatment environment, patterns of patient applications, and treatment strategies.

Results: A total of 124 psychiatrists with a homogenous range of different treatment settings (public hospitals, university hospitals, private clinics etc.) completed the survey. Although most participants (53.6%) reported that they treated more than 20 patients in a day, most of them were following fewer than 10 adult ADHD patients in their clinics. Transition rate from child to adolescent psychiatrists were found to be very low (<10% as reported by 77.3% of participants). Media and the restraint by the social environment turned out to be effective factors for treatment application. There were significant differences of attitudes about the treatment of adult ADHD. Rating questions were asked to survey respondents to compare treatment strategies in order of frequency. 62.6% of the participants reported that they always prefer psychoeducation in addition to medication treatment, whereas only 9.59% of the participants reported that they always combine psychotherapy with medication in the treatment of adult ADHD. The most favored medical treatment was stimulants (31.9% reported as using it "always" and 57.4% reported as using it "frequently"). The other frequently preferred medications were antidepressants (56.6%) and non-stimulants (37.4%). Anxiety disorders have been reported as the most common comorbid disorder with adult ADHD (40.4%), followed by alcohol/substance abuse disorders (29.7%) and depression (15.9%).

Conclusion: The outcomes of this survey show that despite the presence of a rapidly expanding literature on diagnosis and treatment of ADHD in adulthood, there are still only few psychiatrists in Turkey working on adult ADHD. A very low percentage of patients who were diagnosed in childhood are being referred to adult psychiatrists and most of the psychiatrists do not describe themselves as competent enough to diagnose

and treat adult ADHD. Psychoeducation seems to be a more widely embraced treatment choice than psychotherapy in daily clinical practice. Adult ADHD is still a clinical entity that has a lower degree of awareness even among psychiatrists compared to ADHD in childhood and adolescence. We suggest a more comprehensive and standardized training to improve the management of adult ADHD and also to develop the cooperation between child and adolescent psychiatrists and adult psychiatrists for the transition of patients

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Klin Psikofarmakol Bul. 2015;25:S86-S87.

SLEEP HABITS AND RELATED SLEEP DISORDERS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Tasdelen BI, Karakaya E, Kahraman O, et al.

Objective: Attention deficit hyperactivity syndrome (ADHD) is one of the most frequent psychiatric disorders of childhood. The main symptoms of ADHD such as inattention, impulsivity and irritability are also known to be symptoms of sleep deficiency. Although problems regarding sleep structure and efficiency have been reported in children with ADHD in recent studies, underlying factors as well as etiopathogenesis of this potential relationship is unclear. The aim of this study was to identify sleep habits and to investigate sleep problems which can be of a higher incidence than in the general population in children diagnosed as ADHD but not receiving pharmacological intervention.

Methods: This study was conducted at the Child Psychiatry Department of Erciyes University, Medicine School between 2012 and 2014. The study sample consisted of 50 children aged 7-12 years who presented to outpatient clinic with inattention, hyperactivity and impulsivity for the first time and were diagnosed as combined type ADHD based on DSM-IV criteria by using KSADS-PL interview but had not received pharmacological therapy, and 50 age- and sex-matched, healthy children who had no neurological or psychiatric disorder and were not on medication. WISC-R score<80 was an exclusion criterion in both study and control group. All subjects completed Children Sleep Habit Questionnaire (CSHQ), which was then assessed statistically.

Results: Mean age was 9.46±1.51 in study population, and 78% of study population were male. No significant difference was found in WISC-R scores and socioeconomic status between groups. In the study, Cronbach's alpha coefficient of the scale was found to be 0.78. Of 11 items addressed by the scale, significant differences were found between ADHD and control groups regarding awakening (longer time to be alert, awakening in negative mood and tired), sleep-disordered breathing (snoring and gasp), parasomnia (irritability during sleep, bruxism, talking during sleep), sleep duration, sleep latency (sleep onset time). It was seen that 78% of the ADHD group (n=39) and 58% of control group (n=29) achieved >=42 points in the total score of the scale, which is considered to be clinically significant, and there was significant difference between groups (p<0.001). Moreover, it was found that there was a difference in bedtime resistance, which was eliminated in factor analysis. No significant differences were found in sleep disruption, sleep anxiety (being afraid of sleeping in the dark, afraid of sleeping alone, awakening patterns, need for sleeping with another person, daytime sleepiness, and enuresis. No significant differences were found in total sleep duration, bedtime and time to fall asleep in case of night awakenings in open-ended questions.

Conclusion: This study revealed that children have significantly higher degrees of sleep disorders regardless of any drug therapy. In addition, it should be kept in mind that attention and learning issues that can be seen in sleep disorders can exacerbate existing ADHD symptoms and higher rates of parasomnia can cause increased behavioral problems in children with ADHD. In these children, assessment and management of sleep disorders at diagnosis can significantly reduce behavioral symptoms and may improve quality of life for children and families

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Klin Psikofarmakol Bul. 2015;25:S34-S36.

COMPLIANCE WITH METHYLPHENIDATE TREATMENT AND DRUG ABUSE OF ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Sanal Y, Yokusoglu C, Yargic I.

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Klin Psikofarmakol Bul. 2015;25:S88.

EVALUATION OF ANGER AND AGGRESSION LEVEL IN PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kara K, Durukan I, Koparan C, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood which is characterized by hyperactivity, attention deficit and impulsivity. Children diagnosed with ADHD have academic problems, difficulties in peer relationship and frequent problems with their parents. In this study we aimed to assess the aggression and trait anger-anger expression levels in parents of children with ADHD and to investigate the relationship between symptoms of ADHD/oppositional defiant disorder and aggression and anger levels of parents.

Method: The study sample consisted of parents of 58 children between 6-14 ages diagnosed with ADHD. The healthy control group consisted of 54 healthy children's parents. Both ADHD and healthy control group were assessed with sociodemographic data form, Buss- Perry aggression questionnaire and trait anger expression inventory. Symptoms of ADHD in children were evaluated with the DSM-IV Based Behavior Disorders Screening and Rating Scale.

Results: The study group included parents of 45 boys and 13 girls. The healthy control group included parents of 36 boys and 14 girls. Maternal age (p<0.001), paternal age (p<0.001), maternal education level (p<0.001) had statistically significant difference; gender (p=0.093) and education level (p=0.16) of child and paternal education level (p=0.17) were statistically similar. Trait anger level in mothers of children with ADHD group (19.4-¦5.2) was found higher than in mothers of the control group (17.8±2.7). Anger control level of parents in children with ADHD (20.7±5.8, 21.6-¦4.5) was found lower than in the control group (23.8-¦4.6, 24.1±4.6) (p=0.003, p=0.016). Total aggression scores (p=0.04) and hostility subscale scores (p=0.02) of mothers in the study group obtained through the Buss-Perry aggression questionnaire were found higher than in mothers of healthy children. There were statistically significant positive correlations between physical and verbal aggression, anger and total aggression subscale scores of mothers in the ADHD group and Behavior Disorders Screening and Rating Scale attention subscale scores, verbal aggression and total aggression subscale scores and opposition defiance subscale scores. There were statistically negative correlations between physical and indirect aggression, anger and total aggression scores of fathers in ADHD group and behavior disorders screening and rating scale attention subscale scores; verbal aggression scores and behavior disorders screening and rating scale hyperactivity subscale scores. There were positive correlations only between trait anger level of mothers of children with ADHD and behavior disorders screening and rating scale attention deficit subscale scores.

Conclusion: In our study, for the ADHD group, trait anger and anger control levels of mothers, anger control levels of fathers and total aggression level of mothers were found to be higher than in the healthy group. Parents of children with ADHD should be aware of their emotion and behavior related to anger and aggression during the treatment of child

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Klin Psikofarmakol Bul. 2015;25:S41-S43.

UTILIZATION OF THE D-CPT TEST IN DIFFERENTIATION OF ATTENTION DEFICIT-HYPERACTIVITY DISORDER AND ANXIETY DISORDERS IN CHILDREN.

Taskiran S, Semerci B, Sanli I, et al.

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Klin Psikofarmakol Bul. 2015;25:S160.

SHOULD IMMEDIATE RELEASE METHYLPHENIDATE BE THE TREATMENT OF CHOICE FOR INITIATION OF ADHD TREATMENT?

Yidirim V, Killi Y, Gunes S, et al.

Objective: To assess the Conners' Teacher Rating Scale-Revised Short in evaluating improvement in symptomatology with immediaterelease methylphenidate (MPH-IR), methylphenidate extended release (OROS MPH) or atomoxetine (ATX) in attention deficit hyperactivity disorder (ADHD) of children patients.

Method: In a clinical sample, over a period of 12 months, all drug-naive patients with ADHD (n=128; boys, n=92; girls, n=36) were evaluated retrospectively. Patients between 7 and 17 years of age were consecutively selected and diagnosed for ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), by a Child and Adolescent Psychiatrist. The treatment of MPHIR, OROS MPH, ATX was started at 0.5mg/kg/day for 1 week. The dose was increased to 1mg/kg/day at 1 week after treatment initiation till 8 weeks. Efficacy measures were evaluated by Conners' Teacher Rating Scale. We assessed 107 children that completed the first and second teacher scale. Eleven patients used a combination of OROS MPH and MPH-IR. All cases were evaluated between January 2013 and January 2014. The Teachers' Scale was completed before the treatment began and two months after the initiation of treatment. Conners' Teacher Rating Scale (CTRS): Turkish translations of the 28-item Conners' Teacher Rating Scale (CTRS) was calculated with good internal consistency as indicated by Cronbach's alpha coefficients. Factor analytical data from the normal sample studies tested the construct validity of parent and teacher Turkish Conners' rating scales (CRS) despite non-differentiation of the conduct factor from the hyperactivity factor on the teacher scale. The clinical criteria scores proposed the necessity of adapting the item content of all the subscales, except the hyperactivity subscale. The adapted and original subscales of the CRS Turkish forms revealed such psychometric properties that they could be employed in assessing attention deficit and disruptive behavior disorders in Turkish children.

Results: The mean age of 117 patients included in this study was 10.78-¦2.7 years. Stable daily doses were 1 mg/kg/day for ATX, OROSMPH and IR-MPH. All efficacy parameters were significantly improved with the use of the above-mentioned three drugs in respect to baseline.

Conclusion: In the treatment of ADHD, once-daily OROS-MPH produces significant improvements in hyperactivity. But IR-MPH improves hyperactivity, attention deficit and behavioral disorder. ATX treatment is found less effective than other two treatment groups. MPH-IR might be the initial treatment of choice in ADHD treatment during the first 8 weeks of treatment

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Klin Psikofarmakol Bul. 2015;25:S82.

MAINTENANCE OF EFFECT IN ATTENTION DEFICIT HYPERACTIVITY DISORDER: WHAT DO PLACEBO-CONTROLLED RANDOMIZED WITHDRAWAL STUDIES OF ATOMOXETINE AND STIMULANTS TELL US?

Peksel H, Upadhyaya H, Adams DH, et al.

Objectives: Attention Deficit Hyperactivity Disorder (ADHD) persists into adulthood for approximately two thirds of the patient population. There is a limited amount of information available regarding the appropriate duration of treatment. Treatment rates tend to decline from childhood to adulthood, and many patients with ADHD experience a relapse of their symptoms during treatment as well as upon treatment discontinuation. In addition, stimulant and nonstimulant treatments have differences in their efficacy profiles. Published randomized withdrawal studies have examined the maintenance of symptom control in patients with ADHD who respond when active treatment is continued compared to placebo. This analysis is based on published randomized studies and was conducted to better understand the relapse of ADHD symptoms in children, adolescents, and adults after discontinuation of long-term medication treatment.

Methods: This analysis included published randomized withdrawal studies in children with ADHD treated with methylphenidate, lisdexamphetamine, or atomoxetine. Published randomized withdrawal studies conducted in adults with ADHD and treated with methylphenidate modified release, osmotic-release oral system methylphenidate, lisdexamphetamine, or atomoxetine were also included. Relapse data from the atomoxetine studies were re-analyzed using the relapse criteria most commonly used in studies with stimulants (a 50% increase in Conners' Adult ADHD Rating Scales-Investigator Rated: Screening Version total score and a>=2-point increase in Clinical Global Impressions for Severity score).

Results: For stimulants and atomoxetine, among patients who were responders (6 weeks to 1 year of active treatment), the proportion of patients relapsing was significantly higher with placebo compared to active treatment. This suggests that there was a clinically significant benefit with continued long-term pharmacotherapy. However, the proportion of patients relapsing after discontinuing stimulants appeared to be higher than that observed when discontinuing atomoxetine. Of atomoxetine-treated children, 37.9% met the study-defined primary relapse criteria during the 9months after discontinuation of active treatment compared with 61.5% treated with methylphenidate during the 2 weeks after discontinuation and 68% treated with lisdexamphetamine during the 6 weeks after discontinuation. In atomoxetine-treated adults, 7.4% met the primary relapse definition during the 25 weeks after discontinuation of active treatment compared with 49.6% treated with methylphenidate modified release during the 6 months after discontinuation and 75% treated with lisdexamphetamine during the 6 weeks after discontinuation.
Conclusion: In children and adults, the rate of relapse was lower when discontinuing atomoxetine compared with stimulants. This may be a consequence of methodological differences, including study design and response/relapse definitions, or it may reflect differences in mechanisms of action and persistence of the medication effect. Continued investigation is needed regarding factors that affect the risk of symptom relapse on discontinuation of pharmacotherapy. This study was funded by Eli Lilly and Company, Indianapolis, IN, USA. Drs Upadhyaya, Adams, Tanaka, Haynes, and Escobar are full-time employees and stock holders of Eli Lilly and Company. Dr Colla has participated in advisory boards, received speaker's honoraria or participated in Phase 3 studies within the past 3 years with Shire, Eli Lilly, Janssen-Cilag and Novartis

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Klin Psikofarmakol Bul. 2015;25:S85-S86.

VITAMIN B12 LEVELS AND SOCIOECONOMIC STATUS IN ADHD PATIENTS.

Polat B, Yildirim V, Toros F.

Objective: Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood. Prevalence of ADHD varies from country to country. According to DSM-5, prevalence of ADHD is up to 13% in follow-up studies involved school-age children. Vitamin B12 deficiency is a medical condition which may be associated with many psychiatric disorders such as depression, schizophrenia, bipolar disorder and cognitive decline. Poor intake or malabsorption causes vitamin B12 deficiency. It is known that socioeconomic factors may influence dietary quality and vitamin intakes. In the present study, we planned to examine the association between socioeconomic status of ADHD patients and their vitamin B12 blood level.
Methods: Patients between the ages of 3 and 17 years who were first diagnosed with ADHD according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria were approached for this study. Patients who were on vitamin B12 deficiency treatment were excluded from the study. All patients were divided into two groups: low and high socioeconomic status. The catchment area of Mersin State Hospital consists of low-income families. The low socioeconomic status group involved 350 patients who were chosen from Mersin State Hospital, while the high socioeconomic status group involved 253 patients from Mersin University Hospital. Cut-off points for the diagnosis of vitamin B12 deficiency were determined 187 pg/ml for Mersin State Hospital and 197 pg/ ml for Mersin University Hospital. PASW v.18 program was used in the statistical analyses. Independent Samples t test was applied for comparing the groups in terms of continuous variables. Chi-square or Fisher's Exact were applied for categorical variables.
Results: The sample consisted of 603 children and adolescents (412 boys, 191 girls) between 3 and 17 years of age (mean-¦SD=10.10-¦3.45 for the state hospital, mean-¦SD=9.89-¦3.30 for the university hospital). In this study, there were no differences in B12 blood levels by gender. In the high socioeconomic group, B12 blood levels were detected to be higher than in the low socioeconomic group. There were positive correlations between socioeconomic level and vitamin B12 blood level. Vitamin B12 deficiency in Mersin State Hospital (16.3%) was seen more common than at Mersin University (5.1%).
Conclusion: This report emphasizes the importance of assessment of vitamin B12 in ADHD patients. A study in general psychiatric inpatients reports the incidence of vitamin B12 deficiency to be 4-6%. Omega-3, vitamins and minerals have been linked to developmental outcomes including attention deficit hyperactivity disorder. Adolescents who have a borderline level of vitamin B12 can develop signs of cognitive changes. A combined vitamin, mineral, amino acid treatment may be effective in improving attention and self-control in children with ADHD. Vitamin B12 deficiency which is one of the preventable and treatable medical condition,

must be given attention especially in ADHD patients with low socioeconomic status. It can be useful to investigate vitamin B12 deficiency for patients with an ADHD diagnosis and treatment process

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Klin Psikofarmakol Bul. 2015;25:S87-S88.

EVALUATION OF IRON AND IRON-RELATED PARAMETERS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Yazici KU, Percinel I.

Objective: This study aimed to compare parameters of iron deficiency in patients with attention deficit hyperactivity disorder (ADHD) and healthy controls, investigate the differences among subtypes of ADHD, and assess the relationship between level of ferritin and severity of ADHD symptoms.
Methods: The study included 200 patients with ADHD and 100 healthy controls. The ADHD group consisted of 100 patients with ADHDCombined subtype and 100 patients with ADHD-Predominantly Inattentive subtype. The diagnosis was made using the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version, a semi-structured interview. Levels of intelligence were assessed using a short form of the Wechsler Intelligence Scale for Children. The patients with a history of using atomoxetine or stimulants or any psychotropic agents or iron preparations, those with a comorbid psychiatric disorder or any acute/ chronic systemic disease, and those with a history of infection in the last one month were not included in the study. Clinical evaluations were made using socio-demographic data form, DSM-IV Based Attention Deficit and Disruptive Behavior Disorder Screening and Rating Scale (Parent-Teacher) and Conners' Rating Scale - Revised: Long Form (Parent-Teacher) (CPRS-R:L, CTRS-R:L).
Results: No meaningful difference was found between patients with ADHD and healthy controls in serum ferritin, serum iron, iron binding capacity, hemoglobin, hematocrit, mean corpuscular volume, red blood cell count, and red cell distribution width parameters; and ADHD subtypes also did not differ from each other in these parameters. A negative correlation was observed between CPRS-R:L Hyperactivity and CTRS-R:L Hyperactivity scores and serum ferritin levels in the ADHD group.
Conclusion: As can be seen, the results of studies on ADHD and serum ferritin levels are still inconsistent. Clarification of findings is considered to be of importance for the etiology and treatment of ADHD. Our study included pure ADHD patients, and ADHD subtypes were very well defined. Examining the literature, it is seen that our study includes the largest number of patients in identification of ADHD subtypes. There is a need for further studies on this subject with a greater number of cases. For further studies, we recommend the analysis of molecules involved in the regulation of iron homeostasis besides peripheral iron parameters

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Klin Psikofarmakol Bul. 2015;25:S86.

METHYLPHENIDATE HYDROCHLORIDE AND ASYMPTOMATIC OCULAR CHANGES.

Duman NS, Duman R, Gokten ES, et al.

Objective: To examine cataract formation and assess intraocular pressure (IOP) measurement with Goldmann applanation tonometry in children taking methylphenidate hydrochloride.
Methods: Forty children with attention deficit hyperactivity disorder aged 9-18 years for whom methylphenidate hydrochloride was indicated and used for at least one year were included in this study. Examinations including IOP measurement and anterior and posterior segment examination were performed.
Results: In this study we present our preliminary results. We plan to examine consecutively one hundred children. Forty patients received ophthalmic examinations. The 40 patients included 27 males, 13 females, mean age 9.6 (9-18) years; methylphenidate hydrochloride was given for attention deficit hyperactivity disorder. Mean MPH dosage was 0.9-¦0.10 mg/kg/day and mean duration of MPH usage was 25 months. High intraocular pressure was not measured in any of the patients in the study. Cataract formation was observed in 4 eyes of 4 patient.

Conclusion: We detect long-term use of methylphenidate hydrochloride induce cataract formation. In particular, patients using methylphenidate longer than two years should undergo regular eye examination

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Klin Psikofarmakol Bul. 2015;25:S118-S119.

RATE OF PERINATAL NICOTINE EXPOSURE IN CHILDREN WITH THE DIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Evrensel A, Yorbik O, Oncu M.

Objective: Attention Deficit Hyperactivity Disorder (ADHD) is observed 3-5 times more in boys. The etiology of ADHD is not known precisely. Environmental and genetic factors may both play a role . Child adoption and genetic studies support this view. Being a first child is a risk factor. Stress hormones, nicotine, caffeine, alcohol and their metabolites can pass through the placenta and reach the fetal brain. It is thought that nicotine has a role in the development of ADHD by modulating the dopamine receptors.

Methods: 72 children between the ages of 7 and 13who applied to GMMA (Gulhane Military Medical Academy) child and adolescent psychiatry polyclinic and received a diagnosis of ADHD according to DSM-4 diagnostic criteria, 17 girls (23.6%) and 55 boys (76.4%),were included in the study consecutively. A total of 119 children,60 girls (50.4%) and 59 boys (49.6%) who applied to GMMA pediatric polyclinic and in whom no mental disease was detected according to DSM-IV diagnostic criteria were included into the study, matching the age characteristics with the case group. Exposure to nicotine has been studied in two forms, “active” and “passive”. Information on the exposure to nicotine in the perinatal and postnatal period was analyzed and ranked using a semi-structured form.

Results: The level of exposure to nicotine of the case group was found significantly higher than in the control group (Z=-4.154, p<0.001). The level of exposure to nicotine of the boys within the case group was detected significantly higher than among the boys in the control group (Z=-4.403, p<0.001). No significant difference was detected between the level of exposure to nicotine of the girls in the case group and the control group (Z=-1.109, p=0.267).

Conclusion: Nicotine affects and damages especially the structure of dopaminergic pathways and receptors during the development of the central nervous system. It is remarkable that no significant difference was detected between girls with the diagnosis of ADHD and girls in the healthy control group. This finding supports the assumption that factors other than nicotine contribute to ADHD development in girls exposed to nicotine in the perinatal period. Moreover, it was interpreted as one of the reasons for observing ADHD in boys 3-5 times more frequently compared to girls. This finding is compatible with studies that find the estimated relative risk to be lower in girls. As a result, the obtained data suggested that the exposure to nicotine in the perinatal period is a risk factor for ADHD development, although it is not a determining factor separately. It was detected that this effect is more significant in boys than that in girls

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NeuroImage. 2014 Nov;102 Pt 1:207-19.

NON-NEGATIVE MATRIX FACTORIZATION OF MULTIMODAL MRI, FMRI AND PHENOTYPIC DATA REVEALS DIFFERENTIAL CHANGES IN DEFAULT MODE SUBNETWORKS IN ADHD.

Anderson A, Douglas PK, Kerr WT, et al.

In the multimodal neuroimaging framework, data on a single subject are collected from inherently different sources such as functional MRI, structural MRI, behavioral and/or phenotypic information. The information each source provides is not independent; a subset of features from each modality maps to one or more common latent dimensions, which can be interpreted using generative models. These latent dimensions, or "topics," provide a sparse summary of the generative process behind the features for each individual. Topic modeling, an unsupervised generative model, has been used to map seemingly disparate features to a common domain. We use Non-Negative Matrix Factorization (NMF) to infer the latent structure of multimodal ADHD data containing fMRI, MRI, phenotypic and behavioral measurements. We compare four different NMF algorithms and find that the sparsest decomposition is also the most differentiating between ADHD and healthy patients. We identify dimensions that map to interpretable, recognizable dimensions such as motion,

default mode network activity, and other such features of the input data. For example, structural and functional graph theory features related to default mode subnetworks clustered with the ADHD-Inattentive diagnosis. Structural measurements of the default mode network (DMN) regions such as the posterior cingulate, precuneus, and parahippocampal regions were all related to the ADHD-Inattentive diagnosis. Ventral DMN subnetworks may have more functional connections in ADHD-I, while dorsal DMN may have less. ADHD topics are dependent upon diagnostic site, suggesting diagnostic differences across geographic locations. We assess our findings in light of the ADHD-200 classification competition, and contrast our unsupervised, nominated topics with previously published supervised learning methods. Finally, we demonstrate the validity of these latent variables as biomarkers by using them for classification of ADHD in 730 patients. Cumulatively, this manuscript addresses how multimodal data in ADHD can be interpreted by latent dimensions

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NeuroImage Clin. 2015;9:545-54.

EXECUTIVE ATTENTION CONTROL AND EMOTIONAL RESPONDING IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER - A FUNCTIONAL MRI STUDY.

Hwang S, White SF, Nolan ZT, et al.

Background There are suggestions that patients with attention-deficit/hyperactivity disorder (ADHD) show impairment in executive attention control and emotion regulation. This study investigated emotion regulation as a function of the recruitment of executive attention in patients with ADHD.

Methods Thirty-five healthy children/adolescents (mean age = 13.91) and twenty-six children/adolescents with ADHD (mean age = 14.53) participated in this fMRI study. They completed the affective Stroop paradigm viewing positive, neutral and negative images under varying cognitive loads. A 3-way ANOVA (diagnosis-by-condition-by-emotion) was conducted on the BOLD response data. Following this, 2 3-way ANOVAs (diagnosis-by-condition-by-emotion) were applied to context-dependent psychophysiological interaction (gPPI) analyses generated from a dorsomedial frontal cortex and an amygdala seed (identified from the BOLD response ANOVA main effects of condition and emotion respectively).

Results A diagnosis-by-condition interaction within dorsomedial frontal cortex revealed reduced recruitment of dorsomedial frontal cortex as a function of increased task demands in the children/adolescents with ADHD relative to healthy children/adolescents. The level of reduction in recruitment of dorsomedial frontal cortex was significantly correlated with symptom severity (total and hyperactivity) measured by Conner's Parent Report Scale in the children/adolescents with ADHD. In addition, analysis of gPPI data from a dorsomedial frontal cortex seed revealed significant diagnosis-by-condition interactions within lateral frontal cortex; connectivity between dorsomedial frontal cortex and lateral frontal cortex was reduced in the patients with ADHD relative to comparison youth during congruent and incongruent task trials relative to view trials. There were no interactions of group, or main effect of group, within the amygdala in the BOLD response ANOVA (though children/adolescents with ADHD showed increased responses to positive images within temporal cortical regions during task trials; identified by the diagnosis-by-condition-by-emotion interaction). However, analysis of gPPI data from an amygdala seed revealed decreased connectivity between amygdala and lentiform nucleus in the presence of emotional stimuli in children/adolescents with ADHD (diagnosis-by-emotion interaction).

Conclusion The current study demonstrated disrupted recruitment of regions implicated in executive function and impaired connectivity within those regions in children/adolescents with ADHD. There were also indications of heightened representation of emotional stimuli in patients with ADHD. However, as the findings were specific for positive stimuli, the suggestion of a general failure in emotion regulation in ADHD was not supported

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Neuropsychiatr Dis Treat. 2015;11:2721-35.

EFFECTIVENESS OF A FOCUSED, BRIEF PSYCHOEDUCATION PROGRAM FOR PARENTS OF ADHD CHILDREN: IMPROVEMENT OF MEDICATION ADHERENCE AND SYMPTOMS.

Bai G-N, Wang Y-F, Yang L, et al.

OBJECTIVE: To evaluate the efficacy of a psychoeducation program for parents of children with ADHD in enhancing adherence to pharmacological treatment and improving clinical symptoms.

METHODS: We developed a psychoeducation program based on the theory of planned behavior (TPB). Eighty-nine children with ADHD were cluster randomly assigned for their families to receive 3 months of well-structured psychoeducation (intervention group, n=44) or only general clinical counseling (control group, n=45). Parents in the intervention group were given an expert lecture (with slides and a parent manual), attended two expert-guided parent group sessions, and were invited to join a professional-guided online community. Measurement of parents' knowledge about ADHD, components of the TPB model, and child ADHD symptoms were taken before and after intervention. Medication adherence was assessed thoroughly at the end of the first and third months. Satisfaction with the psychoeducation program was assessed only in the intervention group. Two-independent-samples t-test, ANOVA, and chi-square test were employed to compare differences between groups.

RESULTS: Compared to the control group, medication adherence in the intervention group was significantly higher after 1 and 3 months (97.7% intervention vs 75.6% control, P=0.002, and 86.4% intervention vs 53.3% control, P=0.001, respectively). Accordingly, the ADHD rating scale scores were lower in the intervention group than the control group after intervention (33.7±5.4 vs 45.1±7.9, P=0.008). Greater improvements in parents' knowledge about ADHD and many components of the TPB model were observed in the intervention group, especially increased intention to adhere to medication, compared to the control group (P<0.001).

CONCLUSION: This psychoeducation program had a positive impact on both medication adherence and clinical symptoms of ADHD children. It could be considered as a potential beneficial supplement to clinical practice

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Neuropsychology. 2015.

EARLY LANGUAGE MEDIATES THE RELATIONS BETWEEN PRESCHOOL INATTENTION AND SCHOOL-AGE READING ACHIEVEMENT.

O'Neill S, Thornton V, Marks DJ, et al.

Objective: Early inattention is associated with later reading problems in children, but the mechanism by which this occurs is unclear. We investigated whether the negative relation between preschoolers' ADHD symptoms and 8-year-old reading achievement is directly related to the severity of inattention or is mediated by early language skills.

Method: Children (n = 150; 76% boys) were evaluated at 3 time points: preschool (T1), mean (SD) age = 4.24 (.49) years; 1 year later (T2), mean (SD) age = 5.28 (.50) years; and during school age (T3), mean (SD) age = 8.61 (.31) years. At T1, parents' Kiddie-SADS responses were dimensionalized to reflect ADHD severity. Children completed the Language domain of the NEPSY (i.e., A Developmental Neuropsychological Assessment) at T1 and again at T2. At T3, children completed the Wechsler Individual Achievement Test, Second Edition Word Reading, Pseudoword Decoding, Reading Comprehension, and Spelling subtests, and their teachers completed ratings of Reading and Written Expression performance in school. The mediating effect of T2 Language on the relation between preschool Inattention and age 8 Reading was examined using the nonparametric bootstrapping procedure, while controlling for T1 Language.

Results: Language ability at T2 mediated the path from preschool inattention (but not hyperactivity/impulsivity) to 8-year-old reading achievement (both test scores and ratings) after controlling for preschoolers' language ability.

Conclusions: Early attentional deficits may negatively impact school-age reading outcomes by compromising the development of language skills, which in turn imperils later reading achievement. Screening children with attentional problems for language impairment, as well as implementing early

intervention for both attentional and language problems may be critical to promote reading achievement during school years. (PsycINFO Database Record

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Neuropsychology. 2015 Nov;29:888-94.

LACK OF GLOBAL PRECEDENCE AND GLOBAL-TO-LOCAL INTERFERENCE WITHOUT LOCAL PROCESSING DEFICIT: A ROBUST FINDING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER UNDER DIFFERENT VISUAL ANGLES OF THE NAVON TASK.

Song Y, Hakoda Y.

Objective: The Navon effect (Navon, 1977) is an automatic tendency to process the global picture prior to local details when processing compound patterns. However, several recent studies have reported that this effect is lacking in attention-deficit/hyperactivity disorder (ADHD). Although previous research has shown that the Navon effect is strongly affected by visual angles, whether this phenomenon will also be observed in ADHD is yet to be understood. We examine the lack of the Navon effect in ADHD under various visual angles to ensure that this phenomenon is not an artifact of saliency.
Method: By employing three different visual angles for the local stimuli, global and local processing of Navon-type hierarchical letters was examined in participants with ADHD (n = 15) and a comparison group (n = 17).
Results: ADHD participants presented with a lack of the Navon effect without local processing deficit regardless of visual angle, in comparison to non-ADHD participants.
Conclusion: A lack of global precedence and global-to-local interference without local processing deficit can be generalized in ADHD. This suggests that people with ADHD experience difficulties in processing the "whole picture," and it also challenges the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; American Psychiatric Association, 2013) criteria of ADHD in which the failure to pay close attention to details was emphasized. Moreover, the current results have important implications for understanding ADHD and could also have significant clinical value.

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Nord J Psychiatry. 2015;69:546-51.

INCREASED LEVELS OF PLASMA GLIAL-DERIVED NEUROTROPHIC FACTOR IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Shim S-H, Hwangbo Y, Yoon H-J, et al.

Background: Recent evidence suggests that neurotrophic growth factor systems, including brain-derived neurotrophic factor, might be involved in the pathophysiology of attention deficit hyperactivity disorder (ADHD). Glial cell line-derived neurotrophic factor (GDNF) is from the transforming growth factor-+¦ family and is abundantly expressed in the central nervous system, where it plays a role in the development and function of hippocampal cells. To date, no association studies have been done between ADHD and GDNF. Thus, here we investigate the hypothesis that there are differences in plasma GDNF levels between children with ADHD and healthy controls.
Methods: Plasma GDNF levels were measured in 86 drug-na+»ve children with ADHD and 128 healthy children. The severity of ADHD symptoms was determined by scores on the Korean ADHD Rating Scale (K-ARS) in patients and healthy controls.
Results: The median plasma GDNF levels in ADHD patients was 74.0 (IQR: 23.4-280.1) pg/ml versus 24.6 (IQR: 14.5-87.3) pg/ml in healthy controls; thus the median plasma GDNF levels in ADHD patients were significantly higher than in healthy controls (Mann-Whitney U-test, $P < 0.01$). Plasma GDNF levels were correlated positively with K-ARS subscale scores (inattention, hyperactivity-impulsivity and total), determined by Spearman's correlation test in ADHD patients and healthy controls ($r = 0.371$, $P < 0.01$; $r = 0.331$, $P < 0.01$; and $r = 0.379$, $P < 0.01$, respectively).
Conclusions: These findings suggest increased plasma GDNF levels in untreated ADHD patients. In addition, plasma GDNF levels had a significant positive correlation with inattention, hyperactivity-impulsivity

and K-ARS total scores in ADHD patients and healthy controls. Further studies are required to determine the source and role of circulating GDNF in ADHD

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Pediatr Neurol. 2014 Nov;51:675-80.

STIMULANT USE IN PATIENTS WITH STURGE-WEBER SYNDROME: SAFETY AND EFFICACY.

Lance El, Lanier KE, Zabel TA, et al.

BACKGROUND: Sturge-Weber syndrome is characterized by a facial port-wine birthmark, vascular eye abnormalities, and a leptomeningeal angioma. Attention and behavioral issues are common in Sturge-Weber syndrome. However, literature evidence for stimulant treatment is minimal. This study evaluates stimulant medication safety and efficacy in individuals with Sturge-Weber syndrome.

METHODS: The research database of the Hunter Nelson Sturge-Weber Center (n = 210 subjects in the database) was reviewed for stimulant use. Twelve patients (mean age 10.5 years, age range 4 to 21 years) on stimulants were seen between 2003 and 2012. A retrospective chart review obtained comorbid diagnoses, stimulant type and dosage, medication side effects, vital signs, and medication efficacy.

RESULTS: All 12 patients had brain involvement (unilateral, nine; bilateral, three). Additional comorbidities included epilepsy (twelve), hemiparesis (eight), headaches (eight), and vision deficits (six). Eight patients reported side effects, primarily appetite suppression (four) and headaches (three). There were no statistically significant changes in weight or blood pressure 6 months after medication initiation. Medication efficacy was subjectively reported in 11 patients. Seven patients remained on stimulants at their most recent follow-up visit.

CONCLUSIONS: This study preliminarily evaluates stimulant medication use in a small group of Sturge-Weber syndrome patients. Stimulants were tolerated and effective in most subjects. Side effects were mostly minor and medication did not negatively affect growth or vital signs. Stimulant medication may be a safe and effective intervention for Sturge-Weber syndrome children with attention issues/attention deficit hyperactivity disorder. Further studies with larger sample sizes are needed

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Pediatric Diabetes. 2015;16:137.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND METABOLIC CONTROL IN ADOLESCENTS WITH TYPE 1 DIABETES.

Bratina N, Battelino T, Kova-ì A, et al.

Background: Type 1 diabetes mellitus (T1DM) is the most common form of diabetes in childhood. Good metabolic control is crucial for preventing late chronic complications. Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric diagnoses in childhood and can affect daily functioning on many levels. We aimed to identify adolescents with T1DM and ADHD and assess the effect of ADHD on metabolic control.

Materials and methods: A cross-sectional case-control study included 101 patients (11-17 years) with T1DM. Development and Well-Being Assessment (DAWBA) questionnaire and psychiatric clinical examination were used to identify a group with T1DM and ADHD. Indicators of metabolic control were collected from available medical documentation for the last 12 months and compared between cases (patients with T1DM and ADHD) and controls (T1DM patients without ADHD).

Results: 12 of 101 adolescents with T1DM were diagnosed with ADHD according to DAWBA questionnaire and psychiatric examination. We found a statistically significant difference (p = 0.04) in glycated haemoglobin (HbA1c) between the two groups. HbA1c was higher in the group with T1DM and ADHD compared to the control group (8.6 -¦ 0.8% or 70.5 -¦ 6.5 mmol/mol compared to 8.0 -¦ 1.1% or 65 -¦ 9.7 mmol/mol; p > 0.05).

Conclusion: It is known that ADHD significantly affects daily functioning in a child or adolescent. In this study it was confirmed that adolescents with T1DM and ADHD had worse metabolic control than the control group. Managing T1DM in pediatric patients with ADHD needs more attention and parent suppervision. DAWBA

can be used as a screening diagnostic screening tool, but additional psychiatric examination and therapeutical support are needed as well

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Pediatric Diabetes. 2015;16:116.

GROWTH HORMONE DEFICIENCY IS RARE IN SHORT CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER TAKING PSYCHOSTIMULANTS-A REEVALUATION OF GH TESTING IN THIS DIAGNOSTIC GROUP.

Velayutham V, Greer R, Chakrabarty S, et al.

Introduction: Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric/behavioural disorders in childhood. Children with ADHD on psychostimulants may exhibit poor growth necessitating a paediatric endocrine referral to exclude growth hormone deficiency and other causes of poor growth.

Aim: To determine if there are any distinct clinical or biochemical parameters in children with ADHD on psychostimulants compared with children with Idiopathic short stature (ISS) who were referred for GH provocation testing.

Methods: As part of a retrospective chart review of all children who underwent GH provocative testing (combined arginine-glucagon) between 1998 and 2013, we identified 51 subjects with ADHD who were taking pyschostimulants. Data collected included age, sex, height, weight, body mass index (BMI), pubertal staging, ESPE diagnosis code, GH provocation test results, thyroid function tests, serum IGF-1 and IGF-BP3 levels.

Results: The total group with non-GHD short stature included 428 subjects: 283 males (66%) and 146 females (34%). In the ADHD group (n = 51), 45 were males (88.2%) and 6 were females (11.8%). There was statistically significant difference in the gender among the groups (Chi square degrees of freedom one = 13.31; p = 0.00). There was no significant difference in stage of puberty between the two groups with 68.6% prepubertal in the ADHD group compared to 75.6% in non-ADHD group (¤ç2 df (3) = 2.808; p = 0.422). All the subjects in the ADHD group had a normal serum IGFBP3 level while 20 out of 51 patients in ADHD group had a low serum IGF-1.

Summary and conclusion: There was a significant difference in age and gender between subjects within the ADHD and the non- ADHD groups. GHD in children with poor growth associated with ADHD and psychostimulant medication is rare. This suggests GH testing in short children with ADHD is generally unnecessary and perhaps serum IGFBP3 rather than IGF-1 may be used as a surrogate marker of GH sufficiency

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Pediatric Rheumatology. 2015;13:207DUMMY.

INCREASED PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH FAMILIAL MEDITERRANEAN FEVER.

Lavi E, Berger I, Eisenstein E, et al.

Introduction: Attention deficit hyperactivity disorder (ADHD) is a developmental neuropsychiatric disorder characterized by inappropriate levels of inattention, impulsivity and hyperactivity. The cause of ADHD is unknown, but may involve both genetic and environmental factors. It has been suggested that exposure to inflammation in infancy may increase the risk for ADHD in later life. Familial Mediterranean Fever (FMF) is the most common inherited autoinflammatory disorder. In many FMF patients the inflammation persists in attack-free periods. The prevalence of ADHD among FMF patients has not been studied previously.

Objectives: To explore the prevalence of ADHD among FMF patients and to examine the relationship between FMF characteristics and ADHD.

Patients and methods: The cohort consisted of 103 consecutive children with FMF, followed in a single referral center. Clinical manifestations, demographic and genetic data were abstracted from the patients' medical records, supplemented by information obtained by interviews conducted during routine follow up visits. The presence of ADHD was assessed using the Diagnostic and Statistical Manual of Mental Disorders questionnaire (4th ed.; DSM-IV).

Results: ADHD was diagnosed in 33 (32.4%) FMF patients, a rate significantly higher that known in our local unselected population (about 8%). The distribution of ADHD subtypes in our patients was similar to the general population: 10 children had predominantly inattentive type (9.8%), 6 hyperactive-impulsive (5.9%) and 17 combined type (16.7%). FMF patients diagnosed with ADHD had a higher rate of arthritis and family history of FMF than patients without ADHD.
Conclusion: The high prevalence of ADHD in children with FMF may support the neuroimmune hypothesis, in which inflammatory conditions increase the risk for ADHD. Furthermore, our findings suggest that physicians should be alert to the possible presence of ADHD among FMF patients

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Pediatrics. 2015;136:e1178-e1185.
OUTPATIENT VISITS AND MEDICATION PRESCRIBING FOR US CHILDREN WITH MENTAL HEALTH CONDITIONS.
Elizabeth AL, Chen ML, Perrin JM, et al.
OBJECTIVE: To compare the mental health care US children receive from primary care providers (PCPs) and other mental health care providers.
METHODS: Using nationally representative data from the Medical Expenditure Panel Survey (MEPS) from 2008 to 2011, we determined whether children and youth aged 2 to 21 years with outpatient visits for mental health problems in the past year saw PCPs, psychiatrists, and/or psychologists/social workers for these conditions. We compared the proportion of children prescribed psychotropic medications by provider type. Using logistic regression, we examined associations of provider type seen and medication prescribing with race/ethnicity, household income, insurance status, geographical area, and language at home.
RESULTS: One-third (34.8%) of children receiving outpatient care for mental health conditions saw PCPs only, 26.2% saw psychiatrists only, and 15.2% saw psychologists/social workers only. Nearly a quarter (23.8%) of children saw multiple providers. A greater proportion of children with attention-deficit/hyperactivity disorder (ADHD) versus children with anxiety/mood disorders saw a PCP only (41.8% vs 17.2%). PCPs prescribed medications to a higher percentage of children than did psychiatrists. Children seeing a PCP for ADHD were more likely to receive stimulants or a-agonists than children with ADHD seeing psychiatrists (73.7% vs 61.4%). We found only limited associations of sociodemographic characteristics with provider type or medication use.
CONCLUSIONS: PCPs appear to be sole physician managers for care of 4 in 10 US children with ADHD, and one-third with mental health conditions overall. Efforts supporting mental health in primary care will reach a substantial portion of children receiving mental health services

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Personality and Individual Differences. 2015 Nov;86:438-49.
CLINICAL, NEUROPSYCHOLOGICAL AND STRUCTURAL CONVERGENCES AND DIVERGENCES BETWEEN ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND BORDERLINE PERSONALITY DISORDER: A SYSTEMATIC REVIEW.
Xenaki LA, Pehlivanidis A.
Attention Deficit/Hyperactivity Disorder (ADHD) symptoms overlap with Borderline Personality Disorder (BPD). Since ADHD presents earlier than BPD, ADHD might be either a risk factor or a prodromal stage in the development of BPD or in the reinforcement of its symptoms. However, despite the similar phenomenological origin of the two disorders, ADHD and BPD patients often present discrete profiles. The present study reviews literature data of the clinical, neuropsychological and structural convergences and divergences of ADHD and BPD. A total of 185 studies were identified that address the association of ADHD and BPD and relate to clinical, neuropsychological and structural parameters. The total number of articles included was 45. ADHD exhibits a more outwardly expressed symptomatology, with difficulties in inhibition control and dysfunction in ventrolateral prefrontal regions. BPD presents a more mixed picture of externalizing and interrelating clinical features with emotionally conditioned cognitive disturbances and dysfunction in the orbitofrontal and dorsolateral prefrontal regions. When considering the three abovementioned parameters there is no unique clear-cut point that can differentiate the two disorders in a

definitive way. Both disorders share impulsivity, emotional dysregulation, deficits in attention and decision making, brain volume reductions and connectivity impairments in prefrontal and limbic areas.

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PLoS ONE. 2015;10.

CHILDHOOD SYMPTOMS OF ADHD OVERRULE COMORBIDITY IN RELATION TO PSYCHOSOCIAL OUTCOME AT AGE 15: A LONGITUDINAL STUDY.

Selinus EN, Molero Y, Lichtenstein P, et al.

Objective: Neurodevelopmental problems (NDPs) may influence the transition from childhood to adolescence. Our aim was to study long-term psychosocial outcomes of NDPs, focusing on ADHD.

Method: Data was collected through a telephone interview with parents of twins at ages 9 or 12 years. NDP screen-positive children were clinically assessed at age 15; N = 450. Psychosocial outcome concerning peers, school, internalizing problems, antisocial behavior, alcohol misuse, drug misuse, and impaired daily functioning was examined.

Results: Even after controlling for other NDP comorbidity, screen-positivity for ADHD doubled or tripled the odds of later psychosocial problems. When controlling for parental education level, the significant effect of ADHD remained only for antisocial behavior and impaired daily functioning.

Conclusions: Signs of NDPs as well as other psychiatric diagnoses at ages 9 or 12 years are associated with a more problematic adolescence. However, despite the presence of comorbidity, early ADHD symptoms stand out as the most important risk factor for later antisocial development and impaired daily functioning

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PLoS ONE. 2015;10.

INTRINSIC AFFECTIVE NETWORK IS IMPAIRED IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ho N-F, Chong JSX, Koh HL, et al.

Deficits in impulsivity and affect dysregulation are key features of attention-deficit/hyperactivity disorder (ADHD) besides impairing levels of hyperactivity and/or inattention. However, the neural substrates underlying these traits are relatively under-investigated. In this study, we use resting-state functional magnetic resonance imaging to test the hypothesis of diminished functional integration within the affective/limbic network (which includes the amygdala, hippocampus, subgenual cingulate cortex, orbitofrontal cortex and nucleus accumbens) of children with ADHD, which is associated with their behavioral measures of emotional control deficits. Resting state-fMRI data were obtained from 12 healthy control subjects and 15 children with ADHD, all who had a minimum onemonth washout period for medications and supplements. Children with ADHD demonstrated less integrated affective network, evidenced by increased bilateral amygdalar and decreased left orbitofrontal connectivity within the affective network compared to healthy controls. The hyper-connectivity at the left amygdalar within the affective network was associated with increased aggressiveness and conduct problems, as well as decline in functioning in children with ADHD. Similar findings in affective network dysconnectivity were replicated in a subset of children with ADHD three months later. Our findings of divergent changes in amygdala and orbitofrontal intrinsic connectivity support the hypothesis of an impaired functional integration within the affective network in childhood ADHD. Larger prospective studies of the intrinsic affective network in ADHD are required, which may provide further insight on the biological mechanisms of emotional control deficits observed in ADHD

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Psychiatr Invest. 2015;12:563-65.

ASSOCIATION OF THE CATECHOL O-METHYLTRANSFERASE VAL158-MET POLYMORPHISM AND REDUCED INTERFERENCE CONTROL IN KOREAN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Park S, Park J-E, Yoo HJ, et al.

Objective: We tested for association of the catechol-O-methyltransferase (COMT) Val158-Met (rs4680) polymorphism with attention-deficit hyperactivity disorder (ADHD) using family-based test in Korean trios.

Methods: A total of 181 subjects with ADHD along with both of their biological parents were recruited from University Hospitals in Korea. We performed a transmission disequilibrium test (TDT) on 181 trios.
Results: In the TDT, we found the over-transmission of the Val allele in children with ADHD ($\chi(2)=4.21$, $p=0.040$).
Conclusion: These results suggest that the COMT Val158-Met polymorphism is associated with ADHD among the Korean population. However, this study must be replicated in larger populations

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Psychiatr Invest. 2015;12:474-82.

MOTOR ACTIVITY IN ADULT PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Fasmer OB, Mjeldheim K, Førland W, et al.

OBJECTIVE: Hyperactivity is a core symptom of attention-deficit hyperactivity disorder (ADHD), but limited information is available on analysis of activity patterns in this disorder. The aim of the study was to analyze motor activity during daily living in adult patients with ADHD.
METHODS: Patients (n=76) from the private psychiatric practice of two of the authors were recruited, and were compared to patients with other psychiatric disorders and to normal controls. Actigraphs were used to record motor activity for six days, with one minute intervals, and data were analysed using linear and non-linear mathematical methods.
RESULTS: For short recording periods (300 minutes) the activity levels of ADHD patients do not differ from normal controls, but the autocorrelation (lag 1) is lower and Fourier analysis shows higher power in the high frequency range, corresponding to the period from 2-8 min. During recordings for six days there are no significant differences between ADHD patients and the control groups. The combined and inattentive subgroups differ only in the six days recordings. The Fourier analyses show that the combined type has lower power in the high frequency range, corresponding to the period from 4-8 hours, and in the analysis of rhythms the intra-daily variability is lower, compared to the inattentive type.
CONCLUSION: Adult ADHD patients do not show evidence of hyperactivity, but have levels of activity similar to normal controls. However, on several measures ADHD patients display altered activity patterns, indicating that the regulation of motor activity in this disorder is different from controls.

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Psychiatr Invest. 2015;12:545-50.

THE EFFECT OF METHYLPHENIDATE ON NEUROLOGICAL SOFT SIGNS IN ADHD.

Hrtanek I, Ondrejka I, Tonhajzerova I, et al.

Objective: Neurological soft signs are very common in children with the attention deficit hyperactivity disorder (ADHD), and the first line medication of this disorder is methylphenidate. The aim of the study was to assess the effect of methylphenidate on the neurological soft signs in children and adolescents suffering from ADHD depending on the dose of methylphenidate.
Methods: Thirty five patients with ADHD were investigated by the ADHD RS-IV parent version questionnaire and the Revised Neurological Examination for Subtle Signs before treatment adjustment and after four weeks of methylphenidate medication. The changes in hyperactivity symptomatology, neurological soft signs during therapy and the influence of the methylphenidate dose were statistically analyzed.
Results: A significant decrease in hyperactivity symptomatology was found after one month of methylphenidate medication ($p=0.0001$) and significant decrease in neurological soft signs was demonstrated in 21 from a total of 26 items ($p<0.05$). Correlation analysis showed no relationship between the dose of methylphenidate and the improvement of neurological soft signs. Similarly, the improvement of ADHD symptomatology had not correlation with the improvement of neurological soft signs.
Conclusion: The study demonstrated the positive effect of methylphenidate on neurological soft signs in which improvement occurred independently of the dose, indicating that their progress may be due to methylphenidate treatment of any dose. The unrelated effect of methylphenidate on the attention deficit

hyperactivity disorder and neurological soft signs suggest that methylphenidate might be useful in the therapy of clumsy child syndrome and in ADHD treatment of non-responders

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Psychol Assess. 2015.

BIFACTOR LATENT STRUCTURE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)/OPPOSITIONAL DEFIANT DISORDER (ODD) SYMPTOMS AND FIRST-ORDER LATENT STRUCTURE OF SLUGGISH COGNITIVE TEMPO SYMPTOMS.

Lee S, Burns GL, Beauchaine TP, et al.

The objective was to determine if the latent structure of attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) symptoms is best explained by a general disruptive behavior factor along with specific inattention (IN), hyperactivity/impulsivity (HI), and ODD factors (a bifactor model) whereas the latent structure of sluggish cognitive tempo (SCT) symptoms is best explained by a first-order factor independent of the bifactor model of ADHD/ODD. Parents' (n = 703) and teachers' (n = 366) ratings of SCT, ADHD-IN, ADHD-HI, and ODD symptoms on the Child and Adolescent Disruptive Behavior Inventory (CADBI) in a community sample of children (ages 5-13; 55% girls) were used to evaluate 4 models of symptom organization. Results indicated that a bifactor model of ADHD/ODD symptoms, in conjunction with a separate first-order SCT factor, was the best model for both parent and teacher ratings. The first-order SCT factor showed discriminant validity with the general disruptive behavior and specific IN factors in the bifactor model. In addition, higher scores on the SCT factor predicted greater academic and social impairment, even after controlling for the general disruptive behavior and 3 specific factors. Consistent with predictions from the trait-impulsivity etiological model of externalizing liability, a single, general disruptive behavior factor accounted for nearly all common variance in ADHD/ODD symptoms, whereas SCT symptoms represented a factor different from the general disruptive behavior and specific IN factor. These results provide additional support for distinguishing between SCT and ADHD-IN. The study also demonstrates how etiological models can be used to predict specific latent structures of symptom organization

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Psychol Med. 2015 Sep;45:2511-20.

CHILDHOOD HYPERACTIVITY/INATTENTION AND EATING DISTURBANCES PREDICT BINGE EATING IN ADOLESCENCE.

Sonneville KR, Calzo JP, Horton NJ, et al.

Background: Identifying childhood predictors of binge eating and understanding risk mechanisms could help improve prevention and detection efforts. The aim of this study was to examine whether features of attention-deficit/hyperactivity disorder (ADHD), as well as childhood eating disturbances, predicted binge eating later in adolescence.

Method: We studied specific risk factors for the development of binge eating during mid-adolescence among 7120 males and females from the Avon Longitudinal Study of Parents and Children (ALSPAC), a cohort study of children in the UK, using data from multiple informants to develop structural equation models. Repeated assessment of eating disturbances during childhood (mid-childhood overeating, late-childhood overeating and early-adolescent strong desire for food), as well as teacher- and parent-reported hyperactivity/inattention during mid- and late childhood, were considered as possible predictors of mid-adolescent binge eating.

Results: Prevalence of binge eating during mid-adolescence in our sample was 11.6%. The final model of predictors of binge eating during mid-adolescence included direct effects of late-childhood overeating [standardized estimate 0.145, 95% confidence interval (CI) 0.038–0.259, p = 0.009] and early-adolescent strong desire for food (standardized estimate 0.088, 95% CI -0.002 to 0.169, p = 0.05). Hyperactivity/inattention during late childhood indirectly predicted binge eating during mid-adolescence (standardized estimate 0.085, 95% CI 0.007–0.128, p = 0.03) via late-childhood overeating and early-adolescent strong desire for food.

Conclusions: Our findings indicate that early ADHD symptoms, in addition to an overeating phenotype, contribute to risk for adolescent binge eating. These findings lend support to the potential role of hyperactivity/inattention in the development of overeating and binge eating

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Psychol Med. 2015 Nov;45:3159-70.

INFLUENCE OF DAT1 AND COMT VARIANTS ON NEURAL ACTIVATION DURING RESPONSE INHIBITION IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND HEALTHY CONTROLS.

van Rooij D, Hoekstra PJ, Bralten J, et al.

Background: Impairment of response inhibition has been implicated in attention-deficit/hyperactivity disorder (ADHD). Dopamine neurotransmission has been linked to the behavioural and neural correlates of response inhibition. The current study aimed to investigate the relationship of polymorphisms in two dopamine-related genes, the catechol-O-methyltransferase gene (COMT) and the dopamine transporter gene (SLC6A3 or DAT1), with the neural and behavioural correlates of response inhibition.

Method: Behavioural and neural measures of response inhibition were obtained in 185 adolescents with ADHD, 111 of their unaffected siblings and 124 healthy controls (mean age 16.9 years). We investigated the association of DAT1 and COMT variants on task performance and whole-brain neural activation during response inhibition in a hypothesis-free manner. Additionally, we attempted to explain variance in previously found ADHD effects on neural activation during response inhibition using these DAT1 and COMT polymorphisms.

Results: The whole-brain analyses demonstrated large-scale neural activation changes in the medial and lateral prefrontal, subcortical and parietal regions of the response inhibition network in relation to DAT1 and COMT polymorphisms. Although these neural activation changes were associated with different task performance measures, no relationship was found between DAT1 or COMT variants and ADHD, nor did variants in these genes explain variance in the effects of ADHD on neural activation.

Conclusions: These results suggest that dopamine-related genes play a role in the neurobiology of response inhibition. The limited associations between gene polymorphisms and task performance further indicate the added value of neural measures in linking genetic factors and behavioural measures

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Psychol Addict Behav. 2015;29:444-54.

ALCOHOL USE LONGITUDINALLY PREDICTS ADJUSTMENT AND IMPAIRMENT IN COLLEGE STUDENTS WITH ADHD: THE ROLE OF EXECUTIVE FUNCTIONS.

Langberg JM, Dvorsky MR, Kipperman KL, et al.

The primary aim of this study was to evaluate whether alcohol consumption longitudinally predicts the adjustment, overall functioning, and grade point average (GPA) of college students with ADHD and to determine whether self-report of executive functioning (EF) mediates these relationships. Sixty-two college students comprehensively diagnosed with ADHD completed ratings at the beginning and end of the school year. Regression analyses revealed that alcohol consumption rated at the beginning of the year significantly predicted self-report of adjustment and overall impairment at the end of the year, above and beyond ADHD symptoms and baseline levels of adjustment/impairment but did not predict GPA. Exploratory multiple mediator analyses suggest that alcohol use impacts impairment primarily through EF deficits in self-motivation. EF deficits in the motivation to refrain from pursuing immediately rewarding behaviors in order to work toward long-term goals appear to be particularly important in understanding why college students with ADHD who consume alcohol have a higher likelihood of experiencing significant negative outcomes. The implications of these findings for the prevention of the negative functional outcomes often experienced by college students with ADHD are discussed

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Res Autism Spectr Disord. 2016;21:94-108.

EXPLICIT VS. APPLIED THEORY OF MIND COMPETENCE: A COMPARISON OF TYPICALLY DEVELOPING MALES, MALES WITH ASD, AND MALES WITH ADHD.

Hutchins TL, Prelock PA, Morris H, et al.

Using laboratory-type Theory of Mind (ToM) tasks (our measure of 'explicit' ToM competence) and a more ecologically-valid measure of ToM (our measure of 'applied' ToM competence), we found that for composite scores, typically developing (TD) males performed near ceiling levels on both indices and age-matched males with autism spectrum disorder (ASD) performed near floor levels on both indices. The scores for age-matched males with attention-deficit hyperactivity disorder (ADHD) showed a different pattern such that the ADHD group had high scores on the explicit measure and low scores on the applied measure. Subscale scores (early, basic, advanced ToM) for the two indices also revealed that (1) despite variable complexity, explicit ToM almost always distinguished the ASD group from the other two groups but never distinguished the ADHD and TD groups and (2) level of complexity was critical for distinguishing groups with regard to applied ToM. We suggest that although children with ADHD can calculate the content of traditional laboratory ToM tasks, this explicit ToM competence fails to be applied and expressed in real world demonstrations of ToM (especially when advanced ToM skills are assessed). By contrast, the ToM difficulties of children with ASD seem to be attributable to a deeper metarepresentational deficit. Our results have implications for practice and extend current models of social cognition in developmental disabilities by isolating variable aspects of competence that predict specific and testable models for future research

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Res Dev Disabil. 2015 Oct;45-46:103-09.

HYPERACTIVITY IN BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): THE ROLE OF EXECUTIVE AND NON-EXECUTIVE FUNCTIONS.

Hudec KL, Alderson RM, Patros CHG, et al.

Motor activity of boys (age 8–12 years) with (n = 19) and without (n = 18) ADHD was objectively measured with actigraphy across experimental conditions that varied with regard to demands on executive functions. Activity exhibited during two n-back (1-back, 2-back) working memory tasks was compared to activity during a choice-reaction time (CRT) task that placed relatively fewer demands on executive processes and during a simple reaction time (SRT) task that required mostly automatic processing with minimal executive demands. Results indicated that children in the ADHD group exhibited greater activity compared to children in the non-ADHD group. Further, both groups exhibited the greatest activity during conditions with high working memory demands, followed by the reaction time and control task conditions, respectively. The findings indicate that large-magnitude increases in motor activity are predominantly associated with increased demands on working memory, though demands on non-executive processes are sufficient to elicit small to moderate increases in motor activity as well.

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Res Dev Disabil. 2015 Oct;45-46:188-201.

SENSORY PROCESSING IN CHILDREN WITH AUTISM SPECTRUM DISORDER: RELATIONSHIP WITH NON-VERBAL IQ, AUTISM SEVERITY AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER SYMPTOMATOLOGY.

Sanz-Cervera P, Pastor-Cerezuela G, Fernández-Andrés MI, et al.

The main objective of this study was to analyze in a sample of children with ASD the relationship between sensory processing, social participation and praxis impairments and some of the child's characteristics, such as non-verbal IQ, severity of ASD symptoms and the number of ADHD symptoms (inattention and hyperactivity/impulsivity), both in the home and main-classroom environments. Participants were the parents and teachers of 41 children with ASD from 5 to 8 years old (M = 6.09). They completed the Sensory Processing Measure (SPM) to evaluate sensory processing, social participation and praxis; the Gilliam Autism Rating Scale (GARS-2) to evaluate autism severity; and a set of items (the DSM-IV-TR criteria) to evaluate the number of inattention and hyperactivity/impulsivity symptoms in the child. Non-verbal IQ—measured by the Raven's Coloured Progressive Matrices Test—did not show a relationship with any of the

SPM variables. The SPM variables were significant predictors of autism severity and had similar weights in the two environments. In the case of ADHD symptoms, the SPM variables had a greater weight in the home than in the classroom environment, and they were significant predictors of both inattention and hyperactivity/impulsivity—especially inattention—only in the family context. The moderate association between inattention and auditory processing found in the main-classroom suggests the possible utility of certain measures aimed to simplify any classroom's acoustic environment.

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Sleep Biol Rhythms. 2015;13:51.

MANAGEMENT OPTIONS FOR SLEEP DIFFICULTIES IN THE ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) POPULATION.

Hiscock H.

Behavioural sleep problems such as limit setting disorder, sleep onset association disorder, and insomnia secondary to anxiety, are common in children with ADHD and associated with poorer child and parent functioning. Stimulant medications are the mainstay of ADHD treatment but may worsen sleep, particularly insomnia. Similarly, co-morbid mental health problems such as anxiety and oppositional defiant disorder are also associated with poorer sleep. This presentation will discuss common sleep issues in children with ADHD including their risk factors. It will then present a suite of evidence-based interventions, suitable for use in children with ADHD, drawing upon interventions used in our recent successful trial (Hiscock et al BMJ 201). The impact of these interventions on child sleep, behaviour, quality of life and academic functioning and parent mental health will also be discussed

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Sleep Biol Rhythms. 2015;13:11.

BEHAVIORAL SLEEP PROBLEMS IN CHILDREN WITH ADHD: CROSS-SECTIONAL ASSOCIATIONS WITH PARENTING AND SLEEP HYGIENE.

Cheng SJ, Hiscock H, Sciberras E, et al.

Background: Sleep problems are common in children with attention deficit hyperactivity disorder (ADHD) and are typically behavioural in nature. Contributing factors include stimulant medication use and internalising and externalising comorbidities. However, little is known about other potentially modifiable factors such as parenting style and sleep hygiene. We aim to examine the association between behavioural sleep problems and sleep hygiene and parenting in children with ADHD.

Methods: Baseline data from a randomised controlled trial examining the effectiveness of a behavioral sleep intervention program in 5-13 year old children with ADHD.

Inclusion criteria: diagnosis of ADHD by a paediatrician and met DSM 5 criteria for ADHD (ADHD Rating Scale IV) at the recruitment call. Caregivers also needed to report that their child had a moderate to severe sleep problem.

Exclusion criteria: suspected obstructive sleep apnea; serious medical condition or intellectual disability (IQ < 70); or child receiving specialised help for their sleep. Outcome variables included sleep problem subscales of the parentreported Children's Sleep Habits Questionnaire (CSHQ). Multivariable linear regression was used to establish prediction models for the primary outcome variables using social demographic information of families as well as the potential predictor variables sleep hygiene and parenting style. The predictor variables were measured using a parent-reported Sleep Hygiene scale (6-items) and parenting behavior scales assessing warmth (6-items) and consistency (6-items).

Results: One hundred and sixty-nine families completed the survey. For the sleep outcome measures bedtime resistance and parasomnias, the prediction models yielded considerable coefficients of determination (proportion of outcome variance explained about 20%). The main explanatory factors for bedtime resistance were sleep hygiene, parental warmth and parenting consistency. The main predictor variables for parasomnias were parental warmth, ADHD symptom severity and the presence of comorbidities.

Conclusion: Preliminary results suggest that sleep hygiene and parental consistency may be important modifiable predictors of sleep problems in children with ADHD

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Sleep Biol Rhythms. 2015;13:55.

THE BI-DIRECTIONAL RELATIONSHIP BETWEEN SLEEP PROBLEMS AND INTERNALIZING AND EXTERNALIZING PROBLEMS IN CHILDREN WITH ADHD: A PROSPECTIVE COHORT STUDY.

Mulraney M, Giallo R, Lycett K, et al.

Background: Behavioral sleep problems are common in children with Attention-Deficit/Hyperactivity Disorder (ADHD) and longitudinal studies in children with ADHD have found sleep problems to be both a predictor and outcome of internalizing and externalizing problems. Existing studies have yet to examine the potential bi-directional relationship between sleep and internalizing and externalizing problems in children with ADHD. We examined the bidirectional relationship between sleep problems and internalizing/externalizing problems over a 12 month period.

Methods: Children with paediatrician diagnosed ADHD aged 5-13 years were recruited from 21 paediatric practices across Victoria, Australia (N = 270). Parents reported on their child's sleep problems (Child Sleep Habits Questionnaire) and on emotional and behavioural functioning (Strengths and Difficulties Questionnaire) at three time points across a 12 month period. Data were analysed using autoregressive cross-lagged panel models.

Results: Sleep problem severity and emotional/behavioral problem severity were very stable across the 12 month period. Sleep problems at baseline predicted emotional problems at 6 months ($r = .17$, $p < .01$), and emotional problems at baseline predicted sleep problems at 6 months ($r = .07$, $p < .05$). However, there was no evidence of a predictive relationship between sleep problems and emotional problems from 6 months to 12 months. There was no evidence of a bidirectional relationship between sleep problems and conduct problems over the 12 month period.

Conclusions: In children with ADHD there was some evidence of a bidirectional relationship between sleep problems and emotional problems. Both sleep problems and emotional problems are very stable over time therefore the best treatment may be to target both sleep and emotional functioning in these children

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Sleep Med. 2014 Nov;15:1362-69.

PERIODIC LEG MOVEMENTS DURING SLEEP IN CHILDREN SCHEDULED FOR ADENOTONSILLECTOMY: FREQUENCY, PERSISTENCE, AND IMPACT.

Chervin RD, Chung S, O'Brien LM, et al.

OBJECTIVE: The aim of this study was to assess the frequency and potential clinical impact of periodic leg movements during sleep (PLMS), with or without arousals, as recorded incidentally from children before and after adenotonsillectomy (AT).

METHODS: Children scheduled for AT for any clinical indications who participated in the Washtenaw County Adenotonsillectomy Cohort II were studied at enrollment and again 6 months thereafter. Assessments included laboratory-based polysomnography, a Multiple Sleep Latency Test (MSLT), parent-completed behavioral rating scales, neuropsychological testing, and psychiatric evaluation.

RESULTS: Participants included 144 children (81 boys) aged 3-12 years. Children generally showed mild to moderate obstructive sleep apnea (median respiratory disturbance index 4.5 (Q1 = 2.0, Q3 = 9.5)) at baseline, and 15 subjects (10%) had at least five periodic leg movements per hour of sleep (PLMI >/= 5). After surgery, 21 (15%) of n = 137 subjects who had follow-up studies showed PLMI >/= 5 ($p = 0.0067$). Improvements were noted after surgery in the respiratory disturbance index; insomnia symptoms; sleepiness symptoms; mean sleep latencies; hyperactive behavior; memory, learning, attention, and executive functioning on NEPSY assessments; and frequency of attention-deficit/hyperactivity disorder (DSM-IV criteria). However, PLMI >/= 5 failed to show associations with worse morbidity in these domains at baseline or follow-up. New appearance of PLMI >/= 5 after surgery failed to predict worsening of these morbidities (all

p > 0.05), with only one exception (NEPSY) where the magnitude of association was nonetheless negligible. Similar findings emerged for periodic leg movements with arousals (PLMAI >/= 1).
CONCLUSION: PLMS, with and without arousals, become more common after AT in children. However, results in this setting did not suggest substantial clinical impact

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The Journal of Alternative and Complementary Medicine. 2015 Sep;21:546-53.
EQUINE-ASSISTED ACTIVITIES AND THERAPY FOR TREATING CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Jang B, Song J, Kim J, et al.
Objective: To investigate clinical effects of equine-assisted activities and therapy (EAA/T) for treating attention-deficit/hyperactivity disorder (ADHD) in children age 6–13 years.
Methods: This 12-week, prospective, open-label trial included 24 sessions of EAA/T. Twenty participants (19 boys and 1 girl) completed 12 weeks of EAA/T. Various clinical tests were administered at baseline and after EAA/T. Assessments included the investigator-administered ADHD-Rating Scale (ARS-I), Clinical Global Impressions (CGI)–Severity Scale, Clinical Global Impressions–Improvement Scale (CGI-I), Gordon Diagnostic System, Korea-Child Behavior Checklist (K-CBCL), Self-Esteem Scale, second edition of the Bruininks-Oseretsky test of motor proficiency (BOT-2), and quantitative electroencephalography. The primary efficacy measure was the response rate.
Results: The response rate was 90% based on a 30% or greater decline in the ARS-I score or 85% based on CGI-I scores of 1 or 2. The mean ± standard deviation ARS-I score decreased from 33.65-6.42 at baseline to 16.80 ± 6.86 after 12 weeks of EAA/T ($p < 0.001$, paired t-test). EAA/T also resulted in significant improvement in the social problems subscale of the K-CBCL and in the manual dexterity, bilateral coordination, and total motor composite subscales of the BOT-2. The theta/beta ratio on electroencephalography was decreased significantly at the Pz electrode after 12 weeks of EAA/T.
Conclusion: This is the first study demonstrating that EAA/T is effective for improving core ADHD symptoms. On the basis of these results, EAA/T could be a viable treatment strategy as a part of a multimodal therapy for children with ADHD

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The Journal of Pediatrics. 2015 Sep;167:621-26.
DISTRIBUTION AND WITHIN-FAMILY SPECIFICITY OF QUANTITATIVE AUTISTIC TRAITS IN PATIENTS WITH NEUROFIBROMATOSIS TYPE I.
Constantino JN, Zhang Y, Holzhauer K, et al.
Objective: To examine the distribution of quantitative autistic traits (QATs) in an independent neurofibromatosis type I (NF1) sample, the relationships between QAT, sex, and attention deficit hyperactivity disorder (ADHD) symptomatology, and to explore evidence for QAT mutational specificity within families.
Study design: Age-appropriate versions of the Social Responsiveness Scale, second edition and the Conners Adult ADHD Rating Scales were completed for 103 patients with NF1 from the Washington University Neurofibromatosis Center.
Results: Patients with NF1 exhibited a pathologically shifted unimodal distribution for QAT. Forty-four percent of the subjects exhibited a QAT burden at or above 1 SD from the population mean; 13% scored at or above the extreme first percentile of the general population distribution. Elevations in ADHD symptomatology exhibited a distinct bimodal distribution; however, mean ADHD index scores were equivalent in patients who had been diagnosed in the community with ADHD compared with those who had not. We observed striking within-family associations for QAT, reflected by an Social Responsiveness Scale, second edition intraclass correlation of 0.77 in pairings of first degree relatives with NF1.
Conclusions: Impairments in reciprocal social behavior and attention affect a large proportion of patients with NF1 throughout life and are often clinically unrecognized. Further exploration of genotype-phenotype

correlation is strongly warranted for the purpose of gaining insights into mechanisms by which specific mutational variations in the NF1 gene may influence autistic trait severity

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Trials. 2015;16.

COGNITIVE COMPUTER TRAINING IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) VERSUS NO INTERVENTION: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL.

Bikic A, Leckman JF, Lindschou J, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder characterized by symptoms of inattention and impulsivity and/or hyperactivity and a range of cognitive dysfunctions. Pharmacological treatment may be beneficial; however, many affected individuals continue to have difficulties with cognitive functions despite medical treatment, and up to 30 % do not respond to pharmacological treatment. Inadequate medical compliance and the long-term effects of treatment make it necessary to explore nonpharmacological and supplementary treatments for ADHD. Treatment of cognitive dysfunctions may prove particularly important because of the impact of these dysfunctions on the ability to cope with everyday life. Lately, several trials have shown promising results for cognitive computer training, often referred to as cognitive training, which focuses on particular parts of cognition, mostly on the working memory or attention but with poor generalization of training on other cognitive functions and functional outcome. Children with ADHD have a variety of cognitive dysfunctions, and it is important that cognitive training target multiple cognitive functions.

Methods/Design: This multicenter randomized clinical superiority trial aims to investigate the effect of "ACTIVATE™," a computer program designed to improve a range of cognitive skills and ADHD symptoms. A total of 122 children with ADHD, aged 6 to 13 years, will be randomized to an intervention or a control group. The intervention group will be asked to use "ACTIVATE™," at home 40 minutes per day, 6 days per week for 8 weeks. Both intervention and control group will receive treatment as usual. Outcome measures will assess cognitive functions, symptoms, and behavioral and functional measures before and after the 8 weeks of training and in a 12- and 24-week follow-up.

Discussion: Results of this trial will provide useful information on the effectiveness of computer training focusing on several cognitive functions. Cognitive training has the potential to reduce cognitive dysfunctions and to become a new treatment option, which can promote a more normal neural development in young children with ADHD and thus reduce cognitive dysfunctions and symptoms. This could help children with ADHD to perform better in everyday life and school.

Trial registration: ClinicalTrials.gov: NCT01752530, date of registration: 10 December 2012

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Twin Res Hum Genet. 2015.

THE COLORADO LONGITUDINAL TWIN STUDY OF READING DIFFICULTIES AND ADHD: ETIOLOGIES OF COMORBIDITY AND STABILITY.

Wadsworth SJ, DeFries JC, Willcutt EG, et al.

Approximately 60% of children with reading difficulties (RD) meet criteria for at least one co-occurring disorder. The most common of these, attention deficit-hyperactivity disorder (ADHD), occurs in 20ΓÇô40% of individuals with RD. Recent studies have suggested that genetic influences are responsible. To assess the genetic etiologies of RD and the comorbidity of RD and two ADHD symptom dimensions ΓÇôΓÇô inattention (IN) and hyperactivity/impulsivity (H/I) ΓÇôΓÇô we are conducting the first longitudinal twin study of RD and ADHD. Data from twin pairs in which at least one member of the pair met criteria for proband status for RD at initial assessment, and were reassessed 5 years later, were subjected to DeFries-Fulker (DF) analysis. Analyses of reading composite data indicated that over 60% of the proband deficit at initial assessment was due to genetic influences, and that reading deficits at follow-up were due substantially to the same genetic influences. When a bivariate DF model was fitted to reading performance and IN data, genetic influences accounted for 60% of contemporaneous comorbidity and over 60% of the longitudinal relationship. In contrast, analysis of the comorbidity between reading performance and H/I indicated that

common genetic influences accounted for only about 20% of the contemporaneous and about 10% of the longitudinal relationships. Results indicate that (1) genetic influences on RD are substantial and highly stable; (2) the comorbidity between RD and IN is due largely to genetic influences, both contemporaneously and longitudinally; and (3) genetic influences contribute significantly less to the comorbidity between RD and H/I

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Value Health. 2015;18:A747.

STIMULANT USE AND CARDIOVASCULAR RISK AMONG CHILDREN AND ADOLESCENTS WITH ADHD: WHAT PRODUCT LABELING DOES, OR DOES NOT, TELL US.

Palasik B, Sieluk J, Dos RS, et al.

Objectives: Product labeling conveys information about the potential risks of medication for healthcare professionals and consumers, but the consistency (or inconsistency) of such information is unknown. We sought to investigate the consistency of information intended for healthcare professionals versus consumers about cardiovascular risks from stimulants approved in four Englishspeaking countries.

Methods: Professional and consumer drug product labels were obtained in July 2014 from regulatory agencies in Australia, Canada, United Kingdom, and United States. Language describing the nature of the relationship between the drug and four major cardiovascular adverse events (elevated blood pressure and/or heart rate, stroke, myocardial infarction, and sudden death) was extracted verbatim and classified into one of four mutually exclusive categories: confirmed, unconfirmed, mixed and not mentioned.

Results: We obtained professional and consumer product labeling for 24 unique, approved stimulants (16 US, 6 UK, 6 Canada, and 5 Australia). Language regarding the relationship between drug and cardiovascular adverse events was consistent for professional and consumer audiences 54.5% of the time (59% US, 20% Australia, 58% Canada, 67% UK). One in three (32%) labels for professionals and consumers included inconsistent language that described a drug-adverse event relationship as both confirmed and unconfirmed.

Conclusions: Regulator approved product labeling provides healthcare professionals and consumers with inconsistent messages regarding the certainty (or uncertainty) of the relationship between stimulant use and specific cardiovascular risks in children and adolescents. Professionals and consumers often receive mixed messages about the actual risk of a particular cardiovascular event within the same label. The implications towards patient safety and outcomes warrants further study

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Value Health. 2015;18:A413.

PATIENT, CAREGIVER AND TREATMENT FACTORS ASSOCIATED WITH MEDICATION SATISFACTION AMONG TREATED PATIENTS IN THE CAREGIVER PERSPECTIVE ON PEDIATRIC ADHD (CAPPA) STUDY IN EUROPE.

Fridman M, Banaschewski T, Harpin V, et al.

Objectives: To evaluate the association between caregiver's reported attentiondeficit/ hyperactivity disorder (ADHD) medication satisfaction (MS) and child and caregiver socio-demographics; ADHD severity; comorbidities; medication attributes; treatment classes.

Methods: CAPPA is a cross-sectional online survey of caregivers of children (6-17 years) with ADHD receiving pharmacological treatment for ADHD at survey completion (2012-2013) in 10 European countries. ADHD Rating Scale Version IV (ADHD-RS-IV) total score during treatment interruption (off medication) was used as a proxy for baseline severity. Caregivers were asked to rate satisfaction with medication attributes (Convenience: administration frequency, tablet size; Effectiveness: duration of action, time to onset, symptom control; Safety: side effects, abuse/misuse potential, dependence/addiction potential) on a 7-point scale ranging from 'very satisfied' to 'very dissatisfied'. Children's comorbidities at baseline/treatment classes were also reported by caregivers. Significant factors ($p< 0.01$) using bivariate and correlation analyses are reported.

Results: Among 3688 respondents, 2853 (77%) whose child was using ADHD medication at survey completion were evaluated. Children's mean (SD) age was 11.4 (3.1) years, 81% were male; 67% of caregivers were female. MS was rated as: very satisfied (20%), satisfied (39%), moderately satisfied (29%), and combined neither satisfied nor dissatisfied, moderately dissatisfied, dissatisfied or very dissatisfied

(12%). Better MS was reported with lower ADHD severity and fewer comorbidities. Comorbidities significantly associated with lower MS were anxiety, conduct disorder, aggression and oppositional defiant disorder. Medication attributes with strongest correlation to MS were symptom control (r= 0.6), duration of action (0.5) and time to onset (0.4). Significantly higher MS was associated with caregivers who were married, female, employed or a parent with ADHD. MS varied by country.
Conclusions: Lower ADHD severity and fewer comorbidities were associated with higher MS. Effectiveness attributes were of highest priority to caregivers and MS differed by caregiver characteristics. These factors should be considered when making a treatment plan

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World J Biol Psychiatry. 2015.
ETHNIC DIFFERENCES IN COMT GENETIC EFFECTS ON STRIATAL GREY MATTER ALTERATIONS ASSOCIATED WITH CHILDHOOD ADHD: A VOXEL-BASED MORPHOMETRY STUDY IN A JAPANESE SAMPLE.
Shimada K, Fujisawa TX, Takiguchi S, et al .
OBJECTIVES: Attention deficit/hyperactivity disorder (ADHD) is associated with deficits in the dopaminergic fronto-striatal systems mediating higher-level cognitive functions. We hypothesised that a dopamine-regulating gene, catechol-O-methyltransferase (COMT), would have differential effects on the neural systems of different ethnic samples with ADHD. In Caucasian children with ADHD, the COMT Val-homozygotes have been previously shown to be associated with striatal grey matter volume (GMV) alterations. By using voxel-based morphometry, we examined whether Asian children with ADHD would exhibit a pattern opposite to that found in Caucasian samples.
METHODS: Structural brain images were obtained for Japanese children with ADHD (n = 17; mean age = 10.3 years) and typically developing (TD) children (n = 15; mean age = 12.8 years). COMT Val158Met genotype data were also obtained for the ADHD group.
RESULTS: Reduced GMV in the left striatum was observed in the ADHD group versus the TD group. This reduced GMV was modulated by COMT polymorphism; Met-carriers exhibited smaller striatal GMV than the Val/Val genotype.
CONCLUSIONS: Contrasting with previous findings in Caucasians, the COMT Met allele was associated with striatal GMV alterations in Japanese children with ADHD. These results suggest the existence of ethnic differences in the COMT genetic effect on ADHD-related striatal abnormalities.

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World J Psychiatry. 2015 Mar;5:47-55.
RAISING ATTENTION TO ATTENTION DEFICIT HYPERACTIVITY DISORDER IN SCHIZOPHRENIA.
Pallanti S, Salerno L.
Schizophrenia and attention deficit hyperactivity disorder (ADHD) are two psychiatric disorders with a negative impact on quality of life of individuals affected. Although they are classified into distinct disorders categories, attentional dysfunction is considered as a core feature in both conditions, either at the clinical then pathophysiological level. Beyond the obvious clinical overlap between these disorders, the Research Domain Criteria approach might offer an interesting perspective for disentangling common circuits underpinning both disorders. Hence, we review evidences regarding the overlap between schizophrenia and ADHD, at the clinical level, and at the level of underlying brain mechanisms. The evidence regarding the influence of environmental risk factors in the emergence of both disorders, and their developmental trajectories is also reviewed. Among these, we will try to elucidate the complex relationship between stimulants use and psychotic symptoms, discussing the potential role of ADHD medication in inducing psychosis or in exacerbating it. We aim that, taken together, these findings may promote further investigation with important implications both for clinicians and research. In fact, considering the amounting evidence on the overlap between schizophrenia and ADHD, the delineation of their boundaries might help in the decision for diagnosis and treatment. Moreover, it may help to promote interventions focused on the prevention of both schizophrenia and ADHD, by the reduction of recognized environmental risk factors

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ORIGINAL RESEARCH ARTICLE

Safety of Methylphenidate and Atomoxetine in Children with Attention-Deficit/Hyperactivity Disorder (ADHD): Data from the Italian National ADHD Registry

Samuele Cortese[1,2] · Pietro Panei[3] · Romano Arcieri[3] · Elena A. P. Germinario[3] · Annalisa Capuano[4] · Lucia Margari[5] · Flavia Chiarotti[6] · Paolo Curatolo[7]

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Abstract

Objective The aim of this study was to assess the type and frequency of adverse events (AEs) in children with attention-deficit/hyperactivity disorder (ADHD) treated with methylphenidate or atomoxetine over a 5-year period in a large naturalistic study.

Methods We draw on data from the Italian ADHD Registry, a national database for postmarketing phase IV pharmacovigilance of ADHD medications across 90 centers. AEs were defined as severe or mild as per the classification of the Italian Medicines Agency. AE frequency in the two treatment groups was compared using incidence rates per 100 person-years (IR_{100PY}) and incidence rate ratios (IRRs). Mantel–Haenszel adjusted IRRs were calculated to control for psychiatric comorbidity.

Results A total of 1350 and 753 participants (aged 6–18 years, mean age 10.7 ± 2.8) were treated with methylphenidate and atomoxetine, respectively, from 2007 to 2012. Ninety participants (7 %) were switched from methylphenidate to atomoxetine, and 138 (18 %) from atomoxetine to methylphenidate. Thirty-seven children treated with atomoxetine and 12 with methylphenidate had their medication withdrawn. Overall, 645 patients (26.8 %) experienced at least one mild AE (including decreased appetite and irritability, for both drugs) and 95 patients (3.9 %) experienced at least one severe AE (including severe gastrointestinal events). IR_{100PY} were significantly higher in the atomoxetine-treated group compared with the methylphenidate-treated group for a number of mild and severe AEs and for any severe or mild AEs. After controlling for comorbidities, IRR was still significantly higher in the atomoxetine group compared with the methylphenidate group for a number of mild (decreased appetite, weight loss, abdominal pain, dyspepsia, stomach ache, irritability, mood disorder and dizziness) and severe (gastrointestinal, neuropsychiatric, and cardiovascular) AEs.

Conclusions In this naturalistic study, methylphenidate had a better safety profile than atomoxetine.

✉ Pietro Panei
pietro.panei@iss.it

Samuele Cortese
samuele.cortese@gmail.com

1 Developmental Brain-Behaviour Laboratory, Department of Psychology, University of Southampton, Highfield Campus, Southampton, UK

2 New York University Child Study Center, New York, NY, USA

3 Department of Therapeutic Research and Medicines Evaluation, Istituto Superiore di Sanità, Italian National Institute of Health, Viale Regina Elena, 299, 00161 Rome, Italy

4 Department of Experimental Medicine, Regional Center of Pharmacosurveillance and Pharmacoepidemiology, Second University of Naples, Naples, Italy

5 Child Neuropsychiatry Unit, Department of Neuroscience and Sense Organs, Hospital Polyclinic of Bari, University Aldo Moro, Bari, Italy

6 Department of Cell Biology and Neurosciences, Istituto Superiore di Sanità, Italian National Institute of Health, Rome, Italy

7 Systems Medicine Department, Child Neurology and Psychiatry Unit, Tor Vergata University Hospital of Rome, Rome, Italy

Key Points

In this naturalistic study, atomoxetine was less well tolerated than methylphenidate for a number of mild and severe adverse events.

This finding remained significant even after controlling for psychiatric comorbidities in the methylphenidate and atomoxetine groups.

1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder [1], with a worldwide prevalence estimated at approximately 5 % in school-aged children [2] and persistence of impairing symptoms in adulthood in up to 65 % of cases [3]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [4], ADHD is characterized by an age-inappropriate, persistent and impairing pattern of inattention and/or hyperactivity/impulsivity. ADHD is often comorbid with other psychiatric conditions, such as oppositional defiant disorder (ODD)/conduct disorder (CD), specific learning disorders, mood and anxiety disorders [5], sleep disturbances [6] and, in adulthood, personality disorders [7].

Available treatments for ADHD include pharmacological and nonpharmacological strategies. The former are recommended as the first-choice option in several guidelines/practice parameters (e.g. Pliszka [8]), at least for severe cases [9, 10], or as a treatment strategy for patients who did not respond to nonpharmacological interventions [9, 10]. Medications for ADHD include psychostimulant (i.e. methylphenidate and amphetamine derivatives) and nonpsychostimulant drugs (e.g. atomoxetine, clonidine, guanfacine). Psychostimulant medications are indicated as first-line treatment in some guidelines/recommendations (e.g. the UK National Institute for Health and Care Excellence [NICE] guidelines [9]).

As with all medications, and some nonpharmacological interventions, adverse events (AEs) can and do occur during treatment with ADHD drugs [11]. Although the majority of such AEs are clinically manageable [12], the tolerability and safety of medications for ADHD is of concern to regulatory bodies, clinicians, patients and their families. This may result in patients with ADHD being exposed to harm if AEs are overlooked, or not benefitting from effective medications if the potential AEs are overestimated [12]. Therefore, understanding the nature of AEs associated with ADHD medications is paramount. Additionally, tolerability and safety profile is an important element in the choice of the specific class of medication. Evidence of the types of AEs and comparative tolerability/safety of different ADHD medications, particularly methylphenidate versus atomoxetine, is available from a large body of randomized controlled trials (RCTs). Two meta-analyses of such RCTs [13, 14] concluded that methylphenidate and atomoxetine have similar profiles in terms of all-cause discontinuation and incidence of AEs. However, some individual studies reported significantly greater incidence of decreased appetite and insomnia [15], weight loss and heart rate increase [16] with methylphenidate, and significantly higher rates of anorexia, nausea, somnolence, dizziness and vomiting with atomoxetine [17].

Whilst the rigorous design of conventional RCTs allows for a reduction of many confounding factors, such studies may be hampered by selection bias [18] since they often include a selected subpopulation of subjects, which only, in part, reflects the type of patients commonly seen in day-to-day clinical practice. In addition, such trials are usually limited to a few weeks/months, therefore they do not allow for the detection of potential longer-term AEs. In this respect, longer-term naturalistic studies provide additional valuable information.

To address these issues, we draw on data from the Italian National ADHD Registry [19], set up to perform intensive postmarketing phase IV pharmacovigilance of ADHD medications across 90 Italian ADHD centers. We aimed to: (i) assess the type of AEs; and (ii) compare their frequency in children treated with methylphenidate or atomoxetine over a 5-year period. We focused on methylphenidate and atomoxetine, the only two classes of ADHD drugs licensed in Italy at the time of the study. Given the exploratory nature of this study, no a priori hypotheses were formulated.

2 Methods

2.1 Study Population

Participants were children/adolescents (aged 6–18 years) included in the Italian National ADHD Registry from June 2007 to December 2012. This time frame was established by the Italian Medicines Agency as an appropriate period for pharmacovigilance. The diagnosis of ADHD was based on the DSM, Fourth Edition-text revision (DSM-IV-TR) [20] criteria (the classification system used at the time of the study). Given the naturalistic design, no a priori exclusion criteria were applied. Comorbid disorders were not an exclusionary criterion since the presence of comorbid psychiatric disorders is the rule rather than the exception in ADHD.

2.2 Study Drugs

ADHD was treated with either of the following.

(i) *Methylphenidate chlorhydrate immediate release, 10 mg*. Administration was orally at a dosage of 0.3–0.6 mg/kg/dose/day. First, as recommended by the official protocol of the Italian ADHD centers, methylphenidate was administered at a test dose of 0.3 mg/kg. The dosage could then be increased up to 0.6 mg/kg/dose based on clinical response and tolerability. The total dose was administered in two or three doses/day. Methylphenidate immediate-release was the only available formulation of methylphenidate in Italy at the time of the study;

(ii) *Atomoxetine chlorhydrate 5, 10, 18, 25, 40 or 60 mg*. Administration was orally, starting with 0.5 mg/kg once a day, for at least 7 days, then increasing the dose up to 1.2 mg/kg/day, based on clinical response and tolerability.

Since atomoxetine was the only ADHD medication available in Italy until methylphenidate was reintroduced on the market in 2007 in our country, it was and still is customary for some Italian clinicians to use atomoxetine as a first-line treatment. Therefore, four types of participants could be identified based on their ADHD pharmacological treatment history: (i) those treated only with methylphenidate; (ii) those treated only with atomoxetine; (iii) those initially started on methylphenidate, and then switched to atomoxetine; and (iv) those who initially took atomoxetine and were then switched to methylphenidate.

2.3 Data Collection

The prescription of ADHD medications in Italy undergoes systematic monitoring, carried out by means of a national register, with compulsory compilation by local reference centers [21, 22]. An active pharmacovigilance system is performed via notification by clinical centers to the Italian Medicines Agency. Data regarding AEs are collected via a structured form, located in a restricted area of the website of the Italian ADHD registry (available upon request), which allows standardization of the procedure across centers. Information about the following AEs is collected via the aforementioned structured form.

(i) Cardiovascular risk, complemented by data obtained via electrocardiogram (ECG), systematically performed for each participant before starting drug therapy and after 6 months. According to the procedure recommended by the Italian Medicines Agency, cardiovascular risk includes any clinically relevant ECG abnormalities (such as bundle branch block), change in heart rate, changes in at least one standard deviation (SD) of systolic or diastolic blood pressure, and lengthening of the QT interval, defined as any prolongation, in absolute value, in relation to the value detected at the screening before the first administration of the drug.

(ii) Hepatic toxicity, complemented by a specific assessment of liver enzymes, bilirubin, ammonia and, if deemed clinically necessary, ultrasound imaging.

(iii) Any neurological disorder, complemented, if needed, by information obtained via electroencephalogram (EEG) and magnetic resonance imaging (MRI).

(iv) Any psychiatric symptomatology, such as change in mood (depression or elation), hallucinations, suicidal ideation, or psychosis

(v) Acute diseases of the skin, such as rash, eczema, itching, or vasculitis.

(vi) Any clinically relevant gastrointestinal events, including vomiting, nausea, diarrhea, constipation, and abdominal pain.

In the present study, AEs were classified as severe if their occurrence was followed by active notification by clinical centers to the Italian Medicines Agency; otherwise, they were labelled as mild. The Italian Medicines Agency requires active notification when an AE results in death, is life-threatening, requires hospitalisation or prolongation of existing inpatients' hospitalisation, results in persistent or significant disability or incapacity, or leads to a congenital anomaly or birth defect [23].

2.4 Statistical Analysis

Categorical descriptive data (such as prevalence of psychiatric comorbidities) were presented as absolute and percentage frequencies, and were analyzed using the Fisher's exact probability test to assess differences between methylphenidate- and atomoxetine-treated participants. Continuous descriptive data (such as age) were presented as means and SDs, and analyzed using the Mann–Whitney *U* test. Incidence rates per 100 person-years (IR_{100PY}) were computed for any type of AE in methylphenidate- and atomoxetine-treated participants, in all children and separately for children with and without psychiatric comorbidities (one or more of ODD, CD, depression, anxiety, learning disorder). Incidence rates were calculated considering days of exposure to methylphenidate or atomoxetine. Data from any participant first exposed to methylphenidate and then switched to atomoxetine (or vice versa) contributed to the calculation of AE incidence rates for both methylphenidate and atomoxetine, in different time periods. Incidence rate ratios (IRRs) were computed as the ratio between the incidence rate in the atomoxetine

group and the corresponding incidence rate in the methylphenidate group, separately for children with and without psychiatric comorbidities. Confidence intervals (CIs) were computed at the 95 % confidence level. Here, CIs for which the lower limit is higher than 1 indicate that atomoxetine significantly increased the risk of AEs with respect to methylphenidate; CIs for which the upper limit is lower than 1 indicate that atomoxetine significantly decreased the risk of AEs with respect to methylphenidate. When there were no events in the reference group of methylphenidate-treated children (with and/or without comorbidities), the corresponding IRRs could not be computed, therefore only the lower level of the 95 % CI was estimated and reported.

Despite the difference between the subjects initially receiving methylphenidate and those treated with atomoxetine in terms of rates of comorbidities (64 vs. 76 %), a much lower difference was observed between subjects actually receiving methylphenidate or atomoxetine with respect to the percentage of exposure time (methylphenidate: 736.1/1026.0 = 72 %; atomoxetine: 528.3/689.8 = 77 %). However, to take into account this difference, even if quite low, incidence rates were computed separately in subjects treated with methylphenidate, with comorbidities (total exposure = 736.1 person years), treated with methylphenidate, without comorbidities (total exposure = 289.9 person years), treated with atomoxetine, with comorbidities (total exposure = 528.3 person years), and treated with atomoxetine treatment, without comorbidities (total exposure = 161.5 person years). In order to control for the possible confounding effect of psychiatric comorbidities, heterogeneity between crude IRRs in children with and without comorbidities was assessed by means of the Chi-square test. The presence/absence of comorbidities was considered a stratifying factor, and the Mantel–Haenszel IRR with the corresponding 95 % CI was computed to estimate the overall adjusted IRR, for all AEs for which heterogeneity Chi-square test was not significant. STATA 8.1 was used for all statistical analyses (StataCorp LP, College Station, TX, USA). Statistical significance was defined as $p < 0.05$ (two-tailed). As discussed in Rothman [24], no correction for multiple comparison was needed.

3 Results

3.1 Description of the Sample

During the planned study period (June 2007–December 2012 [62 months]), a total of 2411 children enrolled in the national registry were pharmacologically treated for ADHD. The mean age of the study population was 10.68 years (SD 2.79) (Table 1). The sample included 2125 males (88.1 %) and 286 females (11.9 %). The majority of children (2041, 84.7 %) received a diagnosis of ADHD combined subtype, 283 (11.7 %) were diagnosed with ADHD inattentive subtype, and 87 (3.6 %) presented with ADHD hyperactive–impulsive subtype.

At enrolment, 1426 (59.1 %) children and adolescents received methylphenidate and 985 (40.9 %) were treated with atomoxetine. The average dose was 18.3 mg/day for methylphenidate and 38.5 mg/day for atomoxetine. The demographic and clinical characteristics of the methylphenidate- and atomoxetine-assigned groups at enrolment are reported in Table 1. Of note, the atomoxetine-assigned group presented with significantly higher rates of psychiatric comorbid disorders (any, ODD, CD, depressive disorders, anxiety disorders, and specific learning disorders) than the methylphenidate-assigned group.

3.2 Adverse Events

Data on AEs after the first dose of treatment were available for a total of 2331 participants (96.7 % of the subjects initially assigned to either methylphenidate or atomoxetine at enrolment). Of these, 1350 and 753 were treated with methylphenidate and atomoxetine, respectively, throughout the entire study period. Ninety participants (7 %) were switched from methylphenidate to atomoxetine, and 138 (18 %) were switched from atomoxetine to methylphenidate.

Overall, 645 patients (26.8 %) experienced at least one mild AE, including 276 (28.0 %) children treated with atomoxetine, and 369 (25.9 %) children treated with methylphenidate. Ninety-five patients (3.9 %) experienced at least one severe AE, including 31 (3.1 %) children treated with atomoxetine, and 64 (4.5 %) children treated with methylphenidate; 49 (51.6 %) of these children (37 in the atomoxetine group and 12 in the methylphenidate group) had medication withdrawn.

Table 2 reports the absolute number and IR_{100PY} of mild AEs in subjects treated with methylphenidate or atomoxetine, stratified by the presence/absence of psychiatric comorbidities. It also reports significant differences in IR_{100PY} between participants treated with methylphenidate and atomoxetine, with and without comorbidities. Considering children without comorbidities, a significantly higher IR_{100PY} in the atomoxetine- versus methylphenidate-treated group was observed for the following mild AEs: weight loss, dyspepsia, and stomach ache. In children with comorbidities, a significantly higher IR_{100PY} in the atomoxetine- versus methylphenidate-treated group was observed for the following mild AEs: decreased appetite, weight loss, abdominal pain, dyspepsia, stomach ache, irritability, mood disorder, and obsessive behaviour.

Crude and Mantel–Haenszel adjusted IRR of mild AEs in methylphenidate- and atomoxetine-treated children, with

Table 1 Demographic and clinical characteristics in the overall sample and in subsamples stratified by assigned treatment (methylphenidate or atomoxetine) at enrolment

		Overall [$N = 2411$]		Treatment assigned at enrolment				
				MPH [$n = 1426$]		ATMX [$n = 985$]		p value
		Mean	SD	Mean	SD	Mean	SD	
Age at enrolment	Total	10.68	2.79	10.55	2.75	10.87	2.84	$T = 0.013$
	Males	10.67	2.78	10.55	2.76	10.83	2.81	$S = 0.385$
	Females	10.80	2.83	10.54	2.66	11.16	3.06	$T*S = 0.351$
Sex	Males	2125	88.1	1247	87.4	878	89.1	0.224
	Females	286	11.9	179	12.6	107	10.9	
ADHD subtype	Inattentive	283	11.7	165	11.6	118	12.0	0.001
	Combined	2041	84.7	1226	86.0	815	82.7	
	Hyperactive	87	3.6	35	2.5	52	5.3	
Comorbidities	No	750	31.1	514	36.0	236	24.0	<0.001
	Yes	1661	68.9	912	64.0	749	76.0	
ODD	No	1470	61.0	935	65.6	535	54.3	<0.001
	Yes	941	39.0	491	34.4	450	45.7	
CD	No	2261	93.8	1366	95.8	895	90.9	<0.001
	Yes	150	6.2	60	4.2	90	9.1	
Depression	No	2280	94.6	1375	96.4	905	91.9	<0.001
	Yes	131	5.4	51	3.6	80	8.1	
Anxiety	No	2082	86.4	1268	88.9	814	82.6	<0.001
	Yes	329	13.6	158	11.1	171	17.4	
Learning disorder	No	1453	60.3	914	64.1	539	54.7	<0.001
	Yes	958	39.7	512	35.9	446	45.3	

ADHD attention-deficit/hyperactivity disorder, *ATMX* atomoxetine, *CD* conduct disorder, *MPH* methylphenidate, *ODD* oppositional defiant disorder, *S* sex, *SD* standard deviation, *T* treatment assigned at enrolment

and without comorbidities, are reported in Table 3. After adjusting for comorbidities, compared with the methylphenidate-treated group, IRRs were significantly higher in the atomoxetine-treated group for the following mild AEs: decreased appetite, weight loss, abdominal pain, dyspepsia, stomach ache, irritability, mood disorder, and dizziness. Overall, the incidence rate ratio of any kind of AEs was significantly higher in the atomoxetine-treated group than in the methylphenidate-treated group.

Table 4 reports details about severe AEs, grouped by system/type. These included five cases of suicidal ideation (only in the atomoxetine group, including one participant with a history of depressive disorder), four cases of hyperbilirubinemia as proxy of hepatic toxicity (three in the atomoxetine group and one in the methylphenidate group), and one case of prolonged QTc in the atomoxetine group. The mean time to onset (SD) of severe AEs was 4.6 (4.4) months in the atomoxetine group and 6.2 (11.5) months in the methylphenidate group ($p = 0.06$); 26.2 % of severe AEs in the atomoxetine group and 52.8 % of those in the methylphenidate group occurred within 1 month of starting treatment. The mean age at onset (SD) of severe AEs was 10.2 (2.9) years for participants in the atomoxetine group and 10.7 (2.9) years for those in the methylphenidate group ($p = 0.41$).

As reported in Table 5, when considering participants without comorbidities, IR_{100PY} was significantly higher in the atomoxetine-treated group versus the methylphenidate-treated group for severe AEs classified in the gastrointestinal system (atomoxetine 5.6; methylphenidate 0.0). In participants with comorbidities, IR_{100PY} was significantly higher in the atomoxetine-treated group versus the methylphenidate group for severe neuropsychiatric AEs (atomoxetine 4.0; methylphenidate 1.4). Overall, the IRR of any kind of severe AE was significantly higher in atomoxetine recipients than methylphenidate recipients (IR_{100PY}: atomoxetine 12.18, methylphenidate 3.51; IRR 3.47, 95 % CI 2.35–5.13).

Crude and Mantel–Haenszel adjusted IRR of severe AEs in methylphenidate- and atomoxetine-treated children, with and without comorbidities, are reported in Table 6. After controlling for the effect of psychiatric comorbidities, compared with the methylphenidate-treated group, IRRs were significantly higher in the atomoxetine-treated group for severe AEs classified as 'gastrointestinal', 'neuropsychiatric', and 'cardiovascular'.

Table 2 Number of mild adverse events and IR_{100PY} in methylphenidate- and atomoxetine-treated children, with and without psychiatric comorbidities

	Comorbidities							
	MPH				ATMX			
	No (289.9)		Yes (736.1)		No (161.5)		Yes (528.3)	
	n	IR_{100PY}	*n*	IR_{100PY}	*n*	IR_{100PY}	*n*	IR_{100PY}
Anorexia	3	1.0	9	1.2	1	0.6	7	1.3
Decreased appetite	91	31.4	213	**28.9**	51	31.6	199	**37.7**
Weight loss	7	**2.4**	37	**5.0**	21	**13.0**	96	**18.2**
Abdominal pain	7	2.4	22	**3.0**	7	4.3	39	**7.4**
Dyspepsia	3	**1.0**	9	**1.2**	11	**6.8**	28	**5.3**
Stomach ache	7	**2.4**	17	**2.3**	15	**9.3**	51	**9.7**
Headache	32	11.0	62	8.4	21	13.0	61	11.5
Irritability	36	12.4	67	**9.1**	26	16.1	88	**16.7**
Mood disorder	21	7.2	49	**6.7**	15	9.3	58	**11.0**
Insomnia	17	5.9	31	4.2	3	1.9	34	6.4
Obsessive behaviour	7	2.4	6	**0.8**	1	0.6	13	**2.5**
Hallucinations	0	0.2	2	0.3	1	0.9	2	0.5
Tic	12	4.1	27	3.7	3	1.9	27	5.1
Dizziness	1	0.3	5	0.7	3	1.9	10	1.9
Tachycardia	7	2.4	24	3.3	6	3.7	25	4.7
Hypertension	1	0.5	8	1.2	2	1.5	0	0.1
Hypotension	0	0.2	3	0.5	3	2.2	6	1.2

IR_{100PY} significantly different between MPH- and ATMX-treated children (with and without comorbidities) are reported in bold

ATMX atomoxetine, *IR_{100PY}* incidence rates per 100 person-years, *MPH* methylphenidate

4 Discussion

We assessed the type of AEs, both mild and severe, and compared their prevalence in children with ADHD treated with methylphenidate or atomoxetine, drawing on data from a national registry for phase IV pharmacovigilance. To our knowledge, this is one of the largest available databases to evaluate the safety of medications for ADHD, involving approximately 90 ADHD centres.

The type of AEs that we observed in our study is in line with what has been reported in the previous literature [12]. Rather than discussing each individual AE, for ease of presentation we discuss the main AEs, grouping them by category/system.

With regard to cardiovascular events, we found ten cases (nine mild and one severe) of prolonged QTc (four with atomoxetine and six methylphenidate). However, importantly, all observed prolonged QTc intervals were not clinically significant since the prolongations of QTc interval were less than 450 ms, which represents the pathologic cutoff point. In addition, among the severe AEs, we observed other ECG abnormalities, including six cases of tachycardia (four with atomoxetine and two with methylphenidate) and one case of right bundle branch block in a methylphenidate-treated subject, but none of these were clinically significant. We also observed three cases of serious hypertension (one in the atomoxetine-treated participants and two in the methylphenidate-treated participants) and one case (treated with atomoxetine) of relevant hypotension that required drug withdrawal. A number of cases of hypertension (two with atomoxetine and nine with methylphenidate) and hypotension (nine with atomoxetine and three with methylphenidate) were reported as mild AEs and, rather than drug suspension, required only a dosage adjustment. Our findings are in line with the results of a systematic review of the European ADHD Guidelines Group (EAGG) [12], which concluded that there is no evidence supporting that ADHD drugs are associated with significant changes in electrocardiographic values, including QT interval. The EAGG review also concluded that psychostimulant medications and atomoxetine may slightly increase blood pressure (average increase systolic 1–4 mmHg; diastolic 1–2 mmHg) and heart rate (average increase 1–2 beats per min), but in a minority of individuals (5–15 %) this increase may be above the 95th percentile. Importantly, data from the Multimodal Treatment of ADHD (MTA) study at 12-year follow-up showed no systematic significant increase of blood pressure with psychostimulant treatment throughout the study period, although psychostimulants did have a persistent adrenergic effect increasing heart rate [25].

Table 3 Crude and Mantel–Haenszel adjusted incidence rate ratios of mild adverse events in the methylphenidate and atomoxetine groups, with and without comorbidities

	ATMX vs. MPH			ATMX vs. MPH			Mantel–Haenszel			
	No comorbidities			Comorbidities			Heterog *p* value	IRR	95 % CI	
	IRR	95 % CI		IRR	95 % CI					
		Lower	Upper		Lower	Upper			Lower	Upper
Anorexia	0.60	0.06	5.75	1.08	0.40	2.91	0.634	0.98	0.40	2.40
Decreased appetite	1.01	0.71	1.42	**1.30**	**1.07**	**1.58**	0.199	**1.22**	**1.03**	**1.45**
Weight loss	**5.38**	**2.29**	**12.67**	**3.62**	**2.47**	**5.28**	0.402	**3.86**	**2.73**	**5.46**
Abdominal pain	1.80	0.63	5.12	**2.47**	**1.47**	**4.17**	0.592	**2.33**	**1.46**	**3.71**
Dyspepsia	**6.58**	**1.84**	**23.59**	**4.34**	**2.05**	**9.19**	0.579	**4.83**	**2.54**	**9.21**
Stomach ache	**3.85**	**1.57**	**9.43**	**4.18**	**2.41**	**7.24**	0.877	**4.09**	**2.56**	**6.54**
Headache	1.18	0.68	2.04	**1.37**	**0.96**	**1.95**	0.649	**1.31**	**0.97**	**1.77**
Irritability	1.30	0.78	2.15	**1.83**	**1.33**	**2.52**	0.256	**1.66**	**1.27**	**2.17**
Mood disorder	1.28	0.66	2.49	**1.65**	**1.13**	**2.41**	0.518	**1.55**	**1.12**	**2.16**
Insomnia	0.32	0.09	1.08	1.53	0.94	2.49	**0.013**			
Obsessive behaviour	0.26	0.03	2.08	**3.02**	**1.15**	**7.94**	**0.018**			
Hallucinations	5.38	0.22	132.18	1.39	0.24	8.04	0.453	1.98	0.45	8.64
Tic	0.45	0.13	1.59	1.39	0.82	2.38	0.095	1.13	0.70	1.83
Dystonic mood	0.60	0.02	14.69	3.25	0.48	22.02	0.351	2.03	0.44	9.38
Dizziness	5.38	0.56	51.76	**2.79**	**0.95**	**8.15**	0.603	**3.17**	**1.21**	**8.29**
Tachycardia	1.54	0.52	4.58	1.45	0.83	2.54	0.926	1.47	0.89	2.42
Hypertension	2.99	0.40	22.65	0.08	0.01	1.42	**0.013**			
Hypotension	12.56	0.65	243.23	2.59	0.71	9.49	0.310	**3.68**	**1.18**	**11.50**

IRRs are computed as ratio between person-years incidence rates of ATMX vs. MPH. Significant IRRs and the corresponding 95 % CI are reported in bold

Heterog *p* value refers to the significance level of the test for heterogeneity among strata

ATMX atomoxetine, *CI* confidence interval, *IRR* incidence rate ratio, *MPH* methylphenidate

Regarding neuropsychiatric AEs, the most serious was suicidal ideation, which was, however, rare (frequency: 0.51 % of cases, 5/985). No complete suicides were observed. Importantly, the definition of 'suicidal ideation' was standardized across centers, which limited the likelihood of bias and heterogeneity in reporting 'suicidal ideation'. Of note, all cases occurred during treatment with atomoxetine. Although the observed frequency of suicidal ideation was more frequent than expected on the basis of FDA warning [26], overall our findings are once again consistent with the EAGG systemic review, according to which suicide-related events rarely occur with ADHD drug treatment. Importantly, the EAGG pointed out that there is little compelling evidence to suggest that the rate of suicide-related events in children treated with ADHD drugs is greater than the expected rate in the general population.

Among hepatic AEs, hyperbilirubinemia occurred almost exclusively with atomoxetine (three cases vs. one with methylphenidate). This is an AE that has been noted in previous pharmacovigilance reports of atomoxetine tolerability and safety [27]. Although hyperbilirubinemia was reported in a relatively small number of participants, it is a potentially very severe AE, which may lead to liver failure resulting in death or the need for a liver transplant.

Seizures occurred in a limited number of patients (three in the methylphenidate group and two in the atomoxetine group). In four cases they were generalized, and in one case (treated with atomoxetine) they were focal/partial. They all resolved with drug discontinuation, except for one case who presented with previous absence seizures and who was successfully treated with valproate. With regard to seizures, the EAGG [12] concluded that, in patients with well-controlled epilepsy, methylphenidate is associated with a low risk for seizure, whilst it deemed that evidence for atomoxetine is still too limited to draw firm conclusions.

Whilst AEs (mild or severe) were observed both in methylphenidate- and atomoxetine-treated participants, an important finding of our study is that they were significantly more frequent in the latter. Importantly, after controlling for comorbid psychiatric disorders, this difference did remain significant for decreased appetite, weight loss, abdominal pain, dyspepsia, stomach ache, irritability,

Table 4 Severe adverse events in the atomoxetine and methylphenidate groups

Severe AE	ATMX						MPH					
	No. of events	IR_{100PY}	Gender	Age (years)	Dis	TTO	No. of events	IR_{100PY}	Gender	Age (years)	Dis	TTO
Gastrointestinal												
Gastrointestinal disease	10	1.45	M	12	Yes	1	6	0.58	M	13	Yes	11
			M	7	Yes	1			M	7	No	Early
			M	9	No	1			M	7	No	Early
			M	10	No	7			M	8	No	Early
			M	10	No	2			M	11	No	Early
			M	6	Yes	6			F	16	No	Early
			M	7	Yes	3						
			M	7	Yes	3						
			M	6	Yes	1						
			M	9	No	8						
Eating disorders	11	1.59	F	10	Yes	1	1	0.10	M	12	Yes	2
			M	7	Yes	6						
			F	11	Yes	1						
			M	13	No	1						
			M	6	Yes	6						
			M	6	No	6						
			M	14	No	3						
			F	9	Yes	2						
			M	8	No	9						
			M	9	Yes	4						
			M	8	No	9						
Hypernatremia	1	0.14	M	11	Yes	Early						
Liver												
Hyperbilirubinemia	3	0.43	M	8	Yes	10	1	0.10	M	14	Yes	1
			M	16	No	7						
			M	13	Yes	3						
Hepatomegaly	1	0.14	M	14	Yes	7						
Suicidal ideation	5	0.72	M	10	Yes	9						
			M	10	Yes	5						
			F	8	Yes	6.5						
			M	14	Yes	24						
			F	13	Yes	4						
Neuropsychiatric												
Seizures	2	0.29	M	14	Yes	11	3	0.29	M	13	Yes	3
			M	6	Yes	7			M	10	No	8
Impotence	1	0.14	M	17	No	1						
Aphasia							1	0.10	M	9	Yes	44
Neurogenic bladder	1	0.14	F	7	Yes	2						
Headache	5	0.72	F	11	Yes	1	3	0.29	M	14	No	Early
			M	7	Yes	2			F	16	No	Early
			M	10	No	2			M	15	No	Early
			M	11	No	Early						
			M	15	No	4						

Table 4 continued

Severe AE	ATMX						MPH					
	No. of events	IR_{100PY}	Gender	Age (years)	Dis	TTO	No. of events	IR_{100PY}	Gender	Age (years)	Dis	TTO
Neurological disorder	2	0.29	M	13	Yes	17	2	0.19	M	11	Yes	Early
			F	6	No	4			M	9	Yes	6
Sleep disorders	3	0.43	F	11	Yes	1	1	0.10	M	11	Yes	2
			M	10	No	7						
			M	13	No	1						
Asthenia	1	0.14	M	8	No	4						
Psychiatric disorder	6	0.87	M	13	Yes	19	5	0.49	M	9	Yes	Early
			M	9	Yes	10			M	7	Yes	Early
			M	13	Yes	2			M	11	Yes	Early
			M	9	Yes	8			M	7	Yes	Early
			M	9	Yes	4			M	8	Yes	Early
			M	10	Yes	2						
Mood disorders	4	0.58	M	10	No	4	1	0.10	M	10	Yes	Early
			M	15	No	1						
			F	8	Yes	1						
			M	9	Yes	3						
Hallucinations	2	0.29	M	10	No	4						
			M	10	Yes	Early						
Cardiovascular												
Prolonged QTc	1	0.14	M	8	Yes	4						
Tachycardia	4	0.58	M	6	Yes	2	2	0.19	F	7	Yes	12
			M	6	Yes	5			M	16	No	Early
			M	10	Yes	Early						
			M	7	Yes	6						
Severe hypertension	1	0.14	F	16	No	4	2	0.19	M	11	Yes	16
									M	14	Yes	5
Severe hypotension	1	0.14	M	14	Yes	2						
Cardiovascular disease	3	0.43	M	12	Yes	5						
			M	8	Yes	4						
			M	6	Yes	5						
Vasovagal reaction	1	0.14	M	13	Yes	6						
Right bundle branch block							1	0.10	M	12	Yes	Early
Hematological												
Epistaxis							1	0.10	F	12	No	6
Thrombocytopenia	1	0.14	M	15	Yes	5						
Immunological												
Allergy	1	0.14	M	9	Yes	Early						
Rash	3	0.43	M	7	Yes	6						
			M	9	Yes	2						
			M	12	Yes	Early						
Autoimmune disease							1	0.10	M	8	Yes	9

Table 4 continued

Severe AE	ATMX						MPH					
	No. of events	IR_{100PY}	Gender	Age (years)	Dis	TTO	No. of events	IR_{100PY}	Gender	Age (years)	Dis	TTO
Dermatological												
Skin disorders	7	1.01	M	9	Yes	18	3	0.29	M	6	Yes	Early
			M	12	Yes	10			F	8	No	18
			M	7	Yes	6			F	8	No	15
			M	9	Yes	5						
			M	10	Yes	Early						
			F	12	No	Early						
			M	17	Yes	7						
Alopecia							1	0.10	M	12	No	51
Eye disease	1	0.14	F	12	No	Early	1	0.10	M	12	Yes	Early

AE adverse event, *ATMX* atomoxetine, *Dis* Discontinuation, *F* female, IR_{100PY} incidence cates per 100 person-years, *M* male, *MPH* methylphenidate, *TTO* time to onset (months)

Table 5 Number of severe adverse events and incidence rates per 100 person-years in atomoxetine- and methylphenidate-treated children, with and without comorbidities

	ATMX				MPH			
	Comorbidities				Comorbidities			
	No (161.5)		Yes (736.1)		No (289.9)		Yes (528.3)	
	n	IR_{100PY}	*n*	IR_{100PY}	*n*	IR_{100PY}	*n*	IR_{100PY}
Gastrointestinal	9	**5.6**	13	2.5	0	**0.0**	7	1.0
Liver	2	1.2	2	0.4	1	0.3	0	0.0
Suicidal ideation	1	0.6	4	0.8	0	0.0	0	0.0
Neuropsychiatric	6	3.7	21	**4.0**	6	2.1	10	**1.4**
Cardiovascular	6	3.7	5	0.9	2	0.7	3	0.4
Hematological	1	0.6	0	0.0	0	0.0	1	0.1
Immunological	1	0.6	3	0.6	0	0.0	1	0.1
Dermatological	3	1.9	4	0.8	1	0.3	3	0.4
Eye disease	0	0.0	1	0.2	1	0.3	0	0.0

IR_{100PY} significantly different between MPH- and ATMX-treated children (with and without comorbidities) are reported in bold

ATMX atomoxetine, IR_{100PY} incidence rates per 100 person-years, *MPH* methylphenidate

mood disorder and dizziness (mild AEs), as well as for severe gastrointestinal, neuropsychiatric, and cardiovascular events (severe AEs).

We also observed that mild AEs usually occurred after a shorter time of exposure to atomoxetine than methylphenidate. On the basis of the pharmacokinetics, it is not clear why the AEs occurred in patients treated with atomoxetine after a shorter exposure to the drug compared with patients with methylphenidate.

The atomoxetine non-comorbid group displayed low rates of insomnia, suggesting a potential benefit of atomoxetine for insomnia, as pointed out by the EAGG [12].

We note that our study also explored growth delay, defined as (i) height less than or equal to −3 SD, or less than or equal to −2 SD plus height velocity/year less than −1.0 SD for age and gender at 6 months or 0.5 after 2 years; (ii) height less than or equal to −1.5 SD plus height velocity/year less than −1.0 SD for age and gender at 6 months or 0.5 after 2 years; or (iii) height velocity/year <2 SD or −1.5 after 2 years [28]. Indeed, 16 cases of mild growth delay were notified (12 patients treated with methylphenidate and 4 with atomoxetine). In none of these cases was the growth delay more than 2 SD (data available upon request). However, these results should be considered with caution; a longer follow-up period might reveal more reliable data on growth. The EAGG concluded that there is evidence of significant psychostimulant-associated height and weight deficits (length of treatment 0.5–3.5 years). The deficit in height tends to increase with time, but the rate of deficit tends to decrease over time for height and weight,

Table 6 Crude and Mantel–Haenszel adjusted incidence rate ratios of severe adverse events in the methylphenidate and atomoxetine groups, with and without comorbidities

	ATMX vs. MPH						Mantel–Haenszel			
	No comorbidities			Comorbidities						
	IRR	95 % CI		IRR	95 % CI		Heterog *p* value	95 % CI		
		Lower	Upper		Lower	Upper		IRR	Lower	Upper
Severe adverse events										
Gastrointestinal		**3.53**	–	**2.59**	**0.96**	***7.66***		**4.56**	**2.00**	**10.43**
Liver	3.58	0.19	211.22		0.26	–		6.83	0.71	66.08
Suicidal ideation		0.05	–		**0.92**	–				
Neuropsychiatric	1.79	0.48	6.70	**2.93**	**1.32**	**6.96**	0.478	**2.54**	**1.36**	**4.74**
Cardiovascular	**5.37**	**0.96**	**54.41**	2.32	0.45	14.96	0.444	**3.43**	**1.21**	**9.76**
Hematological		0.05	–	0.00	0.00	54.36				
Immunological		0.05	–	4.18	0.34	219.53		5.72	0.66	49.19
Dermatological	5.37	0.43	281.93	1.86	0.31	12.69	0.443	2.64	0.79	8.87
Eye disease	0.00	0.00	69.81		0.04	–				

IRRs are computed as ratio between person-years incidence rates of ATMX vs. MPH. Significant IRRs and the corresponding 95 % CI are reported in bold

When there were no events in the reference group of MPH-treated children (without and/or with comorbidities), the corresponding IRRs could not be computed, and only the lower level of the 95 % CI could be estimated

Heterog *p* value refers to the significance level of the test for heterogeneity among strata

ATMX atomoxetine, *CI* confidence interval, *IRR* incidence rate ratio, *MPH* methylphenidate

suggesting a tendency for the deficit to attenuate with time. As for atomoxetine, a meta-analysis [29] found that the mean actual weight and height at 24 months were 2.5 kg and 2.7 cm lower than the expected values, respectively, based on baseline weight and height percentile. The difference mostly occurred during the first 18 months of treatment.

Taken together, our results are at odds with two meta-analyses of RCTs [13, 14] that, as reported above, showed that methylphenidate and atomoxetine have similar profiles in terms of all-cause discontinuation and incidence of AEs, as well as with individual studies reporting a significantly greater incidence of decreased appetite and insomnia [15], weight loss and heart rate increase [16] with methylphenidate. We hypothesize that the differences between our results and the conclusions of these studies are accounted for by the different design (naturalistic in our study vs. RCTs in the meta-analyses and previous individual studies), as well as by the longer duration of our study compared with standard available RCTs.

Our results should be considered in light of the study limitations. First, this was not a randomized study, therefore differences between participants treated with methylphenidate and those who took atomoxetine may have accounted for the findings. However, it is worthy to note that significant differences in terms of prevalence of mild and severe AEs did stand, even after controlling for the effect of psychiatric comorbidities. Whilst the lack of randomization could be considered as a limitation, the naturalistic design of our study is, at the same time, its strength, allowing for an understanding of the differences in prevalence of AEs in a 'real-world' clinical context. Second, data on AEs were not available for all participants at follow-up visits following the baseline assessment and treatment assignment. However, this only occurred for 3.3 % of participants, therefore it is unlikely that our results were not representative of the entire sample. Third, our study could not be informative with regard to AEs occurring with extended-release formulations of methylphenidate as well as with other class of ADHD drugs since these were not available in Italy during the study period. Fourth, the average doses of methylphenidate and atomoxetine were rather low for usual standards of treatment, reflecting the caution to use ADHD drugs in Italy. However, we do not consider this a confounding factor since the average dose was low for both medications. Fifth, the naturalistic design did not allow to assess if children were adequately titrated, for both medications. Sixth, data on validity and reliability of measures across centres are not available. Finally, the study did not include a control group of healthy participants. However, our study focus was on the comparison of the prevalence of AEs between methylphenidate- and atomoxetine-treated participants rather than on the prevalence of AEs in children treated with ADHD and healthy controls.

As well as the naturalistic design with no exclusion criteria, study strengths were the sample size and the structured and standardized way of AE coding and data collection.

5 Conclusions

Our naturalistic postmarketing phase IV pharmacovigilance observational study showed that while mild and severe AEs were observed in children treated with methylphenidate and in those treated with atomoxetine, those who received atomoxetine were significantly more likely to experience AEs.

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Compliance with Ethical Standards

Disclosures of potential conflict of interest Prof. Curatolo has received honoraria from Shire for participation in Advisory Board Meetings. Drs. Cortese, Panei, Arcieri, Germinaro, Capuano, Margari, and Chiarotti declare no competing interests.

Research involving human participants The study was approved by the Ethic Committee of the Italian National Institute of Health in 2005. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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PHARMACOKINETICS AND DISPOSITION

Therapeutic drug monitoring of second-generation antipsychotics in pediatric patients: an observational study in real-life settings

Marco Pozzi[1] · Dario Cattaneo[2] · Sara Baldelli[2] · Serena Fucile[2] · Annalisa Capuano[3] · Carmela Bravaccio[4] · Liberata Sportiello[3] · Silvana Bertella[1] · Fabiana Auricchio[3] · Renato Bernardini[5] · Carmen Ferrajolo[3] · Giuseppe Guastella[5] · Elisa Mani[1] · Carla Carnovale[2] · Simone Pisano[6] · Concetta Rafaniello[3] · Maria Pia Riccio[6] · Renata Rizzo[7] · Maria Grazia Scuderi[7] · Serena Sperandeo[6] · Laura Villa[1] · Antonio Pascotto[6] · Massimo Molteni[1] · Francesco Rossi[3] · Sonia Radice[2] · Emilio Clementi[1,8]

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Abstract

Purpose Available guidelines on therapeutic drug monitoring of second-generation antipsychotics were designed for adults; therefore, they cannot be transferred as such in pediatric patients, who may have different drug absorption, distribution, metabolism, and elimination. Moreover, available tools that guide dosing in neuropsychiatric pediatric patients are scant, leading to the possibility of reduced efficacy and/or increased risks of toxicity. Here we describe the results of observational therapeutic drug monitoring conducted in three pediatric neuropsychiatry units across Italy in 2012–2014, with the following aims: (1) to describe the distribution of plasma concentrations of second-generation antipsychotics in our pediatric patients and (2) to identify clinical covariates associated with plasma drug levels.

Methods Five hundred fifty-six plasma trough concentrations of the second-generation antipsychotics risperidone (plus 9-hydroxy-risperidone), aripiprazole, olanzapine, and quetiapine were measured from 172 pediatric outpatients overall. The distribution of drug concentrations was described and correlated with drug doses and clinical variables.

Results Risperidone plasma levels were lower than in adults (median 13.6 ng/ml), with a high inter-patient (78.9 %) but lower intra-patient (34.2 %) variability. In multiple regression analyses, risperidone plasma levels depended only on drug dose ($p < 0.001$). Aripiprazole plasma levels were similar to those described in adults (median 165.8 ng/ml) and were widely distributed, with an inter-patient variability of 81.1 %, while the intra-patient variability was much lower (29.3 %). Multiple regression analyses indicated that aripiprazole plasma levels

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✉ Emilio Clementi
emilio.clementi@unimi.it

[1] Scientific Institute IRCCS Eugenio Medea, 23842 Bosisio Parini, Lecco, Italy

[2] Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences L. Sacco, L. Sacco University Hospital, Università di Milano, 20157 Milan, Italy

[3] Campania Regional Centre for Pharmacovigilance and Pharmacoepidemiology, Department of Experimental Medicine, Second University of Naples, 80131 Naples, Italy

[4] Department of Translational Medical Sciences, University Federico II of Naples, 80131 Naples, Italy

[5] Department of Clinical and Molecular Biomedicine, Section of Pharmacology and Biochemistry, School of Medicine, University of Catania, 95131 Catania, Italy

[6] Department of Mental and Physical Health and Preventive Medicine, Child and Adolescent Psychiatry Division, Second University of Naples, 80131 Naples, Italy

[7] Child and Adolescent Neuropsychiatry, Department of Medical and Paediatric Sciences, School of Medicine, University of Catania, 95131 Catania, Italy

[8] Unit of Clinical Pharmacology, CNR Institute of Neuroscience, Department of Biomedical and Clinical Sciences, L. Sacco University Hospital, Università di Milano, 20157 Milan, Italy

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were influenced by the daily doses ($p < 0.001$) and by the number of concomitant drugs ($p < 0.01$).
Conclusion Our study described the distribution of plasma levels of SGAs in a real-life setting involving pediatric patients, significantly increasing the amount of available data for this fragile population. If confirmed in larger dataset, these data may contribute to the definition of optimal therapeutic window for risperidone and aripiprazole plasma levels in pediatric patients.

Keywords Therapeutic drug monitoring · Pharmacokinetics · Risperidone · Aripiprazole · Second-generation antipsychotics

Introduction

The efficacy and safety of second-generation antipsychotics (SGAs) depend, among many factors, also on drug doses, plasma levels, and the use of concomitant drugs [1–8]. Therapeutic drug monitoring (TDM) may thus be useful to direct therapy [9]. However, its application is currently limited: available guidelines have been formulated for a few usage indications and only for adult patients [10]. Moreover, a recent review evidenced a lack of data in the field, such that conclusions can be drawn only regarding clozapine [11]. Little is known about the TDM of SGAs in pediatric patients, and scant information is available on their off-label and long-term use [12–17]. Risperidone is the main SGA used in-label in pediatric patients, for indications identical to those of the adults, plus for aggressive behavior in the context of cognitive impairment (EMA) or autism (FDA). Suggested pediatric doses range from 0.25 to 1–2 mg/day, according to the patient's response [18, 19]. Actually, doses are prescribed up to 3–4 mg/day, with unverified risks and benefits. Moreover, little data are available on risperidone plasma levels in pediatric patients. One study evaluated trough levels (C_t) from 100 patients and found that risperidone plasma concentrations depended on drug doses and sexual development [20]; two studies of small pediatric populations reported no association between C_t and either efficacy or the occurrence of adverse drug reactions (ADRs) [21, 22]. One study, conducted on more than 100 patients, found relationships between C_t and doses, reporting that patients with worsened Clinical Global Impression-Severity (CGI-S) scores had higher C_t [23]. Aripiprazole, another SGA frequently used for schizophrenia and mania in pediatrics, was recently authorized also for irritability associated with autism [24, 25]. Its recommended pediatric doses range from 2 to 15–30 mg/day. Aripiprazole has long been used off-label for Tourette's syndrome [26, 27] and to substitute risperidone in patients experiencing excessive weight gain or hyperprolactinemia [28]. Despite extensive use, information on pediatric plasma levels is scant: only one study reported C_t data [29]. Olanzapine [30, 31] and quetiapine [32, 33] are indicated in adolescents for schizophrenia and mania, but they are used off-label when previous SGAs have failed [34]. Only one report exists on olanzapine C_t in pediatric patients [35], which described plasma levels with respect to administered doses and found high intra-patient variability. Quetiapine was also investigated only in one pediatric study that found no relationship of either efficacy or safety with C_t [36].

In order to increase the available information, we herein applied TDM of risperidone, aripiprazole, olanzapine and quetiapine in neuropsychiatric pediatric patients from real-life clinical settings, aiming to (1) describe the distribution of SGA doses and related C_t in pediatric patients and (2) identify covariates affecting the C_t of SGAs in pediatric patients.

Materials and methods

Study participants and data collection

This observational therapeutic drug monitoring study stems from an active pharmacovigilance project on the use of SGAs in children and adolescents, carried out from March 2012 to March 2014, by three neuropsychiatry and two pharmacology units. Inclusion criteria for this pharmacovigilance project were as follows: less than 18 years of age; assume SGAs in scheduled administration (use as needed was not investigated); an informed consent signed by the parents. The enrolled subjects followed routine clinical procedures for outpatients, with follow-up controls every 3 months, from which data were collected for research purposes. Among all the patients we followed, those sampled at least once for TDM were included in the present study. Data collected for the present study comprised patients' age, gender, weight, height; neuropsychiatric diagnoses (according to DSM-IV TR); indicators of metabolic hepatic function, including serum levels of aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), and, as an indicator of renal function, creatinine; information on drug therapy, including doses of SGAs and concomitant medications; and C_t of SGAs under study.

Therapeutic drug monitoring

In order to perform TDM, an additional volume of blood (3–4 ml) was taken at the steady state (i.e., after that the patient regularly assumed the drug at a fixed dose for a time period of at least five drug half-lives). Sampling usually occurred between 8 a.m. and 9 a.m. prior to neuropsychiatric visits, before the patient took his/her daily drug dose, always at the same time with a window of ±20 min (thus yielding trough levels). Each center collected samples for TDM according to

its clinical practice; therefore, the number of samplings per patient was not pre-determined, i.e., patients who needed more visits or remained in study longer had more samples taken for TDM. The samples were handled on ice, and plasma was separated by centrifugation and stored at −20 °C until analysis at the centralized pharmacokinetics laboratory of one pharmacology unit. The C_t of risperidone (plus 9-OH-risperidone, in accordance with the AGNP consensus guidelines [10]–hereafter simply called "risperidone"), aripiprazole, olanzapine, and quetiapine were quantified using liquid chromatography/tandem mass spectrometry methods [37–39]. The lower limit of quantification (LLOQ) of the method was 5 ng/ml for all analytes (see Supplemental Table 1 for performance details). The performance of these methods was tested during each analytical run using internal quality controls and blinded samples sent monthly as part of the LCG Standard Proficiency Testing Schemes for Psychoactive Drugs (http://www.lgcpt.com/default.aspx). TDM results were returned 1 to 8 weeks after each visit; therefore, dose adjustment was carried out only according to clinicians' decision and was blinded with respect to TDM results.

Data analysis

Data were collected matching data from outpatient visits with exams, based on the date of result delivery. Datasets were verified and incomplete entries were removed (n = 22). For descriptive purposes, categorical variables were shown as numbers and percentages. Two-tailed χ^2 or Fisher's exact tests were performed as allowed by the sample size. Continuous variables were presented as means ± standard deviations (SD), and also as medians with interquartile range (IQR). Histograms were used to describe their distribution. The normality of distributions was assessed with the d'Agostino-Pearson test. Coefficients of variability were calculated as SD/mean on all TDMs for inter-patient variability. For intra-patient variability, calculations were carried out on sets of TDMs from individual patients with at least three determinations made at the same dose, daily fractions, and timing of intake. Univariate relationships were investigated by linear correlations and multivariate relationships with multiple regressions, among these variables: C_t and total daily SGA doses (or alternatively C_t/dose); weight and height; gender; age; serum transaminases AST, ALT, and GGT; serum creatinine; number of concomitant drugs; dose of each concomitant drug; use of first-generation antipsychotics (FGAs); use of selective serotonin reuptake inhibitors (SSRIs); and use of antiepileptic drugs (AEDs). Only variables that are significantly associated with the dependent variable in univariate analyses were included in multivariate models. For all statistical analyses, p values <0.05 (two-tailed) were considered significant. Statistical analyses were conducted using SPSS version 22 (IBM, Chicago, IL, USA).

Results

Study sample

Patients were 13.9 ± 2.3 years of age and 80.1 % were males (additional information in Table 1). Therapeutic indications of SGAs in these pediatric patients comprised disruptive behavioral disturbances, associated with autism spectrum disorders or intellectual disability (59.9 %), or tic disorders/Tourette's syndrome (15.9 %); infrequent indications comprised psychotic spectrum disorders (5.1 %) and ADHD (5.6 %). All SGAs were used in oral, immediate-release formulations. Overall, 172 patients were sampled for TDM and included in this study, with 556 total drug assessments. A total of 132 patients (76.7 %) were sampled more than once and 93 (54.1 %) more than twice. Plasma levels of risperidone (given as the sum of risperidone plus 9-OH-risperidone concentrations, hereafter simply called risperidone) were sampled during polytherapy in 25.5 % cases, those of aripiprazole in 13.1 %. In accordance with the AGNP consensus guidelines [10], most concomitant medications were judged to have only mild effects on metabolism, while potent inducers or inhibitors were scantly used: they were carbamazepine, an inducer of CYP3A4, fluoxetine, levomepromazine, and paroxetine, inhibitors of CYP2D6. Details on the number of determinations and patients regarded by each concomitant drug are shown in Table 2.

Plasma levels below the lower limit of quantification

Trough drug levels were below the LLOQ (BLQ) in 84 samples (15.1 %); aripiprazole was BLQ in 0.9 % (1) samples, as compared to 19.3 % (81) risperidone ($p < 0.001$) and 18.2 % (2) olanzapine ($p = 0.02$). Risperidone dose was less than 1 mg in 55.6 % patients with levels BLQ, while 29.6 % received 1–1.75 mg/day and 14.8 % took more. The average risperidone dose in patients with drug levels BLQ was 1.0 ± 0.8 mg/day, significantly lower as compared to 1.9 ± 1.2 mg/day in patients with quantifiable C_t ($p < 0.001$). The samples with drug levels BLQ were excluded from all further analyses in order to avoid possible biases.

Distribution of risperidone doses and plasma trough concentrations

Averages and medians regarding risperidone are presented in Table 3. As shown in Supplemental Fig. 1a, 13.6 % risperidone doses were below 1 mg/day, the majority being 1–1.75 mg/day (38.6 %) or 2–2.75 mg/day (30.1 %), while 17.8 % were 3 mg/day or more. The distribution of risperidone C_t (Supplemental Fig. 1b) was predominantly between 5–9 and 10–14 ng/ml (respectively, 25.0 and 28.0 %); 15.2 % C_t were between 15 and 19 ng/ml, 28.3 % were above 19 ng/ml.

Table 1 Description of the study population

	Unit	Risperidone	Aripiprazole	Olanzapine	Quetiapine
C_t measurements		420	114	11	11
Patients		139	47	6	5
Gender (males)		120 (86.3 %)	28 (59.6 %)	5 (83.3 %)	5 (100 %)
Age	years	13.3 ± 2.9; 12.0 (4.8)	15.5 ± 2.4; 14.9 (2.7)	15.9 ± 2.2; 15.2 (0.6)	13.9 ± 1.3; 12.6 (2.4)
Weight	kg	53.5 ± 19.0; 52.5 (28.4)	71.5 ± 22.9; 65 (31.8)	71.2 ± 14.5; 79.6 (29.1)	49.4 ± 4.0; 52.4 (2.2)
Height	cm	150.1 ± 17.2; 152.9 (27.2)	158.4 ± 13.1; 157.1 (11.0)	164.1 ± 13.3; 163 (24.3)	148.6 ± 6.2; 147.9 (4.1)
AST	units/l	22.9 ± 6.8; 22 (8)	22.0 ± 6.9; 21 (11)	22.1 ± 4.8; 20 (9)	23.3 ± 5.8; 24 (9)
ALT	units/l	23.0 ± 16.9; 17.5 (17)	29.9 ± 18.4; 27 (26)	31.2 ± 11.6; 27 (12)	31.7 ± 15.4; 31.5 (26)
GGT	units/l	16.1 ± 23.7; 12 (6)	21.9 ± 19.6; 12 (13)	40.8 ± 42.0; 23 (15)	18.2 ± 2.9; 17 (2)
Creatinine	mg/dl	0.59 ± 0.17; 0.53 (0.21)	0.67 ± 0.19; 0.61 (0.28)	0.78 ± 0.14; 0.77 (0.25)	0.56 ± 0.11; 0.43 (0.14)

C_t measurements and patients are reported as numbers; gender is reported both as numbers and percentages. Continuous measures are shown as means with standard deviations and as medians with interquartile ranges within brackets

C_t trough plasma levels, *AST* aspartate transaminase, *ALT* alanine transaminase, *GGT* gamma-glutamyl transpeptidase

Table 2 Description of concomitant medications

	Risperidone		Aripiprazole		Olanzapine		Quetiapine	
	No. det	No. pat	No. det	No. pat	No. det	No. pat	No. det	No. pat
Biperiden	1	1						
Carbamazepine	4	1			2	1		
Chlorpromazine	1	1	3	1				
Clobazam	2	1						
Clonazepam			2	1				
Clothiapine	4	2	3	1				
Delorazepam			4	2				
Diazepam	3	1	1	1	2	1		
Fluoxetine	2	1	6	2				
Haloperidol	2	1						
Hydroxyzine			1	1	1	1	3	1
Levomepromazine	1	1						
Levothyroxine			3	1				
Lithium carbonate	2	1					4	2
Melatonin	7	2	2	1	2	1		
Methylphenidate	16	5						
Olanzapine	2	1						
Oxcarbazepine	9	1	1	1				
Paroxetine			2	1				
Pericyazine			1	1				
Promazine			2	1	2	1		
Sereprile			5	2				
Sertraline	6	3	6	2			3	2
Somatotropin	3	1						
Tamsulosin	1	1					2	1
Topiramate	4	1						
Valproic acid	59	15	9	2	3	1		

No. det number of determinations carried out in the presence of the concomitant medication, *No. pat* number of patients who assumed the concomitant medication

Table 3 Summary of the main SGAs pharmacokinetic data

	Unit	Risperidone	Aripiprazole	Olanzapine	Quetiapine
Daily dose	mg	1.9 ± 1.2; 1.8 (1.5)	10.8 ± 6.6; 10 (10)	12.7 ± 5.7; 10 (11.3)	220.0 ± 75.3; 250 (75)
C_t	ng/ml	17.5 ± 13.8; 13.6 (12.4)	187.0 ± 151.6; 165.8 (191.1)	38.0 ± 16.6; 41 (27.1)	312.2 ± 552.0; 44.7 (421.7)
Intra-patient variability	%	34.2	29.3	-	-
Inter-patient variability	%	78.9	81.1	-	-
Predictors of C_t (from multiple regression)		Daily dose	Daily dose, number of concomitant drugs	-	-
C_t/dose	ng/ml/mg	10.6 ± 7.9; 9.1 (7.3)	18.1 ± 9.9; 16.8 (13.3)	3.2 ± 1.4; 2.8 (1.6)	1.2 ± 2.1; 0.4 (1.7)
Intra-patient variability	%	35.1	29.3	-	-
Inter-patient variability	%	74.0	54.7	-	-
Predictors of C_t/dose (from multiple regression)		Height	Use of FGAs, use of SSRIs	-	-

C_t, dose and C_t/dose measures are shown as both means ± standard deviations and medians with interquartile ranges between brackets. C_t: trough plasma levels

The C_t/dose distribution, shown in Fig. 1, was non-normal ($p < 0.001$), although bell-shaped. Risperidone C_t showed an overall inter-patient variability of 78.9 %, ranging from 46.1 to 88.8 %, when grouping by administered dose. The average intra-patient variability was 34.2 ± 21.8 %, ranging from 4.5 to 92.1 %. The C_t/dose variability was consistent, 74.0 % inter-patient and 35.1 % intra-patient, ranging from 1.9 to 92.1 %. In view of the frequent use of valproic acid, we verified possible influences on the distribution of plasma levels of risperidone, finding no significant effect (see Supplemental Fig. 2).

Clinical parameters correlating with risperidone plasma levels

The analyzable sample size (datasets without missing covariates) was $n = 327$. By univariate analyses, risperidone C_t had significant correlations with dose ($r = 0.41$, $p < 0.001$) and patients' age ($r = 0.21$, $p < 0.001$). Risperidone dose and patients' age were also inter-correlated ($p < 0.001$). By multiple regression, we then analyzed the dependency of risperidone C_t upon dose and age ($R^2 = 0.18$, $p < 0.001$): the association with dose remained significant ($\beta = 4.19$, $p < 0.001$). C_t/dose

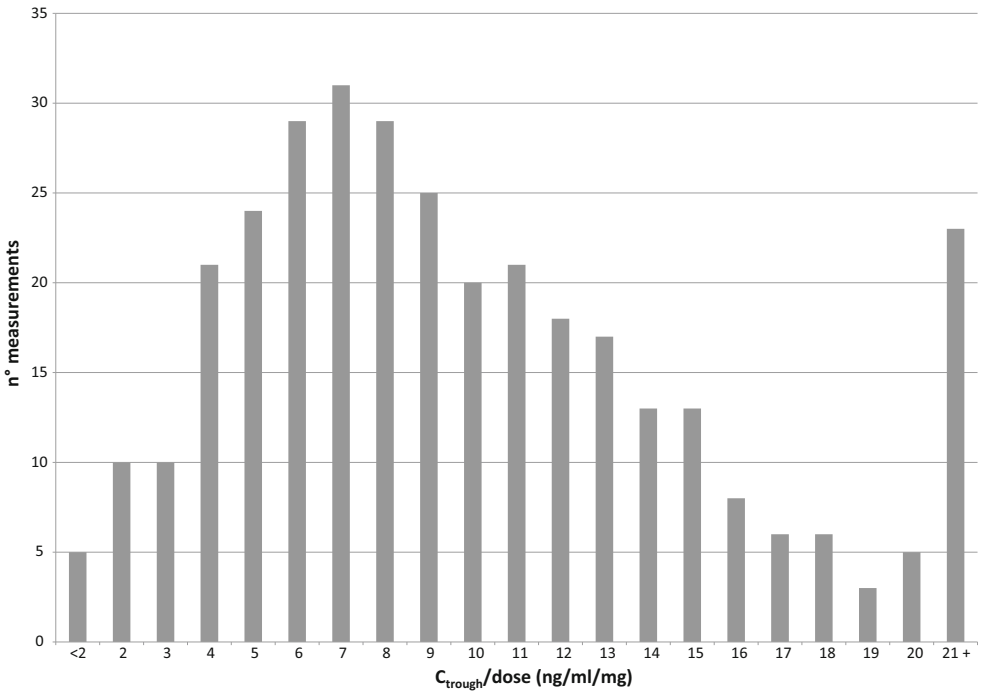

Fig. 1 Distribution of risperidone C_t/dose. *Solid bars* represent the number of measurements corresponding to different intervals of risperidone concentrations. C_{trough} trough plasma level

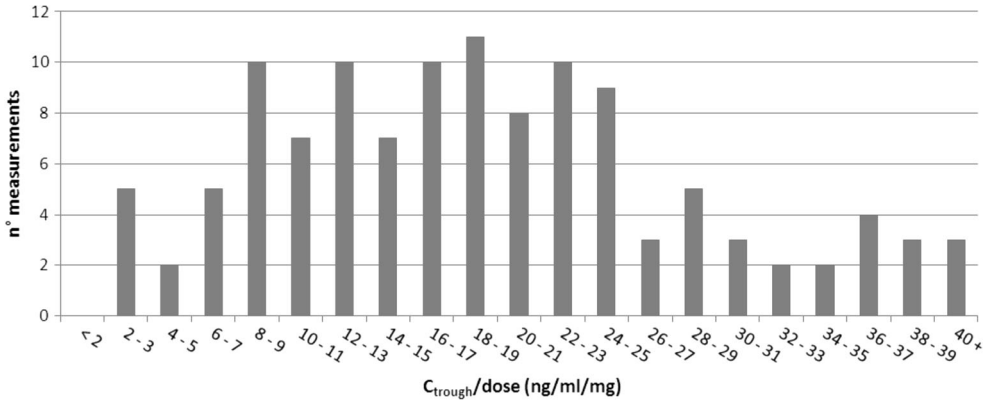

Fig. 2 Distribution of aripiprazole C_t/dose. *Solid bars* represent the number of measurements corresponding to different intervals of aripiprazole concentrations. C_{trough} trough plasma level

correlated inversely with weight ($r = -0.19$, $p < 0.001$), height ($r = -0.24$, $p < 0.001$), and age ($r = -0.16$, $p < 0.01$), while all these variables were inter-correlated ($p < 0.001$). In a multiple regression predicting C_t/dose ($R^2 = 0.06$, $p < 0.001$), only height remained significant ($\beta = -0.11$, $p < 0.01$).

Distribution of aripiprazole doses and plasma trough concentrations

Table 3 shows average and medians regarding aripiprazole. Doses were below 10 mg/day in 40.7 % cases and between 10 and 17.5 in 37.2 %; doses of 20 mg/day or more were 22 % (Supplemental Fig. 3a). Aripiprazole C_t was 187.0 ± 151.6 ng/ml, widely distributed (Supplemental Fig. 3b): 24.8 % values were between 50 and 99 ng/ml, while others were distributed homogeneously up to 299 ng/ml. C_t 6 % fell between 300 and 349 ng/ml; 10.6 % was higher. The C_t/dose distribution (Fig. 2) was non-normal ($p < 0.01$), and the values ranged between 5 and 24 ng/ml/mg. The inter-patient variability of aripiprazole C_t was 81.1 % overall, ranging from 25.2 to 68.4 %, when grouping patients by administered dose. The average intra-patient variability was 29.3 ± 24.4 %, largely heterogeneous: its minimum was 0.7 % and maximum 70.2 %. C_t/dose variability was lower, with an average of 54.7 % inter-patient and 29.3 % intra-patient, ranging from 0.7 to 70.2 %..

Clinical parameters correlating with aripiprazole plasma levels

The analyzable sample size was $n = 113$. By univariate analysis, aripiprazole C_t correlated with dose ($r = 0.69$, $p < 0.001$), patients' weight ($r = 0.29$, $p < 0.01$) and age ($r = 0.21$, $p = 0.03$), with the number of concomitant drugs ($r = 0.37$, $p < 0.001$) and the use of FGAs ($r = 0.33$, $p < 0.001$) and AEDs ($r = 0.28$, $p < 0.01$). Positive inter-correlations were found between dose and weight ($p < 0.001$), age and weight ($p < 0.001$), and age and use of AEDs ($p = 0.03$). Likewise, inter-correlations were positive between the number of concomitant drugs and the use of FGAs or AEDs ($p < 0.001$) and between the use of FGAs and AEDs ($p = 0.01$). We analyzed the dependency of C_t upon these variables by multiple regression ($R^2 = 0.60$, $p < 0.001$). Significant associations with dose ($\beta = 14.83$, $p < 0.001$) and with the number of concomitant drugs ($\beta = 61.82$, $p < 0.01$) were confirmed. C_t/dose correlated with the number of concomitant drugs ($r = 0.29$, $p < 0.01$) and use of FGAs ($r = 0.29$, $p = 0.01$) and of SSRIs ($r = 0.24$, $p = 0.01$). Positive inter-correlations were found between the number of concomitant drugs and the use of FGAs and SSRIs ($p < 0.001$). A multiple regression predicting C_t/dose ($R^2 = 0.13$, $p = 0.001$) confirmed that the use of FGAs ($\beta = 10.22$, $p = 0.03$) and SSRIs ($\beta = 9.49$, $p = 0.03$) remained significant.

Distribution of olanzapine and quetiapine doses and plasma trough concentrations

Data on daily doses and C_t are provided in Table 3, together with a resume of risperidone and aripiprazole. No further analyses were carried out on olanzapine or quetiapine due to the limited sample size.

Discussion

Pediatric studies on plasma levels of SGAs are currently limited in sample size or address specific subgroups of patients [21, 22, 29, 35, 36]. In this study, we observed that aripiprazole plasma levels were similar in pediatric patients as compared to adults, while those of risperidone were lower, such that almost one fifth were below the lower limit of quantification. A high inter-patient and lower intra-patient variability was observed, and plasma levels were found to depend on drug doses and on the administration of concomitant medications. We only reported distributions of dose and concentrations for quetiapine and olanzapine due to the limited sample size.

Our data on the distribution of risperidone plasma trough concentrations in pediatric patients are partially consistent

with the available literature. Indeed previous studies reported an average C_t of 11.2 ng/ml with an average dose of 0.03 mg/kg/day (equal to 1.2 mg/day, considering a 40-kg patient) [20] and of 11.2 ng/ml with a dose of 1.3 mg/day [23]. Our results are consistent, since measured C_t was higher because patients almost reached the maximum indicated pediatric dose. Notably, in more than 70 % cases, C_t was below the lowest threshold indicated for adults. This suggests that the C_t expected in a pediatric setting is lower than that recommended for adults, due to lower doses. The C_t/dose ratio we found was similar to the one indicated for adults (3.5–14 ng/ml/mg) [10], suggesting that the yield of risperidone administration is consistent; the difference we observed in C_t may be due to dose differences, <2 mg/day in pediatric patients, as compared to 4–10 mg/day in adults. We also investigated the variability of risperidone exposure. Whereas the inter-patient variability was large, the intra-patient variability was smaller, which is an ideal condition for the application of TDM. By univariate and multivariate regression analyses, we confirmed the significant association between risperidone plasma trough concentrations and daily doses, as previously reported [23]. This suggests that TDM may also be applied to verify the compliance of patients to risperidone-based maintenance therapies. Given the strong influence of risperidone dose on C_t, we repeated our regression using dose-adjusted trough concentrations (C_t/dose) as dependent variable, finding a significant role of weight, height, and age, previously reported only in animal models [40]. Concomitant medications with a strong metabolic influence were used scantly, which allowed no analysis. We could instead analyze the effect of valproic acid: our results show that it had no effect on risperidone plasma levels, in accordance with a previous report [41]. This is the first study on plasma concentrations of aripiprazole in a sizable pediatric cohort. The only previous report used a fixed-dose design with small groups (average n = 3) of children or adolescents [29]. In that study, aripiprazole C_t ranged from 21.8 ng/ml with 1 mg/day dose in children up to 194.2 ng/ml with 15 mg/day in adolescents. Those concentrations are lower than the ones we observed. We also found that aripiprazole distributions were widespread, both for doses and C_t. At variance with risperidone, aripiprazole dosing in children did not differ significantly from what was indicated for adults; therefore, C_t was closer to the adult reference (150–500 ng/ml) [10]. The C_t/dose average suggested that the yield of aripiprazole administration may be higher in pediatric patients than in adults (8.6–12.8 ng/ml/mg) [10]. We also calculated C_t/dose from the only study reporting on aripiprazole in children [29], finding average values concordant with those we observed. The variability of aripiprazole C_t was similar to that of risperidone: large inter-patients and low intra-patient, suggesting also for aripiprazole the reliability of TDM in pediatric patients. Aripiprazole C_t depended upon the dose and number of concomitant medications, which explained a high fraction of C_t variability. C_t/dose was related to the use of SSRIs, indicating that polytherapy affects aripiprazole plasma levels, as previously observed in adults [42], and suggests caution regarding combination therapies.

This study has several limitations. Its focus on outpatients did not allow a systematic assessment of compliance to drug assumption. An investigation of treatment efficacy was not in the aims of this study due to the observational design and the variety of clinical indications for drug therapy. Only an interventional study designed as fixed-dose vs. concentration-controlled in a homogeneous population may conclusively assess the potential role of TDM-guided dose adjustments on clinical outcomes. By contrast, the naturalistic approach of this study and the fact that TDM results were blind (i.e., not yet available) to clinicians during each dose-adjustment allowed us to represent the heterogeneity typical of a real-life scenario. Another limitation is the absence of information on the potential contribution of allelic variants of genes encoding for protein involved in the disposition of SGAs, which was beyond the purpose of the present study.

Our study described the distribution of plasma levels of SGAs in a real-life setting involving pediatric patients, significantly increasing the amount of available data for this fragile population. Such data may contribute to the definition of a desirable therapeutic window for risperidone and aripiprazole plasma levels in pediatric patients; furthermore, the relationships we describe between plasma levels, drug doses, concomitant drugs, and other variables may be useful for improving the choice of pediatric doses for risperidone and aripiprazole. Notably, a wide distribution of interindividual concentrations of risperidone and aripiprazole but a low intraindividual variability was documented, providing the pharmacokinetic rationale for TDM application in this pediatric population. Further research is needed in order to ascertain whether the therapeutic windows of SGAs we observed may be related with better clinical outcomes and/or safer risk profiles [43], which would constitute the clinical rationale for TDM application.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committees of all participating structures.

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Attention Deficit (AD) and Sluggish Cognitive Tempo (SCT) symptoms in Congenital Hypothyroidism (CH): results from a case-control study.

Annalisa Esposito[1], Ida D'Acunzo[1], Raffaella Di Mase[1], Ennio Del Giudice[1], Mateu Servera[2], Mariacarolina Salerno[1]

[1] Department of Translational Medicine (Section of Pediatrics), Federico II University, Naples, Italy ; [2] Department of Psychology, Baleares Islands University

Introduction and Objective

Despite neonatal screening, children with Congenital Hypothyroidism (CH) may still display behavioural problems such as inattention, distractibility, hyperactivity and restlessness. The aim of present study was to evaluate attention and Sluggish Cognitive Tempo (SCT) symptoms in 32 children with CH compared to 32 healthy matched controls.

Method

▶ The study population consisted of 32 CH children aged 9-14 years. CH children were diagnosed by neonatal screening and treated at a mean age of 19.3±4.5 days with mean starting L-thyroxine (L-T4) dose of 11.8±1.4 µg/kg/day (range 10-15 µg/kg/day). Hormonal features at diagnosis are reported in Table 1.

▶ 32 healthy subjects, comparable for age, sex and socioeconomic status were enrolled as control.

CH patients and controls underwent **Child and Adolescent Disruptive Behaviour Inventory-Plus (CADBI-plus)** to evaluate attention and SCT symptoms. Teacher and both parents cooperation was required to enter the study.

SCT is a newly defined childhood disorder associated with a slow cognitive processing, sluggishness, daydreaming, drowsiness, lethargy and under-activeness.

Tab. 1: Hormonal features of 32 enrolled CH children at diagnosis.

Age at diagnosis (days)	19.34±4.5
Serum TSH at diagnosis (mcUI/ml)	442.77±214.6
Serum FT4 at diagnosis (ng/dl)	0.46±0.21
L-T4 at diagnosis (µg/kg/day)	11.84±1.4

Results

CH children scored significantly higher than controls in:

▶ **Attention Problems** reported by both mothers (M) (5.29±5.01 vs 3.17±2.54; p 0.04), and teachers (T) (7.2±8.49 vs 2.69±3.28, p <0.01) **(Fig.1)**;

▶ **SCT symptoms** reported by both parents (F 9.61±7.04 vs 5.41±4.77, p<0.01; M 10.63±9.57 vs 4.9±4.68, p <0.01) and teachers (T 13.2±13.01 vs 4.28±5.63, p <0.01) **(Fig.2)**.

No significant differences were found in hyperactivity or oppositive behaviors.

Concerning academic performance, teachers report lower **scores in Mathematics** in CH children compared to controls (6.25±2.13 vs 7.1±1.13, p 0.05).

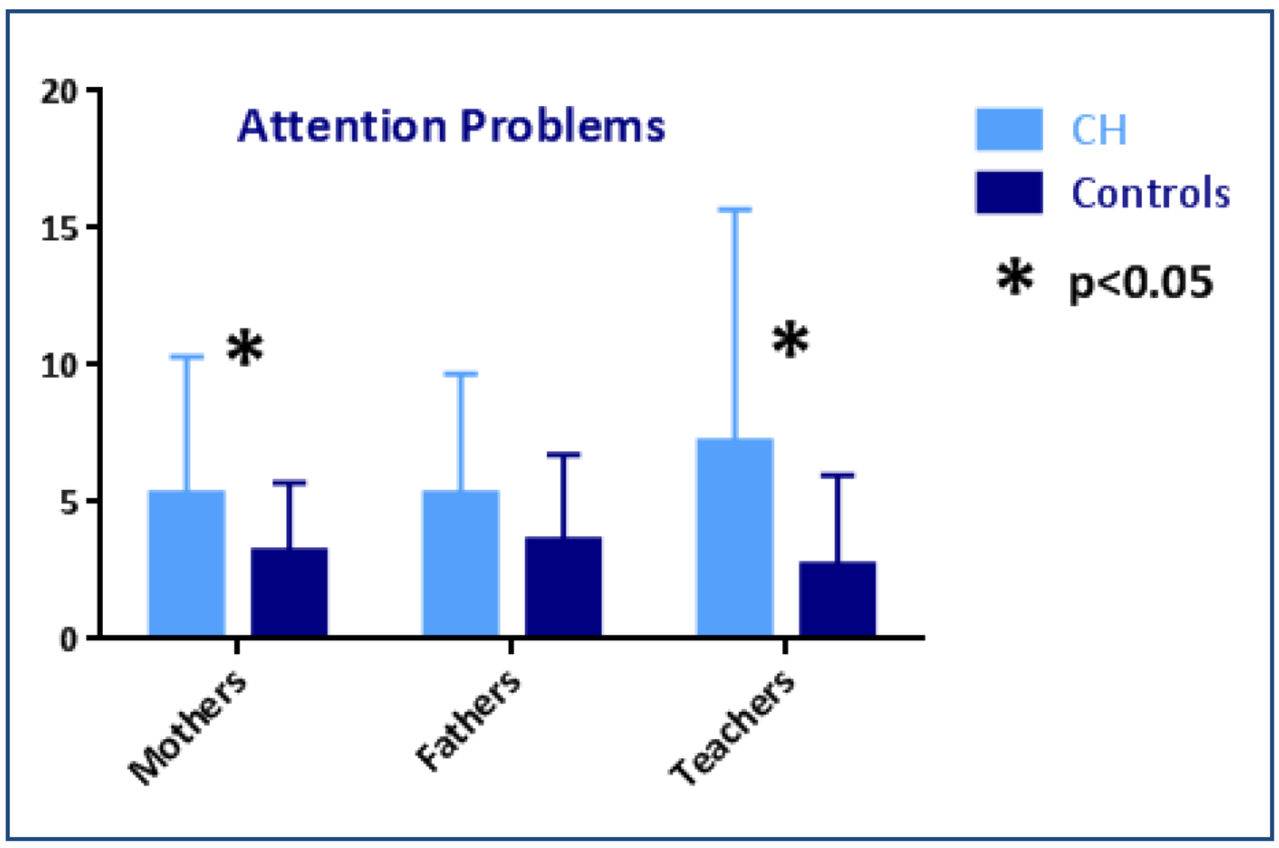

Fig.1. Comparison between Attention Problems reported by mothers, fathers and teachers in CH children and Controls.

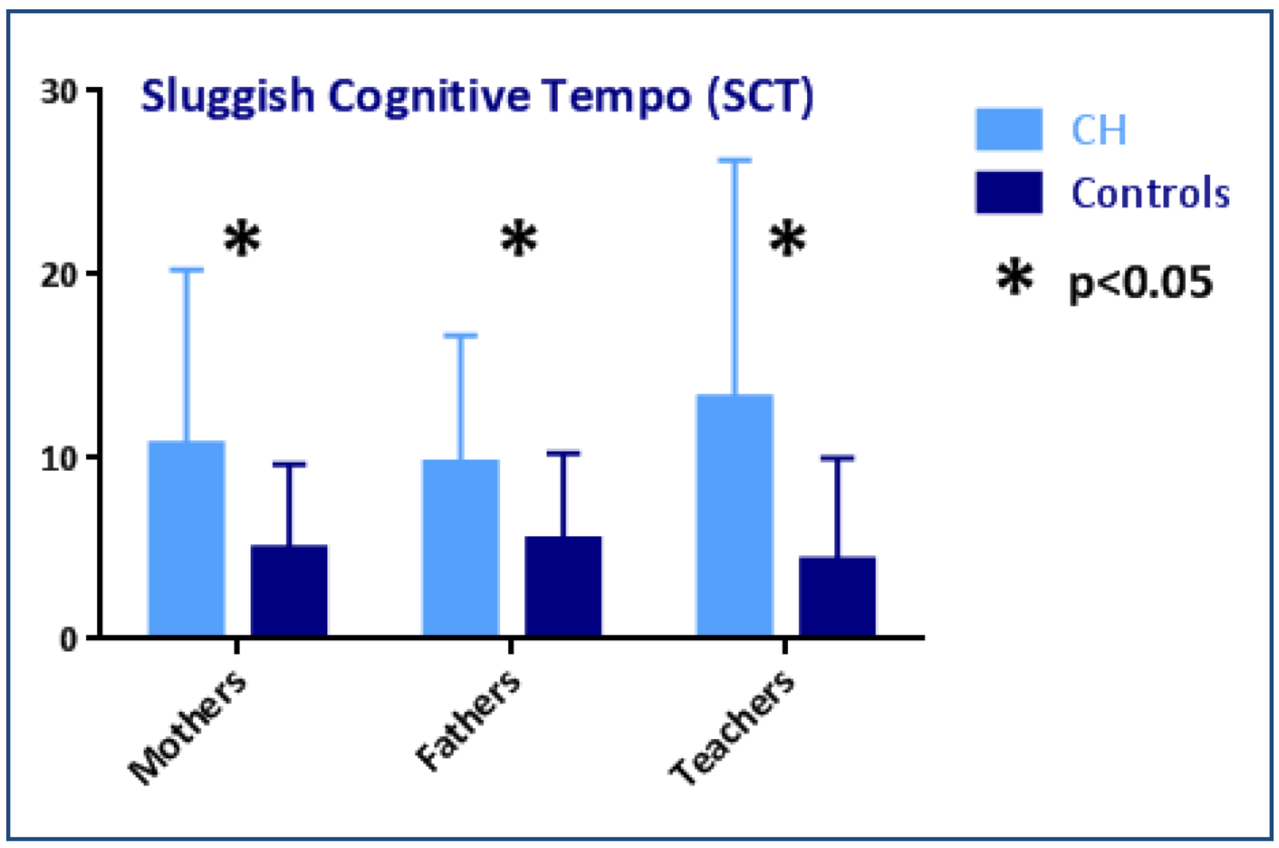

Fig.2. Comparison between Sluggish Cognitive Tempo (SCT) symptoms reported by mothers, fathers and teachers in CH children and Controls.

Conclusions

The results of our study suggest that CH children may have attention deficits, SCT symptoms and impaired mathematical abilities, despite early replacement therapy and high starting L-T4 doses.

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Thyroid

Annalisa Esposito

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ADHD: Auditory and Visual Stimuli in Automatic and Controlled Processes

Rosa Angela Fabio[1], Claudia Castriciano[1], and Alessia Rondanini[2]

Abstract

Objective: Deficits in ADHD executive function (EF) task have been widely documented in a number of different studies. The aim of this work is to analyze the characteristics of auditory vigilance in ADHD and control subjects in two conditions: with and without interference. **Method:** in the first study the Merrill's (1992) procedure on automaticity with the dual-task interference paradigm was used; in the second study the auditory test with automatic procedure was used. **Results:** The results of the study confirm that people with ADHD show deficits in auditory vigilance tests and become less careful when interference is introduced. **Conclusion:** Results were discussed in terms of a deficit in automaticity process. *(J. of Att. Dis. 2015; 19(9) 771-778)*

Keywords

ADHD, executive functions (EFs), auditory attention

Introduction

Hyperactivity, impulsivity, and inattention are all major symptoms of the most common childhood mental disorder "ADHD" (*Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text rev. [*DSM-IV-TR*]; American Psychiatric Association, 2000).

Some authors (Swanson et al., 1998) argue that the three main symptoms of this disorder are due to a deficit in executive functions (EFs). Children with ADHD have difficulty in maintaining attention, in focusing their attention on a task, and, in particular, inhibiting visual and sound distractors. In addition to attentional difficulties, these children present impairments in working memory and EFs and, in particular, an inhibition deficit and planning difficulties. The inability to inhibit or defer an answer explains many of the behavioral symptoms (hyperactivity, impulsiveness, and intolerance with frustration) and cognitive symptoms (notably difficulty in resisting distractors; Barkley, 2003; Mayes & Calhoun, 2006; Shanahan et al., 2006).

The precise cause of attentional dysfunctions in ADHD remains unclear. From a neuropsychological perspective, ADHD is associated with deficits in well-defined cognitive domains, including sustained attention and executive functioning (Barkley, 1998; Pennington & Ozonoff, 1996). Some theorists focus on executive deficits (Shallice et al., 2001); children with ADHD show deficits in executive functions, including response inhibition, working memory, and conflict resolution (Bush et al., 1999; Casey et al., 1997; Doyle, 2006; Pliszka et al., 2006; Rubia, Smith, Brammer, Toone & Taylor, 2005; Vaidya et al., 2005); other theorists recognize a difficulty in ADHD in the automatic processing of basic skills (Ackerman, Anhalt, Holcomb, & Dykman, 1986; Fabio, 2001, 2009) or in the modality of stimulus presentation (Fabio & Antonietti, 2012). Moreover, Hazell et al. (1999) suggested that participants affected by ADHD show, along with a deficit in the central controlled processes, a deficit in the encoding and in the automaticity of processes. This distinction was acknowledged for the first time by Shiffrin and Schneider (1977). The two authors argue that the controlled processes have a limited capacity, require attention, and can be used flexibly in different circumstances, whereas automatic processes have a limited capacity, do not require attention, and are very difficult to change. Automatic processing is no longer required for attention, it is the result of prolonged practice, it is not conscious, and it is inevitable.

Both automatic and controlled information processing have been investigated in studies on the cognitive performance of children with ADHD, but results are inconsistent. Several authors have shown that children with ADHD do not perform as well as controls in situations demanding

[1]Department of Cognitive Science and Education, University of Messina, Italy
[2]Department of Psychology, Catholic University of Milan, Italy

Corresponding Author:
Claudia Castriciano, University of Messina, Via Concezione 6-8, 98122 Messina, Italy.
Email: ccastriciano@unime.it

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automatic and/or more controlled processing strategies (Ackerman et al., 1986; Borcherding et al., 1988; Hazell et al., 1999), whereas other authors have not (Van der Meere & Sergeant, 1988).

Hurks et al. (2004) examined the performance of ADHD children on semantic category fluency (SCF) versus initial letter fluency (ILF) tasks. For each participant, word production was recorded for each 15-s time slice on each task. The authors hypothesize that children with ADHD perform significantly worse on both types of information processing (automatic vs. controlled) than do healthy control participants. Results were taken to indicate that children with ADHD symptoms show a delay in the development of automating skills for processing abstract verbal information.

This last hypothesis, that hyperactive children fail to develop automatic processing, is less consolidated; recent research (Ackerman et al., 1986; Borcherding et al., 1988; Ott & Lyman, 1993) suggests that ADHD children have no deficit in innate automatic tasks but they could display difficulties in acquired automatic skills.

The purpose of this study is to test the hypothesis that deficits of EF are at least partly due to a deficit in automatic processing. The logic of our investigation is that if the basic processes are not well automatized, they will result in a high cognitive load and compete for limited resources used by EFs.

Automatic processes can be observed by examining differences in the automatization of basic skills in children with and without ADHD, because these processes can be accomplished simultaneously with other cognitive processes without interference (Fabio & Cossutta, 2001; Hasher & Zacks, 1979; Melnik & Das, 1992).

In this study we examined the hypothesis that task inefficiency in ADHD children can be caused by EF deficit, as well as by automatic learning dysfunctions.

Study 1: Visual Test

The specific aims of the first study are twofold. Firstly, as suggested by the Joston and Heinz (1978) and Hommel (1998) multimodal model, the type of task has relevance to the processes of automaticity. In fact, when selective attention is focused on the physical characteristics of the stimulus, participants use less cognitive resources, decrease the reply time, and increase precision in respect to selective attention when the recognition of stimulus is at semantic level. In this case, the correct passage from a perceptual task of identification to a semantic identification may indicate good automatization, whereas an inaccurate or slow passage could indicate difficulty in automating or in EFs. The second aim is to analyze Merril's (1992) theory on automaticity. If normal participants and ADHD participants are able to perform the tasks of selection equally well, both in the absence and in the presence of memory load, the selection could be automatic; if there are errors in the memory interference, the selection is not automatic.

Method

Participants. For the initial phase of this study, a sample of 912 students aged between 8 and 10 years, attending Classes III and V of the elementary school, were selected.

It was possible to perform the procedure in all the public schools of Lombardia that had given their consent to participate in the survey.

The pretest phase involved the administration of two questionnaires, which were conducted by teachers to their students:

1. The Sindrome Deficit Attentivo e Iperattività (SDAI) scale (Marzocchi & Cornoldi, 2000), can be used to highlight the subtypes of ADHD. The SDAI scale consists of 18 items, which correspond to the symptoms described and listed in the *DSM-IV-TR*, containing two subscales of 9 items each: one related to inattention and the other hyperactivity-impulsivity. The teacher, for each item that will indicate the severity of behavioral disorders of children, gives a score ranging from 0 = *absent behavior* to 3 = *very frequent behavior*. The cutoff for each item is 1.5 points. It is, therefore, considered problematic behavior of a child if, in at least one subscale, an overall score equal to or greater than 14 is achieved.
2. The Scala Comportamenti Dirompenti (SCOD) scale or "scale for the assessment of disruptive behavior" (Marzocchi et al., 2001) is present in two versions: one for parents (Scala Comportamenti Dirompenti - Genitori; SCOD-G) and one for teachers (Scala Comportamenti Dirompenti - Insegnanti; SCOD-I).
3. The SCOD consists of 42 items and can be divided into four subscales, respectively: a rating scale of aggressive behavior; information about the socioeconomic family, a series of 5 items related to school learning problems, and general information aimed at discriminating against individuals with ADHD from other related diagnosis.

Both scales were administered by teachers to their students.

Based on data collected through two questionnaires, the final sample of the research selected consists of 30 participants divided into two groups:

- Group 1 consists of 15 children aged between 8 and 10 years with ADHD.

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- Group 2 consists of 15 children aged between 8 and 10 years constituted the control group.

Due to lack of authorization from the parents of 3 children, the sample was then reduced to 27. Consequently, the sample used was as follows:

- Group 1 consists of 13 ADHD children.
- Group 2 consists of 14 normal developing children.

The administration of the visual test was made with the aid of a portable computer, using a program for Mac called "Super Card." Participants were asked to sit in front of it.

The test took place in front of the PC screen in a quiet classroom in the school of origin for a maximum of about 40 min.

Prior to conducting the test, the load of individual memory was calculated, both for patients with ADHD and for normal participants, on the basis of the test of the *digit span* of the Wechsler scale.

Each participant was asked to repeat a series of numbers: first two numbers, then three, then four, until the participant made a mistake. If an error in repeating the numbers was made, another series of the same numbers was presented and if the participant mistook that series as well, the test was stopped. Specifically, the full memory load was the number of series in which the test was stopped, whereas the half memory load was the full memory load divided by two. Subsequently, they were asked to click a button on the computer when they saw physically identical pairs on the screen (first test: perceptual identity) and pairs of figures belonging to the same nominal category (second test: categorical identity).

Each test, both perceptual identity and categorical identity, was presented three times to each participant. During the test, each participant had to repeat at the same time, $n - 1$ digits (full load), $(n - 1) / 2$ digits (half load), and 0 digits (empty load).

As the automatic processes require minimal cognitive resources to be carried out, the purpose of this test is to note that the automaticity of the processes of encoding can be highlighted by the absence of penalty due to the memory load. Children with ADHD may not automate, however, the underlying processes and present the effects of penalty due to the memory load.

Procedure. Once parents were informed about the aims of the study and written consents were obtained, participants participated in a single testing session that was divided into two experiments: visual test and auditory test. The administration of visual test was made using a portable computer. A Mac program called "Super Card" was used. The participants were invited to sit down. The test took place on a computer in a quiet classroom of the school for approximately 40 min.

Before the test, individual memory load was calculated, both for ADHD participants and for normal participants, on the basis of *digit span* test of the Wechsler scale.

The participants were instructed to recognize, as quickly as possible, the two stimuli belonging to the same category. The methodology of memory load was integrated with the methodology of the function of codification. Participants had to repeat a list of numbers during the codification task. Memory load was manipulated by increasing or decreasing the memory set. The purpose was to measure the level of cognitive load that interferes with performance in ADHD and in normal groups. Automatic processes, in fact, can be accomplished simultaneously with other cognitive processes without interference. Thus, difference on interference of memory load could reflect a difference in automatic performance in participants with and without ADHD.

As automatic processes can be accomplished simultaneously with other cognitive processes without interference (Hasher & Zacks, 1979; Lavie, 1995; Posner & Snyder, 1975), any difference in interference of memory load could reflect a difference in automatic performance in participants with and without ADHD.

In the first task, participants were asked to circle, as quickly as possible, the pairs of identical pictures, whereas in the second task, participants were asked to circle, also as quickly as possible, the stimuli belonging to the same semantic category.

Each selective attention task was repeated three times for each participant. Participants were asked to listen and repeat a list of numbers read aloud by an experimenter.

Memory load was manipulated by increasing or decreasing the memory set (full load = span − 1 digit, half load = span − 0.5 digit, and no load = 0 digits).

During experimental blocks of trials, we measured response time and error rates. Our primary aim was to investigate how task difficulty interacted with distractor salience in the three participant groups. For this analysis, response times and error rates from the mixed display experiment were measured and submitted to analysis with repeated measures ANOVA, with participant group as a between-participant factor, and discrimination difficulty and distractor salience as within-participants factors (Friedman-Hill et al., 2010).

Data analyses. The data were analyzed using a $2 \times 2 \times 3$ repeated measures ANCOVA, with one between-group factor (participants: normal vs. ADHD-combined [ADHD-C]) and two within-group factors: experimental condition (perceptive vs. categorical identification) and cognitive load (zero load vs. half load vs. full load).

Two measures of task performance were recorded:

- the number of correct responses and
- the number of errors (number of false alarms + number of mistakes).

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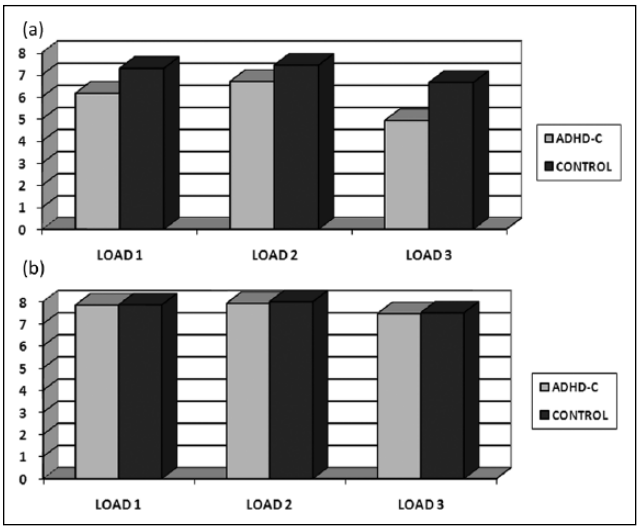

Figure 1. Mean of correct responses in the task of (a) category identity and (b) perceptive identity.
Note. ADHD-C = ADHD-combined.

Results

Data analysis of the procedure perceptive/category identification. The main effects of group and task were significant, respectively, $F(1, 25) = 11.34$, $p < .01$ and $F(1, 25) = 54.69$, $p < .001$. ADHD children showed higher correct responses. With reference to the task in categorical identification, all the participants showed a lower number of correct responses than in the perceptual identification task (Figure 1). The task × group interaction was also significant, $F(1, 25) = 11.46$, $p < .001$: ADHD participants showed a lower number of correct responses in categorical identification tasks than control participants. Whereas in perceptual identification tasks, the performances of both groups were similar. There was also a significant effect of load condition, $F(2, 50) = 23.39$, $p < .001$.

The results are summarized in Table 1 with reference to two parameters: number of correct responses and number of errors and omissions.

Correct responses. The main effect of group was significant $F(1, 25) = 11.34$, $p < .01$; Experiment condition × group interaction was also significant, $F(1, 25) = 13.46$, $p < .001$. Also the type of task showed significant effect: $F(1, 25) = 54.69$, $p < .001$.

This shows that, with the task of categorical identification, the participants have a lower number of correct responses. Data show a significant interaction effect type of task × groups of participants. ADHD participants have a more considerable decrease in the number of correct responses when the type of task is of categorical identification with respect to when the type of task is of perceptive identification. When the type of task is of perceptive identification, the performances of normal participants are similar to ADHD participants, whereas when the type of task is of categorical identification, there are differences in the performances.

Data analysis also evidence a significant effect of *load:* $F(2, 50) = 23.39$, $p < .001$.

Errors. Figure 2 and Table 2 indicate media and standard deviation in all the considered conditions.

The main effect of group was significant, $F(1, 25) = 36.58$, $p < .001$. ADHD participants made more errors than control participants; significant main effect of task was also found, $F(1, 25) = 36.58$, $p < .001$. A significant interaction task × group of participants was found, $F(1, 25) = 4.78$, $p = .038$.

ADHD participants showed higher number of errors in categorical identification task than control participants.

Last variable with significant effects is the level of full-load cognitive; the errors are increased to strengthen the load of memory.

Discussion

A three-way interaction, group × task × condition, was also significant, $F(2, 51) = 5.98$, $p < .001$. This means that in categorical task, ADHD-C participants showed higher levels of errors in full-load condition than control participants.

It has been suggested that ADHD children fail to acquire certain learning skills because they differ in encoding abilities. Group differences were obtained in the present study.

First, with respect to correct responses, all groups disclosed lower performance in categorical tasks compared with perceptual tasks, but the ADHD group showed a lower performance than the control group in categorical task. With reference to errors, ADHD participants presented higher error rates when both categorization task and full-load condition appeared.

The main finding of this study is that if intensive mental processes are requested, as in category task, requiring central information-processing level, ADHD participants increase error rates and decrease correct responses.

The main result of this study is that when forceful mental processes are requested, as in the categorical task, ADHD participants increase error rates and decrease correct responses. Worthily, this cost in performance appears higher in full-load condition. Inaccurate performance in full load condition may be interpreted as a partial deficit in automatic processing.

Study 2: Auditory Test

Method

In the second study, the aim is to verify if the participants with ADHD present fewer elements of automatization in respect to normal participants, or give correct number of replies and a higher number of errors in the fourth test in respect to the first.

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Table 1. Means and Standard Deviations of Correct Responses in Categorical and Perceptual Tasks.

	Categorical identification task						Perceptual identification task					
	No load		Half load		Full load		No load		Half load		Full load	
Groups	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
ADHD-C	6.154	0.344	6.692	0.177	4.923	0.351	7.846	0.129	7.923	0.053	7.462	0.287
Control	7.286	0.332	7.429	0.171	6.643	0.339	7.857	0.124	8.000	0.051	7.500	0.276

Note. ADHD-C = ADHD-combined.

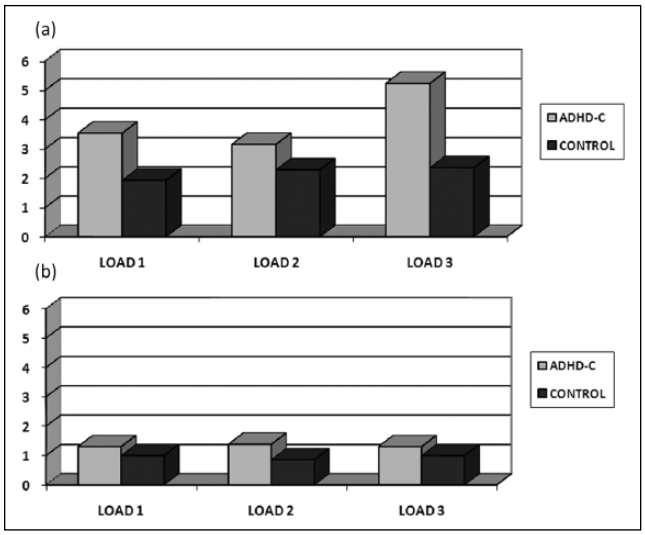

Figure 2. Mean of the errors in the task of (a) category identity and (b) perceptive identity.
Note. ADHD-C = ADHD-combined.

Participants. Participants were the same as those reported in Experiment 1.

In this experiment, a program called "Super Card" was used. A list of items was made by letter and number (see, for example, D2 in Table 3). These files were recorded as vowel and they were inserted in the program computer. During the test, the participants were invited to sit down in front of the screen. They had to listen to the combination of letter-numbers by means of four computer phases (e.g., T5).

During the test, the participants had to press a key of the computer when they heard the precise target that was previously communicated by an experimenter (B5). The four phases were composed each of 100 letter-number files and in each there were 10 targets to pick out.

The aim of this test was to measure the automatic effects on performance and care. The automation of mechanisms of selection implies the increase of correct responses and the reduction of errors during the four phases.

The aim of this second study was to analyze if ADHD participants have a lower index of automation in respect to normal participants.

Data analyses. The design was a 2 (group: normal vs. ADHD) × 4 (phases: 1, 2, 3, and 4).

Two measures of task performance were recorded:

- the number of correct responses and
- the number of errors (false alarms + omission).

Results

The focus of the present study was to evaluate whether the ADHD participants had a lower index of selective automatization than the control group.

A 2 × 4 ANCOVA repeated measures design with two factors, 2 (group) × 4 (number of phases).

Correct responses. Table 4 shows the means and standard deviations.

With reference analyzing to the "number of correct responses," there are no significant differences (Figure 3).

Errors. Table 5 shows the means and standard deviations for each group in the four phases. The main effect was significant: $F(1, 25) = 6.309$, $p < .001$.

The overall number of errors (false alarms + omissions) was calculated.

The control group shows a decrease of this parameter during the four phases, whereas the ADHD-C group keeps the number of errors high and constant.

The main effect of phases was also significant, $F(3, 75) = 2.81$, $p < .045$. Figure 4 shows that errors decrease in ADHD participants, whereas the errors are stable in ADHD group, $F(3, 75) = 2.81$, $p = .045$. This suggests that control participants did not have deficit in automatic components. In contrast, the ADHD-C group found more difficulty in acquisition of automatic processing.

Discussion

The data analysis suggests that there are differences between the groups. With reference to the parameter "correct responses," there are no significant differences between ADHD participants and normal controls. The differences arise with reference to the parameter "errors." The number of errors is higher in the ADHD-C participants. During the four phases, the errors of control participants decrease,

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Table 2. Means and Standard Deviations of Errors in Categorical and Perceptual Tasks.

	Categorical identification task						Perceptual identification task					
	No load		Half load		Full load		No load		Half load		Full load	
Groups	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
ADHD-C	3.538	0.416	3.154	0.599	5.231	0.488	1.308	0.418	1.385	0.363	1.308	0.418
Control	1.929	0.401	2.286	0.577	2.357	0.471	1.000	0.403	0.857	0.350	1.000	0.403

Note. ADHD-C = ADHD-combined.

Table 3. List of Files of the Auditory Test.

B2	T5	T3	P5	B3	D2	B2	B6
N2	P2	T5	B3	P5	B3	N5	T2
B5	B8	P6	N8	L3	P2	T5	N3
D5	T6	B2	T2	N5	T2	N6	T5
T2	N3	D3	B5	P3	B6	T3	L6
N6	T2	B5	T6	L2	P3	P2	N5
L2	T5	P2	T3	B5	L2	B3	P2
B3	N2	T5	B2	P6	T6	T2	B5
N5	B5	T2	P5	T2	D3	L8	D6
T6	N5	D5	B5	D5	T3	B5	B2
B5	T2	T3	L3	N2	N2	P6	L6
P2	T8	N6	T5	D6	L5	N2	T6
T3	P5	B3	D2	B2	B6	L3	B5
T5	B3	P5	B3	N5	T2	T8	P2
P6	N8	L3	P2	T5	N3	P5	N5
B2	T2	N5	T2	N6	T5	B3	T2
D3	B5	P3	B6	T3	L6	T2	T8
B5	T6	L2	P3	P2	N5	B5	D5
P2	T3	B5	L2	B3	P2	B2	T3
T5	B2	P6	T6	T2	B5	L6	N6
T2	P5	T2	D3	L8	B2	T5	B5
D5	B5	D5	T3	B5	N2	P2	L3
T3	L3	N2	N2	P6	B5	B8	T5
N6	T5	D6	L5	N2	D5	T6	D5
B3	D2	B2	B6	L3	T2	N3	N2
P5	B3	N5	T2	T8	N6	T2	B5
L3	P2	T5	N3	P5	L2	T5	T3
N5	T2	N6	T5	B3	B3	N2	N2
P3	B6	T3	L6	T2	N5	B5	L5
L2	P3	P2	N5	B5	T6	N5	B3
B5	L2	B3	P2	B2	B5	T2	T2
P6	T6	T2	B5	L6	P2	T8	B3
T2	D3	L8	B2	T5	T3	P5	N5
D5	T3	B5	N2	P2	T5	B3	N2
N2	N2	P6	B5	B8	P6	N8	B5
D6	L5	N2	D5	T6	B2	T2	T5
B2	B6	L3	T2	N3	D3	B5	T2
N5	T2	T8	N6	T2	B5	T6	B2
T5	N3	P5	L2	T5	P2	T3	P5
N6	T5	B3	B3	N2	T5	B2	P6
T3	L6	T2	N5	B5	T2	P5	T2
P2	N5	B5	T6	N5	D5	B5	T6
B3	P2	B2	B5	T2	T3	L3	D3
T2	B5	L6	P2	T8	N6	T5	
L8	B2	T5	T3	P5	B3	D2	
B5	N2	P2	T5	B3	P5	B3	
P6	B5	B8	P6	N8	L3	P2	
N2	D5	T6	B2	T2	N5	T2	
L3	T2	N3	D3	B5	P3	B6	
T8	N6	T2	B5	T6	L2	P3	
P5	L2	T5	P2	T3	B5	L2	

Table 4. Means and Standard Deviations of the Correct Responses in the Four Phases.

	Auditory test							
	Phase 1		Phase 2		Phase 3		Phase 4	
Groups	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
ADHD-C	5.308	0.692	5.923	0.565	5.231	0.627	5.154	0.681
Control	6.071	0.667	6.714	0.545	6.5	0.604	6.286	0.656

Note. ADHD-C = ADHD-combined.

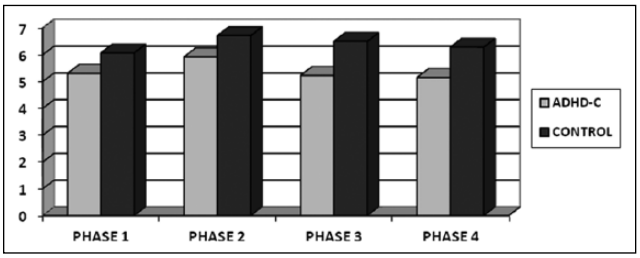

Figure 3. Mean of the correct responses in the auditory test.
Note. ADHD-C = ADHD-combined.

Table 5. Mean of the Errors Relative to the Task of the Auditory Test.

	Auditory test							
	Phase 1		Phase 2		Phase 3		Phase 4	
Groups	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
ADHD-C	8.923	1.033	7.308	0.663	7.462	0.985	7.385	1.066
Control	6.857	0.995	6.0	0.639	4.786	0.95	4.214	1.027

Note. ADHD-C = ADHD-combined.

whereas the errors of ADHD participants are stable from the second phase onward.

The differences may be due to the automatization. In the ADHD participants, the deficits of codification of the information seem to charge the sensorial auditory canal. The

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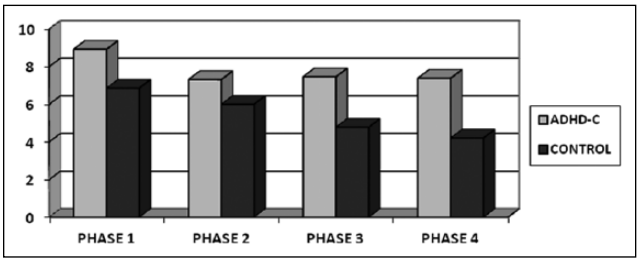

Figure 4. Mean of the errors in the auditory test.
Note. ADHD-C = ADHD-combined.

conclusion is that EF deficits may be at least partially due to a deficit in automatic processing. Moreover, it is possible that when the stimuli require a decoding to auditory level, the ADHD participants might involve higher cognitive effort.

The aim of this study is to demonstrate that even if partially deficits of EF are at least partly due to a deficit in automatic processing, in fact if the basic processes are not well automatized, they will result in a high cognitive load and compete for limited resources used by EFs. Automatic processes can be observed by examining differences in the automatization of basic skills in children with and without ADHD, because these processes can be accomplished simultaneously with other cognitive processes without interference.

As previously seen, in this study we examined the hypothesis that task inefficiency in ADHD children can be caused both by EF deficit and by dysfunctions in automatic learning.

In the first study, three-way interaction shows a deficit in the automatization tasks in ADHD participants, with higher levels of errors in full-load condition than control participants; in fact, ADHD participants fail to acquire certain learning skills because they differ in encoding abilities. The main result of this study is that when effortful mental processes are requested, as in the categorical task, ADHD participants increase error rates and decrease correct responses. This cast in performance appears higher in full-load condition. Inaccurate performance in full-load condition may be interpreted as a partial deficit other than in central process also in automatization process.

The second study suggests differences that arise to the parameter "errors," because the number of errors is higher in the ADHD-C participants. These differences may be due to the automatization. In the ADHD participants, the deficits of codification of the information seem to charge the sensorial auditory canal. The conclusion is that EF deficits may be at least partially due to a deficit in automatic processing. Moreover, it is possible that when the stimuli require a decoding to auditory level, the ADHD participants might involve higher cognitive effort.

Conclusion

The data on this study will not allow us to come to any definitive conclusions about the automatic/controlled processes in ADHD children. The present work can be seen as a pilot study and as a first and provisional attempt to complete literature on cognitive processes in ADHD children. Future studies need to have relatively large sample sizes and to verify further the type of experimental paradigm used here.

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

Rosa Angela Fabio, PhD is a professor of General Psychology at the Department of Cognitive Science and Education of the university of Messina. She is author of several experimental works on attention process and cognitive empowerment.

Claudia Castriciano is a PhD student of the Cognitive Science PhD of the University of Messina. She works on attention process.

Alessia Rondanini is an Educator of the Catholic University of Milan. She works on cognitive rehabilitation.

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REVIEW

Raising attention to attention deficit hyperactivity disorder in schizophrenia

Stefano Pallanti, Luana Salerno

Stefano Pallanti, Luana Salerno, Istituto di Neuroscienze, 50134 Florence, Italy
Stefano Pallanti, Department of Psychiatry and Behavioral Sciences, University of California, Sacramento, CA 95817, United States
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Correspondence to: Stefano Pallanti, MD, PhD, Istituto di Neuroscienze, Via Lamarmora, 24, 50134 Florence, Italy. stefanopallanti@yahoo.it
Telephone: +39-55-7949707
Fax: +39-55-581051
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Abstract

Schizophrenia and attention deficit hyperactivity disorder (ADHD) are two psychiatric disorders with a negative impact on quality of life of individuals affected. Although they are classified into distinct disorders categories, attentional dysfunction is considered as a core feature in both conditions, either at the clinical then pathophysiological level. Beyond the obvious clinical overlap between these disorders, the Research Domain Criteria approach might offer an interesting perspective for disentangling common circuits underpinning both disorders. Hence, we review evidences regarding the overlap between schizophrenia and ADHD, at the clinical level, and at the level of underlying brain mechanisms. The evidence regarding the influence of environmental risk factors in the emergence of both disorders, and their developmental trajectories is also reviewed. Among these, we will try to elucidate the complex relationship between stimulants use and psychotic symptoms, discussing the potential role of ADHD medication in inducing psychosis or in exacerbating it. We aim that, taken together, these findings may promote further investigation with important implications both for clinicians and research. In fact, considering the amounting evidence on the overlap between schizophrenia and ADHD, the delineation of their boundaries might help in the decision for diagnosis and treatment. Moreover, it may help to promote interventions focused on the prevention of both schizophrenia and ADHD, by the reduction of recognized environmental risk factors.

Key words: Attention deficit disorder with hyperactivity; Central nervous system stimulants; Psychotic disorders; Schizophrenia; Toxic psychoses

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Core tip: In line with the translational approach of viewing disorders in terms of dysregulation of brain basic mechanisms, there is increasing evidence of overlap between different mental disorders. Here, we explore relationships between attention deficit hyperactivity disorder and schizophrenia, in light of recent insights into potential common etiological mechanisms explaining some of the observed overlap in both disorders. Using evidence from clinical epidemiology and neuropsychology, we propose a biologically-based reconsideration of these brain diseases. We have also summarized environmental risk factors for both disorders, aiming to promote awareness

regarding the need of appropriate interventions to prevent the onset and development of these diseases.

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INTRODUCTION

There is a mounting interest in discovering the links between neurodevelopmental disorders and psychiatric disorders in adulthood. Although the relationship between schizophrenia and attention deficit hyperactivity disorder (ADHD) has been poorly studied, it has been reported that the majority of individuals with schizophrenia, and their offspring, show early symptoms including attentional difficulties.

The concept of attention dysfunction in schizophrenia has changed over time, since the first descriptions of the disorder. Kraepelin made a distinction between active attention (*i.e.,* aufmerksamkeit) and passive attention (*i.e.,* auffassung) in schizophrenia, indicating with the former the ability to voluntary keep attention fixed for a period of time, whereas the latter concerned the attraction towards external stimuli[1]. Years later, these concepts have been called vigilance and distractibility respectively[2]. Also Jung explored cognitive features of schizophrenia. Using his word association task, he elaborated that attention of patients with schizophrenia appeared to be caught up in a series of feeling-organized ideas[3] , resulting from an internal distraction[4]. Jung's theory strongly influenced Bleuler.

In Bleuler's conceptualization, schizophrenia was characterized by two types of symptoms (*i.e.*, fundamental and accessory), and psychotic symptoms were considered as secondary to fundamental symptoms[5]. In fact, whereas accessory symptoms had a waxing and waning course, fundamental symptoms were more stable over time[5,2]. Regarding attention, Bleuler[5] reported that the tendency to fatigue sometimes was the cause of the reduction of attention.

Since impaired attention is a core characteristic of ADHD, and since the individuals who developed schizophrenia-spectrum disorders in adulthood have more often a history of childhood ADHD[6], it would be of interest exploring the relationship between ADHD and schizophrenia. In line with the focus of Research Domain Criteria project[7,8], we aim to use clinical epidemiological and neuropsychological findings as a point of departure for discussing the need of future investigation on potential common aberrations in fundamental neural system and neuropsychological functioning of these illnesses, that may impact on their treatment responsiveness, level of impairment and recovery processes.

CLINICAL EPIDEMIOLOGY

A history of ADHD symptoms has been commonly found in a sub-set of individuals who develop schizophrenia in adulthood[9-13], and ADHD is diagnosed in a high proportion of children at genetic risk for schizophrenia[14]. In the prospective longitudinal study of Kim-Cohen *et al*[15], more than 50% of adults with schizophrenia met the criteria for another psychiatric disorder in early adolescence, and ADHD, conduct disorder and oppositional defiant disorder were, among them, the most frequently reported. Moreover, a retrospective study performed by Rubino *et al*[16] found that a diagnosis of ADHD in childhood was most predictive of schizophrenia in adulthood compared to unipolar depression. Follow-up studies focusing on adult outcome of childhood ADHD[17,18] confirmed that youth with ADHD constitute a high risk group for developing a wide range of psychiatric diseases[17], and that children and adolescents with ADHD were 4.3 times more likely to develop schizophrenia later in adulthood compared to controls[18]. Moreover, females with ADHD presented a greater risk ratio for schizophrenia (RR = 20.1, 95%CI: 4.1-58.6), compared to males with ADHD (RR = 2.9, 95%CI: 1.1-6.8). Interestingly, duration of treatment with stimulants was not associated significantly with the development of schizophrenia[18]. Taken together, these findings indicate that children and adolescents with ADHD are at higher risk of developing schizophrenia than those who do not have ADHD.

NEUROPSYCHOLOGICAL FUNCTIONING

There are only a few studies comparing attentional dysfunction in schizophrenia and ADHD, and in some cases research findings are difficult to compare because of the definition of attention used, and also because of the varying methodology. As Luck *et al*[19] (2008) reported, the term "attention" has been defined so broadly in literature that it is difficult to compare the extent of attentional deficits among the disorders. Moreover, the interrelation between attention and other cognitive functions, such as working memory and executive functioning, it make difficult to isolate the attention deficit from disturbances in other cognitive functions. Another methodological concern is that studies performed in these groups typically use different versions of continuous performance tests (CPTs): whereas the CPT versions used in schizophrenia typically require the subjects to uphold vigilance to a multitude of stimuli, and to respond only to few of them, in ADHD the CPT protocol requires subjects to respond almost continuously[20,21]. This is because the goal is to investigate diminution in attention in schizophrenia, and to study the inhibition of impulsive responses in ADHD. Results show that adults with ADHD are more impaired to auditory

CPT compared to controls[22], presenting a slower reaction time, more errors of omission and late responses. Conversely, patients with schizophrenia present a reduced sensitivity without the increase of omission errors, considered measures of sustained attention[23,24]. Such differences have been suggested as reflecting distinct neurobiological underpinnings: a compromised ability to discriminate target from non-target noise stimuli in schizophrenia, and a difficulty in deciding if a stimulus is or not the target in ADHD[25].

Event-related potentials have been extensively used as measures of attention, and abnormalities have been found both in schizophrenia and ADHD. Specifically, patients with schizophrenia appear to be characterized by the inability to suppress the auditory event-evoked potential P50[25], by an amplitude reduction and a prolonged latency of auditory P3[26]. Since P50 alterations in P50 auditory evoked response-a measure of sensory gating-have also been found in first-degree relatives of patients with schizophrenia[27,28], in subjects with schizotypical personality[29], and in patients in remission who are not pharmacologically treated[30], dysfunction in sensory gating has been proposed as a potential biological marker for schizophrenia. However, a defective gating P50 is present also in other neuropsychiatric disorders, such as bipolar disorder[31,32], panic disorder[33], or post-traumatic stress disorder[34]. It seems that sensory gating dysfunction in schizophrenia has a genetic basis[35,36], and is associated with the chromosome 15q14locus of the gene encoding the α7 nicotinic receptor agonists[37,38]. Also the prepulse startle inhibition (PPI)-a measure of sensory motor gating-has been found impaired in schizophrenia, confirming the dysfunction in automatic or pre-attentional gating.

Moreover, altered visual N2 and P3[39,40] have been found in schizophrenia, although not in all studies[41,42]. N2 and P3 abnormalities are not specific to schizophrenia, having been also found in some studies with childhood ADHD[43-47]. A recent study performed on adolescents with early onset schizophrenia and subjects with ADHD on auditory oddball task and a visual go/no-go task found that the early schizophrenia group showed reductions in auditory oddball P3 and N2 amplitude, as well in the go/no-go visual P3[48]. Conversely, ADHD group showed a different ERP pattern, characterized by reduced visual N2 in the go/no-go task and a normal P3 amplitude in the go/no-go and auditory oddball tasks. However, previous results in ADHD[49-51] suggest that such P3 differences could be the results of developmental trajectories, tending to normalize with age[48].

PPI has been consistently reported as normal in ADHD[52-54], but a recent study found an abnormal P50 suppression also in ADHD[52]. This finding seems in line with the hypothesis that the attention deficit associated with ADHD may reflect a different neural substrate compared to schizophrenia.

Some studies have used measures of visual scanning in order to investigate the relationship between ADHD and schizophrenia. Indeed, even eye movements involve attentional processes, and increased anticipatory saccades are thought to represent an inability to select task appropriate behavior, which leads to increased task-inappropriate attentional shifts[55]. Deficits in early visual processing have been largely reported in schizophrenia[56-58]; studies of smooth pursuit eye movement have consistently shown greater anticipatory saccades in children of schizophrenic parents[55], adult schizophrenia[59,60] and children and adolescents affected by the disease[61] . However, increased premature saccades have been found also in ADHD during an oculomotor delayed response task[59,60]. Even though impairment in inhibiting responses to task irrelevant information seems to be present in both groups, patients with schizophrenia appeared to be more compromised, since it has been found they also have impaired selection of appropriate targets[59,60] .

Studies investigating affect recognition reported some differences in visual scanning style[62-64], and brain imaging studies seem to support the notion that impairment noticed in schizophrenia and ADHD involve different circuits. For example, perception of negative emotions in schizophrenia has been associated with decreased responses in both amygdala and medial prefrontal cortex[65,66], whereas a fMRI study performed by Hare *et al*[67] showed an amygdlar activation in subjects with ADHD during evaluation of negative emotions. Impairments in emotion perception in ADHD and schizophrenia may result from different abnormalities in prefrontal and subcortical circuits, key regions for emotional processing and also for motivational behavior. It would worthwhile to explore this further.

EPIGENETICS

A heritability estimate of 80% has been reported for schizophrenia[68], whereas it ranges from 60% to 80% in ADHD[69]. Although increasing evidence points towards the role of genetic factors in etiology of both schizophrenia and ADHD, environmental risk factors have been also explored and implicated[70,71]. Epigenetics concerns the functional modification of a genome expressions that is not associated with an alteration in sequence of the nucleotide[72]. Interactions between genes and environment are the basis of epigenetics, and are responsible for modifications in the expression of the genetic background of the individual, contributing to psychopathology[73]. In fact, potential epigenetic factors may confer risk for both disorders at various developmental phases, and environmental factors seem to have important roles in the etiology of psychotic illnesses both in pre- and post-natal periods[74]. Therefore, the early perinatal period is fundamental for proper brain development, and potential stress-inducing factors have been associated with schizophrenia, but also with ADHD[75,76].

Environmental risk factors

Studies on incidence and prevalence of both disorders show variations in rates according to place and time. Although this variance could be explained by the use of different methodologies and diagnostic classifications, analysis of these aspects may help to recognize potential environmental risk factors for the development of both these disorders.

A recent study performed on the health database of the Kaiser Permanente Southern California showed an ADHD prevalence rate of 0.36% in 2006 and of 0.65% in 2009[77], that is clearly in contrast with the overall prevalence of 2.9%-5.2% of the disorder as reported in adults[78]. In a meta-regression analyses to 135 studies, Polanczyk *et al*[79] found that differences in ADHD prevalence estimates could be mostly explained by methodological issues characterizing these studies. Therefore, the higher incidence of ADHD could be attributed to the lack of standardized assessment in most studies.

However, in literature some modifiable risk factors have been implicated in the pathophysiology of ADHD, which should be also taken into account. Among these, the most frequently mentioned are prenatal substances exposure, nutritional deficits and psychosocial factors[76]. Recently, low birth weight has been found significantly associated with ADHD even after controlling for environmental and genetic variables shared within twin pairs[80]. Prenatal maternal stress has been linked to increased risk of ADHD[81,82], and maternal smoking during pregnancy is the most cited among prenatal risks for the disorder[83,84], such as alcohol and illicit substances use during pregnancy[85]. Concerning nutritional factors, there are some controversial findings on the associations between low iron and ferritin and ADHD emergency, with some studies reporting such associations[86,87], and others do not[88,89]. However, deficiencies of folate, zinc, magnesium and polyunsaturated fatty acids have been shown to increase risk for ADHD[76,84].

Regarding schizophrenia, a review by McGrath *et al*[90] reporting incidence data for schizophrenia from 1965 to 2001, showed an incidence rate of 15.2 per 100000 and a range of 7.7-43 per 100000, suggesting an influence of environmental factors on these different rates, since genetic differences seem unlikely to explain such variations. Moreover, risk for schizophrenia seems to increase for individuals raised in urban areas, compared to those living in rural areas[91-93], providing support to the environmental hypothesis. Among peri-natal risk factors for schizophrenia, infections, nutritional deficits, toxins, and other sociocultural factors have been reported[71,94]. Infections during pregnancy with viruses such as rubella, varicella-zoster, polio, herpes as well parasites as toxoplasma, have been demonstrated to increase risk for the disease[71,95]. Maternal infections and inflammatory processes have been involved in preterm labor[96,97]. Obstetric complications are reported as factors contributing susceptibility for schizophrenia[71] and, as in ADHD, also in schizophrenia low birth weight was found associated with an increased risk to develop the disorder[98]. Although it is not possible to establish a causal effect, literature on nutritional deficiencies and schizophrenia susceptibility show some evidence of iron and vitamin D deficiencies as maternal risk factor for schizophrenia[71], such as a decreased choline[99]. Interestingly, considering that amniotic choline activates fetal α7-nicotinic acetylcholine receptors and promotes cerebral inhibition, it seems plausible that the increase of such activation through choline supplementation may protect infants from future mental diseases[100].

Stimulants and psychosis

In examining relationship between schizophrenia and ADHD, it is necessary to consider the fear regarding the potential of psychostimulants in producing psychosis or in increasing risk to develop schizophrenia. On this issue, literature reports controversial findings. A study reported that 77% of youth with psychosis had been exposed to psychostimulants[101]. The age of onset of psychosis was lower in subjects exposed to psychostimulants compared to non-exposed individuals[102], and there are some reports describing the emergence of hallucinations and delusions in ADHD induced by stimulant medication[103].

Both methylphenidate and *d*-amphetamine are considered effective and well tolerated pharmacological agents, and are still considered first-line choice for the treatment of ADHD[104]. Even though there is reluctance to treat patients with ADHD and psychosis with such medications, several studies show that stimulant treatment is safe. In fact, there are case studies demonstrating that stimulants have been well tolerated in subjects with psychosis, with or without concomitant antipsychotic treatment[105-109], with positive effects on cognition[110,111]. It has been suggested that the positive effect of methylphenidate, described in some studies, may be due to a regulation of frontal hypodopaminergic state[110,112]. In fact, methylphenidate affects dopamine D1 receptors in frontal regions improving cognition, whereas antipsychotics block D2 receptors in mesolimbic systems, without influencing D1 receptors[110]. On the other hand, it has been suggested that small but repeated doses of stimulants produce some alterations in the brain resulting in psychotic symptoms resembling schizophrenia[113]. This theory of sensitization has received support from some animal experiments[114], but has been also debated[115]. Curran *et al*[116] performed a systematic review investigating relationship between stimulant use and psychosis in humans. They examined 32 experimental studies, of which 28 involved the administration of a single dose of oral or intravenous dexamphetamine or methylphenidate to patients with schizophrenia. Their review reported evidence that a large administration of stimulant medication can produce a psychosis, usually lasting only some hours, and that positive symptoms

make individuals more likely to experience a worsening of psychotic symptoms. However, they did not found sufficient support for the sensitization theory, except in two studies[117,118].

Unfortunately, literature on adult ADHD as comorbid condition in psychotic symptoms is still scarce, and there is a lack of recommended pharmacological interventions for the treatment of patients affected by both conditions. Trying to differentiate some peculiarities of psychosis in presence of ADHD, Bellak *et al*[119] proposed a separate diagnostic category called ADD Psychosis. According to Bellak and colleagues, attention deficit disorder (ADD) could impact on the development of personality predisposing the individual, in some cases, to psychosis during the years of late adolescence or early adulthood, with distinctive features. In fact, ADD Psychosis was different from Schizophrenia because of rare or no hallucinations (that were brief and simple if present), concrete thinking (no thought disorder), poor impulse control, little or no social withdrawal, soft neurological signs, presence of dyslexia or dysgraphia, lack of response by neuroleptics, and favourable response to psychostimulants.

On the basis of case reports by Huey *et al*[120], Bellak *et al*[119], Pine *et al*[121], Opler *et al*[112] suggested a trial of psychostimulants in patients presenting both ADD and psychosis, with a poor response to neuroleptics. The cited studies show no worsening of psychotic symptoms but an amelioration of both attentional deficits and psychotic symptoms, probably by increasing perfusion to the frontal lobes[112].

In evaluating controversial results in literature regarding psychosis-induced by stimulant medication, Kraemer *et al*[122] suggested that psychosis in ADHD may be due to the combination of methylphenidate with other substance such as cannabis, alcohol, or illegal drugs. It is also possible that psychosis co-existed with ADHD, or even that psychosis was be the result of a undetected bipolar disorder, rather than to the stimulant treatment effect. Therefore, further research is needed in order to elucidate the potential of psychostimulant in producing psychotic symptoms. This is especially important considering that ADHD is currently recognized as a disorder affecting the entire course of life, consequently the use of psychostimulant medication could be continued over the lifespan[123].

Genetics and Neurobiology

The hypothesis regarding shared underpinnings between ADHD and schizophrenia has been supported by recent studies by Hamshere *et al*[124] and Larsson *et al*[125]. Such observation is consistent with an observation of an overlap in genetic susceptibility between ADHD and schizophrenia for rare copy number variants reported elsewhere[126]. Moreover, recent evidence from Hart *et al*[127] showed that SNPs associated with response to a dopaminergic drug challenge were enriched for those SCNPs associated with disorders usually treated with dopaminergic agonists (*i.e.,* ADHD) and antagonists (*i.e.,* schizophrenia), consequently SNPs nominally associated with schizophrenia and ADHD resulted associated with d-amphetamine response. They also found that the increased euphoric effects of d-amphetamine resulted associated with a decreased risk for both schizophrenia and ADHD. As has been suggested, these results provide support for the dopamine involvement in the pathogenesis of these disorders, and the acute amphetamine response may be further explored as an endophenotype for both schizophrenia and ADHD. However, it has been found a higher risk of a comorbid bipolar disorder rather than schizophrenia in people with ADHD[125]. This may be due to the fact that ADHD and bipolar disorder share more symptoms than ADHD and schizophrenia[128]. Irritability, distractibility, overactivity and impulsivity are very common among individuals with ADHD and/or bipolar disorder, and may therefore be of limited utility in differentiating the two groups, and their impact on the emergence of psychosis. Comparative studies examining common substrates across these disorders are warranted.

CONCLUSION

Until now only a few studies have made efforts to unravel the genetic and neurophysiological aetiology of ADHD symptoms in schizophrenia. It is still uncertain whether ADHD comorbid with psychosis constitutes a more severe subgroup of psychosis[129], or is an index of the severity of psychosis[102]. ADHD and schizophrenia share some features that require further investigation because it is possible that attentional disturbance characterizing both disorders may be fundamentally different.

The first difference of course is that attentional dysfunction emerges before 12 years of age in ADHD (DSM 5, APA 2013)[130], whereas this is not reported for Schizophrenia. Therefore, this difference has to be considered in the assessment.

Direct comparisons between these disorders will add to our knowledge of potential common aberrations in fundamental neural systems, and allow the identification of neural systems that are critical for the characterization of brain abnormalities and structural endophenotypes detectable by neuroimaging. Research is also needed in order to clarify the controversies regarding the differential diagnosis between BD and ADHD, and the relationship of these disorders with the emergence of psychosis in people using stimulant drugs.

Taken together, the findings reviewed above suggest the importance of screening for an ADHD diagnosis in neuroleptic refractory adult patients with psychosis. Although follow-up studies are warranted in order to have a better understanding of the risks and benefits of combining antipsychotics and psychostimulants in such clinical settings, the few studies, in which ADHD symptoms have been assessed in the second place,

did not report additional risk to the augmentation with drugs for ADHD treatment to antipsychotics in the stabilization phase. Deepening our understanding of the circuits underpinning these disorders may offer insights into phenotypes and more targeted interventions, which may also lead to plan early intervention and prevention.

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Via Giuseppe La Masa, 19 - 20156 Milano MI - Italia - www.marionegri.it
tel +39 02 39014.511 - fax +39 02 3550924 - mother_child@marionegri.i