NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD FEBBRAIO 2019

Acta Paediatr Int J Paediatr. 2019.
OWN-GENDER BIAS IN SCHOOL STAFF'S RECOGNITION OF CHILDREN WITH ADHD.
Ghosh E, Nilsson KW, Isaksson J.

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ADHD Atten Deficit Hyperact Disord. 2019.
THE IMPORTANCE OF AVOIDANT PERSONALITY IN SOCIAL ANXIETY DISORDER WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Yoldas C, Dogan B, Kocabas O, et al.
In the present study, our primary aim was to compare the generalized social anxiety (GSAD) patients with and without attention-deficit/hyperactivity disorder (ADHD) in terms of avoidant personality disorder (AVPD), and some clinical variables. We also investigated the relationship of AVPD and depression with ADHD and GSAD. We hypothesized that ADHD may be associated with AVPD in patients with GSAD. Seventy-six patients with GSAD were evaluated for depression, AVPD, and childhood and adulthood diagnoses of ADHD. The GSAD patients with (n = 34) and without adulthood ADHD (n = 30) were compared with respect to some sociodemographic and clinical variables. GSAD patients with adulthood ADHD had significantly higher comorbid diagnosis of AVPD, more avoidant personality and depression symptoms than those without ADHD. PearsonΓÇÖs correlation coefficient in total sample (n = 76) showed that the mean number of AVPD criteria was significantly associated with the severity of Beck Depression Inventory, Wender Utah Rating Scale (WURS), and inattention symptoms of ADHD. There were no correlations between the total and subscale scores of Liebowitz Social Anxiety Scale and the mean number of AVPD criteria. The scores of WURS significantly predicted the mean number of AVPD criteria (+¦ = 0.305, p= 0.007). The severity of current depression (+¦ = 0.143, p = 0.30) and inattention symptoms of adulthood ADHD (+¦ = 0.112, p = 0.46) were not associated with the severity of AVPD symptoms. These results might demonstrate that comorbid AVPD in adult SAD patients was related to a childhood ADHD independent from depression, and inattention symptoms of ADHD in adulthood

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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.

Alcohol Clin Exp Res. 2019;43:342-52.

ROLE OF ADHD IN THE CO-OCCURRENCE BETWEEN HEAVY ALCOHOL USE AND DEPRESSION TRAJECTORIES IN ADULTHOOD.

Wang FL, Pedersen SL, Joseph H, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is associated with greater heavy alcohol use and depressive symptoms in adulthood. Yet, few studies have investigated whether childhood ADHD predicts an increased association between heavy drinking and depression in adulthood when this co-occurrence becomes more common. We examined associations among heavy alcohol use and depression longitudinally from ages 21 to 29 and whether these associations differed for those with or without childhood ADHD, as well as for those with or without persistent ADHD in adulthood.

Methods: Data were from the Pittsburgh ADHD Longitudinal Study, a prospective cohort of children diagnosed with ADHD and demographically similar individuals without ADHD histories. ADHD symptoms in adulthood were self- and parent reported; depressive symptoms and frequency of drinking 5 or more drinks in a single drinking occasion were self-reported and measured at 5 time-points from ages 21 to 29. Depression and alcohol use were modeled in a multiple-group, parallel process longitudinal growth model.

Results: The slopes of heavy alcohol use and depression were significantly and positively associated from ages 25 to 29 but not at the younger ages. Although the strength of these associations did not differ by group (with or without ADHD, childhood or adulthood), the slopes of depression and heavy drinking at the older ages were highly variable and individuals with ADHD showed significantly faster growth in depression from ages 25 to 29.

Conclusions: Due to the strengthening association between heavy drinking and depression for adults in their late 20s, and increasing depression for adults with ADHD histories, individuals with ADHD may be at greater risk for co-occurring depression and binge drinking. Negative reinforcement-related alcohol use may strengthen as these individuals age toward the fourth decade of life. More rigorous testing of this possibility is warranted

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Arthritis and Rheumatology. 2018;70:270-71.

PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG PATIENTS WITH FIBROMYALGIA.

Moyano S, Berrios W, Gandino IJ, et al.

Background/Purpose: Chronic diseases involve cognitive aspects. Attention deficit hyperactivity disorder (ADHD) is a chronic condition, marked by persistent inattention, impaired concentration, hyperactivity, impulsivity, emotional lability, anxiety and disorganized behavior. Fibromyalgia (FM) includes a range of symptoms affecting memory, attention and concentration. High rates of comorbidity between ADHD and FM have been reported, as well as some evidence that patients with both conditions experience heightened symptom severity. In addition, recent studies suggest that vitamin D deficiency is associated with cognitive impairment.

Methods: Consecutive patients, older than 18 years, with diagnosis of fibromyalgia (2010 ACR criteria) seen at the outpatient Rheumatology Unit between May 2016 and April 2017, were included. During the inclusion visit the following data were collected: Revised Fibromyalgia Impact Questionnaire (FIQ-R), HAQ-A (Health Auto Questionnaire-simplified, Argentine validation); pain (Visual Analogue Scale, VAS), fatigue (VAS) and serum 25 -hydroxyvitamin D (25(OH)D) level. During the Neurology visit, the following tests were performed: Conners Continuous Performance Test II (CPT II), Wender-Utah Rating Scale (WURS) and Structured Clinical Interview for Personality Disorders (SCID-II). Descriptive statistics were calculated. Correlations were calculated between CPT II and pain, fatigue, FIQ-R, HAQ-A and 25(OH)D, using Spearman's test.

Results: 37 patients with FM were included. Patients' characteristics are shown in table 1. 73% (n=27) of the patients tested positive for adult ADHD. In 40.7% (11/27) of them, the diagnosis had been missed in childhood. Participants with both FM and a positive adult ADHD screening test did not score significantly higher on the FIQ-R (54.9, SD= 16.3 vs 48.8, SD= 11,3; p= 0.3320) and did not have lower vitamin D levels (27,4 ng/ml, SD= 13,1 vs 36,7 ng/ml, SD= 9,6; p= 0.1050). There was a very good positive correlation between ADHD and fatigue (r= -0.9607; p= 0.0086). No association was found between ADHD and severity of perceived cognitive symptoms (p= 0,673). There was no correlation with pain (r= 0.1688 p=0.3325), HAQ-A (r= 0.1340; p= 0.4429) or vitamin D level (r= -0.3211; p=0.1176). No correlation was observed between

vitamin D levels and FIQ-R (r= -0.1848; p= 0.3662). The most frequent personality disorders found were narcissism (32,4%) and obsessive-compulsive disorder (32,4%).
Conclusion: The co-occurrence of adult ADHD in FM was highly prevalent. The diagnosis had been often overlooked in childhood. ADHD was associated with fatigue but not with pain, disease impact or functional capacity. Vitamin D levels were no associated with disease impact or dyscognition. Patients with FM should be assessed for the presence of adult ADHD. More investigations are needed to understand the impact of cognitive disorders in FM

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Aust New Zealand J Psychiatry. 2019.

ASSOCIATION OF MATERNAL PRENATAL ACETAMINOPHEN USE WITH THE RISK OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN OFFSPRING: A META-ANALYSIS.

Gou X, Wang Y, Tang Y, et al.

Background: Acetaminophen is a widely used medication for fever and pain management during pregnancy. However, recent studies have found a possible connection between maternal prenatal acetaminophen use and attention deficit/hyperactivity disorder in children.
Objective: We aimed to explore the association between maternal acetaminophen use during pregnancy and the risk of attention deficit/hyperactivity disorder in offspring.
Data sources: PubMed, Embase, Web of Science and Cochrane Library were searched from their initial publications through November 2018 for studies.
Study selection: We included all studies that examined the association between maternal acetaminophen use during pregnancy and the risk of attention deficit/hyperactivity disorder in offspring if the authors reported odds ratios, risk ratios, hazard ratios, regression coefficient, standard error and 95% confidence intervals.
Data extraction and synthesis: Two reviewers independently extracted data on the definition of exposure and outcome, exposed, non-exposed and total number of participants in the sample population, adjusted potential confounders and outcome parameters. Study quality was also assessed.
Results: Eight cohort studies with a total of 244,940 participants were included. Maternal exposure to acetaminophen during pregnancy increased the risk of attention deficit/hyperactivity disorder in offspring with a pooled adjusted risk ratio of 1.25 (95% confidence interval = [1.17, 1.34]). Children exposed prenatally to acetaminophen in the third trimester seemed to have the greatest risk of developing attention deficit/hyperactivity disorder (risk ratio: 1.26; 95% confidence interval = [1.08, 1.47]). In addition, a longer duration of maternal acetaminophen use during pregnancy was correlated with a higher risk ratio. Children whose mothers used acetaminophen for 28 or more days during gestation had a higher risk of developing attention deficit/hyperactivity disorder (risk ratio: 1.63; 95% confidence interval = [1.23, 2.16]).
Conclusion: There is an association between maternal acetaminophen use during pregnancy and the risk of attention deficit/hyperactivity disorder in offspring. The timing and duration of acetaminophen use during pregnancy may have a major effect on the risk of attention deficit/hyperactivity disorder

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Autism. 2019;23:468-76.

FACTORS ASSOCIATED WITH DSM-5 SEVERITY LEVEL RATINGS FOR AUTISM SPECTRUM DISORDER.

Mazurek MO, Lu F, Macklin EA, et al.

The newest edition of the Diagnostic and Statistical Manual of Mental Disorders (5th ed., DSM-5) introduced substantial changes to the diagnostic criteria for autism spectrum disorder, including new severity level ratings for social communication and restricted and repetitive behavior domains. The purpose of this study was to evaluate the use of these new severity ratings and to examine their relation to other measures of severity and clinical features. Participants included 248 children with autism spectrum disorder who received diagnostic evaluations at one of six Autism Treatment Network sites. Higher severity ratings in both domains were associated with younger age, lower intelligence quotient, and greater Autism Diagnostic Observation ScheduleΓÇôSecond Edition domain-specific symptom severity. Greater restricted and repetitive behavior severity was associated with higher parent-reported stereotyped behaviors. Severity ratings were not

associated with emotional or behavioral problems. The new DSM-5 severity ratings in both domains were significantly associated with behavioral observations of autism severity but not with measures of other behavioral or emotional symptoms. However, the strong associations between intelligence quotient and DSM-5 severity ratings in both domains suggest that clinicians may be including cognitive functioning in their overall determination of severity. Further research is needed to examine clinician decision-making and interpretation of these specifiers

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Autism. 2019.

CLINICAL EFFECTIVENESS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION TREATMENT IN CHILDREN AND ADOLESCENTS WITH NEURODEVELOPMENTAL DISORDERS: A SYSTEMATIC REVIEW.

Masuda F, Nakajima S, Miyazaki T, et al.

Neurodevelopmental disorders, including autism spectrum disorder, are common in children and adolescents, but treatment strategies remain limited. Although repetitive transcranial magnetic stimulation has been studied for neurodevelopmental disorders, there is no clear consensus on its therapeutic effects. This systematic review examined literature on repetitive transcranial magnetic stimulation for children and adolescents with neurodevelopmental disorders published up to 2018 using the PubMed database. The search identified 264 articles and 14 articles met eligibility criteria. Twelve of these studies used conventional repetitive transcranial magnetic stimulation and two studies used theta burst stimulation. No severe adverse effects were reported in these studies. In patients with autism spectrum disorder, low-frequency repetitive transcranial magnetic stimulation and intermittent theta burst stimulation applied to the dorsolateral prefrontal cortex may have therapeutic effects on social functioning and repetitive behaviors. In patients with attention deficit/hyperactivity disorder, low-frequency repetitive transcranial magnetic stimulation applied to the left dorsolateral prefrontal cortex and high-frequency repetitive transcranial magnetic stimulation applied to the right dorsolateral prefrontal cortex may target inattention, hyperactivity, and impulsivity. In patients with tic disorders, low-frequency repetitive transcranial magnetic stimulation applied to the bilateral supplementary motor area improved tic symptom severity. This systematic review suggests that repetitive transcranial magnetic stimulation may be a promising intervention for children and adolescents with neurodevelopmental disorders. The results warrant further large randomized controlled trials of repetitive transcranial magnetic stimulation in children with neurodevelopmental disorders

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Behav Brain Res. 2019;363:126-34.

STRESS RESPONSE GENES ASSOCIATED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A CASE-CONTROL STUDY IN CHINESE CHILDREN.

Chen X, Wang M, Zhang Q, et al.

To explore the associations between stress response genes and attention deficit hyperactivity disorder (ADHD) in children, we conducted a case-control study consisting of 406 newly diagnosed ADHD cases and 432 controls in Wuhan, China. We genotyped the candidate genes, nuclear receptor subfamily 3 group C member 1(NR3C1) and solute carrier family 6 member 4(SLC6A4), using the Sequenom MassARRAY technology. After correction by Bonferroni ($\alpha' = 0.05/6 = 0.008$), the rs6191 SNP was found to be associated with a reduced risk of ADHD in the dominant model (OR=0.564, 95% CI=0.389-0.819, P=0.003) while the rs25531 SNP was associated with an increased risk of ADHD in the multiplicative model (OR = 1.380, 95% CI=1.111-1.714, P=0.004). Additionally, both the rs6191 and rs25531 SNPs were significantly associated with the attention deficit factor (P = 0.006, P = 0.003, respectively) but not with the hyperactivity/impulsivity factor in the Swanson, Nolan and Pelham-IV Questionnaire (SNAP-IV) scale. Furthermore, we found that these two SNPs were significantly associated with pure ADHD, and not affected by the comorbidities (P=0.001, P=0.007, respectively). Besides, there was an interaction between these two SNPs.

This study demonstrated the role of NR3C1 and SLC6A4 polymorphisms in ADHD, yet independent replication of the findings of this study in multi-center and multi-stage studies with large samples is warranted in the future

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Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2019.

FUNCTIONAL CONNECTIVITY OF FRONTOPARIETAL AND SALIENCE/VENTRAL ATTENTION NETWORKS HAVE INDEPENDENT ASSOCIATIONS WITH CO-OCCURRING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN CHILDREN WITH AUTISM.

Yerys BE, Tun B, Satterthwaite TD, et al.

Background: Children with autism spectrum disorder (ASD) and co-occurring attention-deficit/hyperactivity disorder (ADHD) symptoms have worse functional outcomes and treatment response than those without ADHD symptoms. There is limited knowledge of the neurobiology of ADHD symptoms in ASD. Here, we test the hypothesis that aberrant functional connectivity of two large-scale executive brain networks implicated in ADHD the frontoparietal and salience/ventral attention networks also play a role in ADHD symptoms in ASD.
Methods: We compared resting-state functional connectivity of the two executive brain networks in children with ASD (n = 77) and typically developing control children (n = 82). These two executive brain networks comprise five subnetworks (three frontoparietal, two salience/ventral attention). After identifying aberrant functional connections among subnetworks, we examined dimensional associations with parent-reported ADHD symptoms.
Results: Weaker functional connectivity in ASD was present within and between the frontoparietal and salience/ventral attention subnetworks. Decreased functional connectivity within a single salience/ventral attention subnetwork, as well as between two frontoparietal subnetworks, significantly correlated with ADHD symptoms. Furthermore, follow-up linear regressions demonstrated that the salience/ventral attention and frontoparietal subnetworks explain unique variance in ADHD symptoms. These executive brain network ADHD symptom relationships remained significant after controlling for ASD symptoms. Finally, specificity was also demonstrated through the use of a control brain network (visual) and a control co-occurring symptom domain (anxiety).
Conclusions: The present findings provide novel evidence that both frontoparietal and salience/ventral attention networksΓÇÖ weaker connectivities are linked to ADHD symptoms in ASD. Moreover, co-occurring ADHD in the context of ASD is a source of meaningful neural heterogeneity in ASD

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BMJ Evidence-Based Medicine. 2019.

DETERMINANTS OF INTER-PRACTICE VARIATION IN ADHD DIAGNOSIS AND STIMULANT PRESCRIBING: CROSS-SECTIONAL DATABASE STUDY OF A NATIONAL SURVEILLANCE NETWORK.

Hoang U, James AC, Liyanage H, et al.

Early recognition, identification and treatment of children with attention deficit hyperactivity disorder (ADHD) can reduce detrimental outcomes and redirect their developmental trajectory. We aimed to describe variations in age of ADHD diagnosis and stimulant prescribing among general practitioner practices in a nationwide network and identify child, parental, household and general practice factors that might account for these variations. Cross-sectional study of children aged under 19 years registered within a general practice in the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) network in 2016, RCGP RSC has a household key allowing parent and child details to be linked. Data from 158 general practices and 353 774 children under 19 were included. The mean age of first ADHD diagnosis was 10.5 years (95% CI 10.1 to 10.9, median 10, IQR 9.0-11.9) and the mean percentage of children with ADHD prescribed stimulant medications among RCGP RSC practices was 41.2% (95% CI 38.7 to 43.6). There was wide inter-practice variation in the prevalence of diagnosis of ADHD, the age of diagnosis and stimulant prescribing. ADHD diagnosis is more likely to be made later in households with a greater number of children and with a larger age difference between adults and children. Stimulant prescribing for children with ADHD was higher in less deprived practices. Older parents and families with more children fail to

recognise ADHD and may need more support. Practices in areas of higher socio-economic status are associated with greater prescribing of stimulants for children with ADHD

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Clinical and Experimental Ophthalmology. 2019.

INCIDENCE AND RISK OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH AMBLYOPIA: A NATIONWIDE COHORT STUDY.

Su C-C, Tsai C-Y, Tsai T-H, et al.

Importance: The association between visual deficits and attention disorders has been reported but remains unproven.

Background: The objective of this study was to evaluate the risk of attention-deficit hyperactivity disorder (ADHD) in children with amblyopia.

Design: Population-based, cohort study. Participants: The dataset from the Taiwan National Health Insurance Research Database in 2000 to 2010. Methods: A total of 6817 patients aged <18 years with newly diagnosed amblyopia were identified. Four age-matched and sex-matched controls without amblyopia were included for each patient, that is, 27 268 controls.

Main Outcome Measures: The primary outcome was the risk of ADHD. The secondary outcomes were age at ADHD onset and use of ADHD medication. Results: During a mean observation period of 7.18 years, the incidence of ADHD per 1000 person-years was 7.02 in the amblyopia group and 4.61 in the control group (P < 0.0001). The ADHD risk in the amblyopia group was 1.81 times that in the control group (hazard ratio 1.81; 95% confidence interval 1.59-2.06). After stratification by amblyopia subtype, the greatest risk was in the deprivation type (hazard ratio 2.14; 95% confidence interval 1.56-2.92) followed by the strabismic (hazard ratio 2.09; 95% confidence interval 1.15-3.79) and refractive (hazard ratio 1.76; 95% confidence interval 1.54-2.02) types. Age at ADHD onset was younger in the amblyopia group (median 8.14 vs 8.45 years; P = 0.0096). The average duration of neuropsychiatric medication was comparable between groups (P = 0.98).

Conclusions and Relevance: The ADHD risk is higher in children with amblyopia

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Clin Psychopharmacol Neurosci. 2019;17:105-12.

INCREASED SERUM HEPCIDIN LEVELS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Yazici KU, Yazici IP, Ustundag B.

Objective: In this study, we aimed to evaluate the serum hepcidin levels in attention deficit hyperactivity disorder (ADHD) patients that were newly diagnosed with no history of psychotropic drugs.

Methods: A total of 70 ADHD patients and 69 healthy controls were enrolled in our study. During the diagnosis, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version were applied. The sociodemographic data form, Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale, and Conners Rating Scales-Revised: Long Form were used for the clinical evaluation. Serum hepcidin levels were measured and compared between the groups.

Results: No significant difference between the groups in terms of age (p=0.533) and gender (p=0.397) was determined. In addition, the groups did not differ significantly for the other sociodemographic variables recorded. Serum hepcidin levels were found to be significantly higher in the patients with ADHD than healthy controls (p=0.019).

Conclusion: To the best of our knowledge, this study is the first to evaluate the total serum hepcidin levels in ADHD patients. Our study findings may suggest that high levels of hepcidin may cause iron dysregulation in ADHD patients. However, further studies are required to establish a definite conclusion

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Deutsches Arzteblatt International. 2018;115:A1708-A1709.

ATTENTION DEFICIT HYPERACTIVITY DISORDER: PREFERRING METHYLPHENIDATE ESPECIALLY FOR CHILDREN AND AMPHETAMINES FOR ADULTS.

Heinzl S.

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Dev Cognitive Neurosci. 2019;36.

EVIDENCE FOR AN ALTERED ARCHITECTURE AND A HIERARCHICAL MODULATION OF INHIBITORY CONTROL PROCESSES IN ADHD.

Chmielewski W, Bluschke A, Bodmer B, et al.

Inhibitory control deficits are a hallmark in ADHD. Yet, inhibitory control includes a multitude of entities (e.g. inhibition of interferencesΓÇÖ and ΓÇÿaction inhibitionΓÇÖ). Examining the interplay between these kinds of inhibitory control provides insights into the architecture of inhibitory control in ADHD. Combining a Simon task and a Go/Nogo task, we assessed the interplay of ΓÇÿinhibition of interferences and action inhibition. This was combined with EEG recordings, EEG data decomposition and source localization. Simon interference effects in Go trials were larger in ADHD. At the neurophysiological level, this insufficient inhibition of interferences in ADHD related to the superior parietal cortex. Simon interference effects were absent in action inhibition (Nogo) trials in ADHD, compared to controls. This was supported by bayesian statistics. The power of effects was higher than 95%. The differential effects between the groups were associated with modulations of neurophysiological response selection processes in the superior frontal gyrus. ADHD is not only associated with deficits in inhibitory control. Rather, the organization and architecture of the inhibitory control system is different in ADHD. Distinguishable inhibitory control processes operate on a hierarchical first come, first serve basis and are not integrated in ADHD. This is a new facet of ADHD

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Dev Med Child Neurol. 2019.

MENTAL HEALTH DISORDERS, PARTICIPATION, AND BULLYING IN CHILDREN WITH CEREBRAL PALSY.

Whitney DG, Peterson MD, Warschausky SA.

Aim: To examine how social factors might mitigate the elevated risk of mental health disorders in children with cerebral palsy (CP).

Method: This cross-sectional study included 6- to 17-year-olds with (n=111; 40.4% 6ΓÇô11y, 59.6% 12-17y) and without (n=29-á909; 50.2% 6-11y, 49.8% 12-17y) CP from the 2016 National Survey of Children's Health. Mental health disorders included depression, anxiety, behavior/conduct problems, and attention-deficit/hyperactivity disorder. Social factors included participation in activities, bully victimization, and difficulty with friendships.

Results: After adjusting for sociodemographic factors and the presence of chronic pain, children with CP had higher odds of anxiety (odds ratio [OR] 4.4; 95% confidence interval [CI] 1.9ΓÇô8.5), behavior/conduct problems (OR 3.9; 95% CI 1.4-11.3), and multimorbidity (OR 2.8; 95% CI 1.1-7.0), but not depression (OR 1.4; 95% CI 0.6-3.8) or attention-deficit/hyperactivity disorder (OR 1.7; 95% CI 0.6-4.6), compared to controls. With adjustment for participation in activities, the odds of anxiety, behavior/conduct problems, and multimorbidity remained increased in children with CP. With adjustment for difficulty with friendships, the odds of anxiety, behavior/conduct problems, and multimorbidity were no longer increased in children with CP. With adjustment for bully victimization, the odds of behavior/conduct problems and multimorbidity were attenuated in children with CP; however, the odds of anxiety remained increased.

Interpretation: The elevated prevalence of certain mental health disorders in children with CP is partly associated with modifiable social factors

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Drug Ther Bull. 2019.
LIMITED EVIDENCE FOR NON-DRUG TREATMENT OF CHILDHOOD ADHD.
Anon.

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Environ Health. 2019 Jan;18:4.
VERY LOW-LEVEL PRENATAL MERCURY EXPOSURE AND BEHAVIORS IN CHILDREN: THE HOME STUDY.
Patel NB, Xu Y, McCandless LC, et al.
BACKGROUND: Mercury is toxic to the developing brain, but the lowest concentration associated with the development of behavior problems is unclear. The purpose of this study was to examine the association between very low-level mercury exposure during fetal development and behavior problems in children.
METHODS: We used data from 389 mothers and children in a prospective pregnancy and birth cohort study. We defined mean prenatal mercury concentration as the mean of total whole blood mercury concentrations in maternal samples collected at 16- and 26-weeks of gestation, delivery, and neonatal cord blood samples. We assessed parent-reported child behavior up to five times from two to 8 years of age using the Behavioral Assessment System for Children (BASC-2). At 8 years of age, we assessed self-reported child anxiety using the Spence Children's Anxiety Scale (SCAS). We used multiple linear mixed models and linear regression models to estimate the association between mean prenatal mercury concentrations and child behavior and anxiety, respectively.
RESULTS: The median prenatal total blood mercury concentrations was 0.67 mug/L. Overall, we did not find statistically significant associations between mean prenatal mercury concentrations and behavior problems scores, but a 2-fold increase in mercury concentrations at 16-weeks gestation was associated with 0.83 point (95% CI: 0.05, 1.62) higher BASC-2 anxiety scores. Maternal and cord blood mercury concentrations at delivery were associated with parent-reported anxiety at 8 years.
CONCLUSION: We found limited evidence of an association between very-low level prenatal mercury exposure and behaviors in children, with an exception of anxiety

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Environ Int. 2019;33-42.
EARLY-LIFE EXPOSURE TO PERSISTENT ORGANIC POLLUTANTS (OCPS, PBDES, PCBS, PFASS) AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A MULTI-POLLUTANT ANALYSIS OF A NORWEGIAN BIRTH COHORT.
Lenters V, Iszatt N, Forns J, et al.
Background: Numerous ubiquitous environmental chemicals are established or suspected neurotoxicants, and infants are exposed to a mixture of these during the critical period of brain maturation. However, evidence for associations with the risk of attention-deficit/hyperactivity disorder (ADHD) is sparse. We investigated early-life chemical exposures in relation to ADHD.
Methods: We used a birth cohort of 2606 Norwegian mother child pairs enrolled 2002-2009 (HUMIS), and studied a subset of 1199 pairs oversampled for child neurodevelopmental outcomes. Concentrations of 27 persistent organic pollutants (14 polychlorinated biphenyls, 5 organochlorine pesticides, 6 brominated flame retardants, and 2 perfluoroalkyl substances) were measured in breast milk, reflecting the child's early-life exposures. We estimated postnatal exposures in the first 2 years of life using a pharmacokinetic model. Fifty-five children had a clinical diagnosis of ADHD (hyperkinetic disorder) by 2016, at a median age of 13 years. We used elastic net penalized logistic regression models to identify associations while adjusting for co-exposure confounding, and subsequently used multivariable logistic regression models to obtain effect estimates for the selected exposures.
Results: Breast milk concentrations of perfluorooctane sulfonate (PFOS) and exachlorocyclohexane (+¦-HCH) were associated with increased odds of ADHD: odds ratio (OR) = 1.77, 95% confidence interval (CI): 1.16, 2.72 and OR = 1.75, 95% CI: 1.22, 2.53, per interquartile range increase in ln-transformed concentrations, respectively. Stronger associations were observed among girls than boys for PFOS (pinteraction = 0.025). p,p Dichlorodiphenyltrichloroethane (p,p¦-DDT) levels were associated with lower odds of ADHD (OR = 0.64, 95% CI: 0.42, 0.97). Hexachlorobenzene (HCB) had a non-linear association with

ADHD, with increasing risk in the low-level exposure range that switched to a decreasing risk at concentrations above 8 ng/g lipid. Postnatal exposures showed similar results, whereas effect estimates for other chemicals were weaker and imprecise.
Conclusions: In a multi-pollutant analysis of four classes of chemicals, early-life exposure to +¦-HCH and PFOS was associated with increased risk of ADHD, with suggestion of sex-specific effects for PFOS. The unexpected inverse associations between p,p¦-DDT and higher HCB levels and ADHD could be due to live birth bias; alternatively, results may be due to chance findings

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Epilepsia. 2019;60:284-93.
MEDICATION TREATMENT FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THE RISK OF ACUTE SEIZURES IN INDIVIDUALS WITH EPILEPSY.
Brikell I, Chen Q, Kuja-Halkola R, et al.
Objective: Attention-deficit/hyperactivity disorder (ADHD) affects 10%-30% of individuals with epilepsy, yet concerns remain regarding the safety of ADHD medication in this group. The objective of this study was to examine the risk of acute seizures associated with ADHD medication in individuals with epilepsy.
Methods: A total of 21-á557 individuals with a seizure history born between 1987 and 2003 were identified from Swedish population registers. Within this study population, we also identified 6773 youth (<19-áyears of age) who meet criteria for epilepsy, and 1605 youth with continuous antiepileptic drug (AED) treatment. ADHD medication initiation and repeated medication periods were identified from the Swedish Prescribed Drug Register between January 1, 2006 and December 31, 2013. Acute seizures were identified via unplanned visits to hospital or specialist care with a primary seizure discharge diagnosis in the Swedish National Patient Register during the same period. Conditional Poisson regression was used to compare the seizure rate during the 24 weeks before and after initiation of ADHD medication with the rate during the same 48 weeks in the previous year. Cox regression was used to compare the seizure rate during ADHD medication periods with the rate during nonmedication periods. Comparisons were made within-individual to adjust for unmeasured, time?constant confounding.
Results: Among 995 individuals who initiated ADHD medication during follow-up, within-individual analyses showed no statistically significant difference in the rate of seizures during the 24-áweeks before and after medication initiation, compared to the same period in the previous year. In the full study population 11-á754 seizure events occurred during 136-á846 person-years and 1855 individuals had at least one ADHD medication period. ADHD medication periods were associated with a reduced rate of acute seizures (hazard ratio [HR]-á0.73, 95% confidence interval [CI] 0.57-0.94), compared to nonmedication periods within the same individual. Similar associations were found in youth with epilepsy and continuous AED treatment, when adjusting for AEDs, and across sex, age, and comorbid neurodevelopmental disorders.
Significance: We found no evidence for an overall increased rate of acute seizures associated with ADHD medication treatment among individuals with epilepsy. These results suggest that epilepsy should not automatically preclude patients from receiving ADHD medications

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Eur Child Adolesc Psychiatry. 2019.
ABNORMAL FUNCTIONAL NETWORK CENTRALITY IN DRUG-NA+»VE BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Zhou M, Yang C, Bu X, et al.
Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder in childhood and is characterized by inattention, impulsivity, and hyperactivity. Observations of distributed functional abnormalities in ADHD suggest aberrant large-scale brain network connectivity. However, few studies have measured the voxel-wise network centrality of boys with ADHD, which captures the functional relationships of a given voxel within the entire connectivity matrix of the brain. Here, to examine the network patterns characterizing children with ADHD, we recruited 47 boys with ADHD and 21 matched control boys who underwent resting-state functional imaging scanning in a 3.0 T MRI unit. We measured

voxel-wise network centrality, indexing local functional relationships across the entire brain connectome, termed degree centrality (DC). Then, we chose the brain regions with altered DC as seeds to examine the remote functional connectivity (FC) of brain regions. We found that boys with ADHD exhibited (1) decreased centrality in the left superior temporal gyrus (STG) and increased centrality in the left superior occipital lobe (SOL) and right inferior parietal lobe-á(IPL); (2) decreased FC between the STG and the putamen and thalamus, which belong to the cognitive cortico-striatalΓ ÇôthalamicΓÇôcortical (CSTC) loop, and increased FC between the STG and medial/superior frontal gyrus within the affective CSTC loop; and (3) decreased connectivity between the SOL and cuneus within the dorsal attention network. Our results demonstrated that patients with ADHD show a connectivity-based pathophysiological process in the cognitive and affective CSTC loops and attention network

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Eur Child Adolesc Psychiatry. 2019.

SELF-REPORTED ATTACHMENT STYLES IN CHILDREN WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Hornstra R, Bosmans G, van den Hoofdakker BJ, et al.

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Eur Child Adolesc Psychiatry. 2019;28:281-88.

INCREASED RISK OF ADHD IN FAMILIES WITH ASD.

Septier M, Peyre H, Amsellem F, et al.

Attention Deficit and Hyperactive Disorder (ADHD) and Autism Spectrum Disorders (ASD) are frequent comorbid neurodevelopmental conditions and the overlap between both disorders remains to be delineated. A more complete understanding of the shared genetic and environmental factors is needed. Using a family-based method, we evaluated the risk of ADHD in a group of relatives with an ASD proband (ASDΓêÆ) and a group of relatives with an ASD and ADHD proband (ASD+). We enrolled 1245 individuals in the study: 499 probands, their 746 first-degree relatives and 140 controls. We used a multivariate generalized estimating equation (GEE) model, in which the dependent variable was the ADHD diagnosis in the relatives and the independent variable the ASD+ or ASD in probands. We adjusted for sociodemographic factors (age, sex, IQ) and for the nature of the familial relationship with the affected proband (parent or sibling). Among the probands, there were 287 ASDΓêÆ and 212 ASD+ individuals. ADHD was more frequent in relatives (19%) than in the control group (7%) (p = 0.001). The risk of ADHD was higher in the ASD+ relatives group than in the ASDΓêÆ relatives group (GEE model OR 1.58 [95% CI 1.04ΓÇô2.38], p = 0.032). This result was found in parents (OR 1.96 [95% CI 1.14ΓÇô3.36], but not in siblings (OR 1.28 [95% CI 0.84ΓÇô1.94], p = 0.434). Our study provides a representative estimate of the family distribution of ADHD in relatives of ASD probands but supports the modest effect of shared genetic and environmental factors between both disorders

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Eur Child Adolesc Psychiatry. 2019.

CHARACTERISATION OF DEPRESSIVE SYMPTOMS IN YOUNG CHILDREN WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Joseph CI, Evans S, Youssef GJ, et al.

Depressive symptoms and attention deficit hyperactivity disorder (ADHD) are prevalent and commonly co-occur in childhood. To assist with early identification of depression in children with ADHD, we aimed to: (1) use factor analysis to determine whether the construct of depression is measured consistently in those with and without ADHD; and (2) determine whether overall depressive symptoms and specific depressive symptoms were elevated in children with ADHD relative to controls. Participants comprised a community-based sample of 179 children with ADHD (51% Combined-ápresentation, 35% Inattentive-ápresentation) and 212 non-ADHD controls aged 6ΓÇô8-áyears. Participants were screened for ADHD and underwent a

structured diagnostic interview which confirmed ADHD status and assessed depressive symptoms. The factor structure of depressive symptoms was similar, enabling comparisons between the two groups to be made. Eighteen children with ADHD (10%) and three control participants (1%) experienced either MDD or subthreshold MDD. Children with ADHD experienced more depressive symptoms than controls (CohenΓÇÖs d =1.19, p < 0.001), with the following symptoms elevated in children with ADHD relative to controls: sadness (32% vs. 14%, p < 0.001), irritability (52% vs. 19%, p < 0.001), insomnia (56% vs. 22%, p < 0.001), psychomotor agitation (53% vs. 9%, p < 0.001), feeling bad about oneself (50% vs. 24%, p < 0.001), difficulty concentrating (75% vs. 14%, p < 0.001) and making decisions (56% vs. 17%, p < 0.001). This study provides support for the occurrence of depressive symptoms in children with ADHD as young as six and highlights the importance of early assessment for depressive symptoms in children with ADHD

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Eur Child Adolesc Psychiatry. 2019.

GENETIC AND ENVIRONMENTAL AETIOLOGIES OF ASSOCIATIONS BETWEEN DISPOSITIONAL MINDFULNESS AND ADHD TRAITS: A POPULATION-BASED TWIN STUDY.

Siebelink NM, Asherson P, Antonova E, et al.

To get additional insight into the phenotype of attentional problems, we examined to what extent genetic and environmental factors explain covariation between lack of dispositional mindfulness and attention-deficit/hyperactivity disorder (ADHD) traits in youth, and explored the incremental validity of these constructs in predicting life satisfaction. We used data from a UK population-representative sample of adolescent twins (N = 1092 pairs) on lack of dispositional mindfulness [Mindful Attention Awareness Scale (MAAS)], ADHD traits [ConnersΓÇÖ Parent Rating Scale-Revised (CPRS-R): inattentive (INATT) and hyperactivity/impulsivity (HYP/IMP) symptom dimensions] and life satisfaction (StudentsΓÇÖ Life Satisfaction Scale). Twin model fitting analyses were conducted. Phenotypic correlations (rp) between MAAS and CPRS-R (INATT: rp = 0.18, HYP/IMP: rp = 0.13) were small, but significant and largely explained by shared genes for INATT (% rp INATTΓÇôMAAS due to genes: 93%, genetic correlation rA = 0.37) and HYP/IMP (% rp HYP/IMPΓÇôMAAS due to genes: 81%; genetic correlation rA = 0.21) with no significant contribution of environmental factors. MAAS, INATT and HYP/IMP significantly and independently predicted life satisfaction. Lack of dispositional mindfulness, assessed as self-reported perceived lapses of attention (MAAS), taps into an aspect of attentional functioning that is phenotypically and genetically distinct from parent-rated ADHD traits. The clinically relevant incremental validity of both scales implicates that MAAS could be used to explore the underlying mechanisms of an aspect of attentional functioning that uniquely affects life satisfaction and is not captured by DSM-based ADHD scales. Further future research could identify if lack of dispositional mindfulness and high ADHD traits can be targeted by different therapeutic approaches resulting in different effects on life satisfaction

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Eur Child Adolesc Psychiatry. 2019.

STIMULANT TREATMENT PROFILES PREDICTING CO-OCCURRING SUBSTANCE USE DISORDERS IN INDIVIDUALS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Groenman AP, Schweren LJS, Weeda W, et al.

Adolescents with attention-deficit/hyperactivity disorder (ADHD) are at increased risk of developing substance use disorders (SUDs) and nicotine dependence (ND). It remains unclear whether and how stimulant treatment may affect this risk. We aimed to investigate how stimulant use profiles influence the risk of SUDs and ND, using a novel data-driven community detection analysis to construct different stimulant use profiles. Comprehensive lifetime stimulant prescription data and data on SUDs and ND were available for 303 subjects with ADHD and 219 controls, with a mean age 16.3-áyears. Community detection was used to define subgroups based on multiple indicators of treatment history, start age, treatment duration, total dose, maximum dose, variability, stop age. In stimulant-treated participants, three subgroups with distinct medication trajectories were distinguished (late-and-moderately dosed, n = 91; early-and-moderately dosed, n = 51; early-and-intensely dosed, n = 103). Compared to stimulant-na+»ve participants (n = 58), the early-

and-intense treatment group had a significantly lower risk of SUDs and ND (HR = 0.28, and HR = 0.29, respectively), while the early-and-moderate group had a significantly lower risk of ND only (HR = 0.30). The late-and-moderate group was at a significantly higher risk of ND compared to the other two treatment groups (HR = 2.66 for early-and-moderate, HR = 2.78 for early-and-intense). Our findings show that in stimulant-treated adolescents with ADHD, long-term outcomes are associated with treatment characteristics, something that is often ignored when treated individuals are compared to untreated individuals

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Eur J Clin Pharmacol. 2019 Feb 7. [Epub ahead of print]

THE EVIDENCE-BASED CHOICE FOR ANTIPSYCHOTICS IN CHILDREN AND ADOLESCENTS SHOULD BE GUARANTEED.

Putignano D, Clavenna A, Reale L, Bonati M.

PURPOSE: Drug use in the pediatric population still often features off-label prescriptions, particularly for psychotropic drugs. We reviewed the registration status, scientific evidence, and recommendations from the guidelines for antipsychotics used for psychiatric disorders in children.

METHODS: Antipsychotic drugs marketed in Italy, the United Kingdom (UK) and United States (US) were identified with the ATC Classification System. The licensing status and Summary of Product Characteristics (SPC) were taken from the national formularies. We analyzed reviews and guidelines on antipsychotics use in children and adolescents in the MEDLINE, EMBASE, and PsycINFO databases.

RESULTS: Out of 67 drugs, 19 were marketed with a pediatric license in at least one country: three in all the selected countries, and only paliperidone with the same indications. Haloperidol was the only antipsychotic authorized for autism in Italy and the UK, and as well as risperidone and aripiprazole in the US. Aripiprazole and paliperidone were licensed in all three countries for schizophrenia. Aripiprazole was licensed for bipolar disorders in all three countries. Haloperidol was licensed for Tourette syndrome in Italy and the UK, and pimozide and aripiprazole in the US. We retrieved 21 pertinent reviews and 13 guidelines for the management of neuropsychiatric disorders in pediatrics. There was a complete overlap between the authorized therapeutic indications and the available scientific evidence for autism in the US, for conduct disorders and bipolar disorders in the UK, and for Tourette syndrome and tics in the UK and Italy.

CONCLUSIONS: These results highlight the different regulatory processes that deny to many children and adolescents the most appropriate and rational antipsychotic therapy.

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Eur Neuropsychopharmacol. 2019;29:S141-S142.

PHARMACOLOGICAL TREATMENT OF ADHD: AN EVIDENCE MAP USING MINERVA DATABASE, A NEW TOOL FOR CLINICAL PSYCHOPHARMACOLOGY RESEARCH.

Castells X, Cunill R.

Introduction: The publication of randomized controlled clinical trials (RCCT) investigating the efficacy and safety of pharmacological interventions for Attention Deficit Hyperactivity Disorder (ADHD) is widespread. In this context, evidence mapping is a methodology that, using a systematic review approach, identifies knowledge gaps and future research needs [1]. To the best of our knowledge, no evidence map of pharmacological interventions for ADHD has been performed so far.

Aim: To describe the evidence available on the efficacy and acceptability of pharmacological interventions for ADHD and, eventually, identify evidence gaps and research priorities.

Methods: Design: an evidence map was performed. Source of information: Minerva database is a research tool that contains comprehensive information of all RCCT that have investigated the efficacy and safety of pharmacological interventions for ADHD. Minerva has data of more than 300 RCCTs published in more than 400 scientific articles, clinical trial registers, and regulatory agencies and industry web pages. Minerva stores information on study design, interventions and patients characteristics, efficacy results on multiple outcomes, treatment discontinuation, safety, physiological variables and the risk of bias of each RCCT. Minerva can be used to perform systematic reviews, meta-analyses and clinical trial simulations. Inclusion criteria: placebo-controlled RCCT investigating approved psychostimulants and non-stimulant drugs in patients with ADHD. RCCT with a study duration shorter than 3 weeks were excluded. Study outcomes: efficacy on ADHD

symptoms, drug use, accidents, academic achievement and acceptability (treatment discontinuation). Statistical analysis: Standardized mean difference and odds ratio were calculated for continuous and dichotomous outcomes. Effect estimates for each RCCT were pooled using meta-analytic techniques. Quality of the evidence was generated using GRADE methodology. Bubble charts were plotted to depict the type of intervention, the effect size of each outcome, the number of RCCT and the quality of the evidence.
Results: We included 145 RCCT that enrolled over 20.000 patients. Most studies were conducted in the United States, had a short duration (< 12 weeks) and a commercial sponsorship. We found moderate quality evidence that 1) psychostimulants had a medium-large efficacy on ADHD symptoms in children and adolescents, 2) outperformed placebo on acceptability in children and adolescents, but 3) did not in adults, and 4) non-stimulant drugs did not outperform placebo on acceptability in children, adolescents and adults. Furthermore, we found low quality evidence that 1) psychostimulants had a small-medium efficacy on ADHD symptoms in adults, 2) did not improve drug use in patients with comorbid substance use disorder (SUD), and 3) non-stimulant drugs had a moderate efficacy on ADHD symptoms in children and adolescents, 4) small efficacy on ADHD symptoms in adults, and 5) did not improve drug use in patients with a comorbid SUD. No evidence on pragmatic outcomes like accidents, prevention of drug use or academic achievement was found.
Conclusions: Numerous RCCT have investigated the efficacy and acceptability of pharmacological interventions for ADHD. Most studies were short-term and had a commercial sponsorship. The following gaps of research were identified: long-term studies and the investigation of the efficacy on pragmatic outcomes with clinical interest. More studies with an independent sponsorship should be performed, particularly in Europe

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Eur Neuropsychopharmacol. 2019;29:S433-S434.
A ROBOT-ASSISTED KINEMATIC MEASUREMENT FOR CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Kim SH, Min A, Ahn D.
Background: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by inattention, hyperactivity and impulsivity. Prior to 1980, it was called as attention deficit disorder (ADD). ADD has changed into ADHD to emphasise the importance of hyperactivity symptoms. Even after the change from ADD to ADHD, it has been not easy to measure the behavior of the children objectively since the most assessments tools for diagnosis are dependent on the subjective observation of the therapists and caregivers.
Objective: In this study, we verified whether a robot-assisted kinematic measurement for children with ADHD is useful as a diagnostic tool by using objective measuring the amount of activity. To accomplish this objective, we examined behavioural levels using robot-assisted kinematic measure for ADHD and compared the characteristics with the currently using questionnaire type diagnostic tools.
Methods: In this study thirty-five children diagnosed with ADHD and fifty children without ADHD between the ages of 5 to 12 year were participated. The response scores to robot-assisted kinematic measure stimuli were measured on the basis of 1) correct reaction, 2) commission error, 3) omission error and 4) complete rate. The robot-assisted kinematic measure variables were measured on the basis of 1) reaction time, 2) migration distance, 3) migration speed. The independent t-test and correlation analysis were performed to determine the differences between two groups in clinical variables of the robot evaluation and ADHD diagnostic evaluation which was done by the current methods using the Child Behavior Checklist (CBCL) and the Korean Attention Deficit Hyperactivity Disorder Diagnostic Scale (K-ADHDDS), which are the current standard evaluation tools for ADHD diagnosis. Statistical analysis was done using the SPSS ver. 20.0.
Results: There were significant differences between the ADHD and normal group in their mean CBCL score in attention problem, DSM ADHD and the K-ADHDDS score. There were also differences between the ADHD group and normal group in their robot-assisted kinematic measure variables in the mean of correct reaction, commission error, omission error, completion rate, reaction time, migration distance and migration speed score, except complete rate. The results of correlation analysis showed that the K-ADHDDS score and robot-assisted kinematic measure variables were significantly correlated in correct reaction, commission error, omission error, migration distance, and migration speed. The reaction time was significantly correlated with completion rate, and migration distance was significantly correlated with the correct reaction. Also

commission error, omission error, completion rate and migration speed were significantly correlated with correct reaction, commission error, omission error in robot-assisted kinematic measure variables. The results showed that the migration distance and speed of the children were significantly related to the score of CBCL and K-ADHDDS. In particular, children with ADHD were characterised by moving small distances faster than children without ADHD during the tasks.
Conclusion: The robot-assisted kinematic measure seems to be a useful diagnostic tool as this makes it possible to overcome limitations of previous questionnaire type diagnostic tools by measuring objective kinematic information about the children's behavior

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Eur Neuropsychopharmacol. 2019;29:S434-S435.

THE COURSE OF ADHD DIAGNOSIS OVER A 6-YEAR TIMEFRAME IN A ROMANIAN INPATIENT SAMPLE.

Andrei LE, Cerlinca AI, Neacsu RD, et al.

Introduction: As it is mentioned by the DSM-5 [1], the prevalence of ADHD according to population studies is about 5% of children and about 2.5% of adults. In most cases, the diagnosis is identified for the first time during the first years of primary school, due to the functional impairment caused by inattention and/or hyperactivity. The development and course of ADHD throughout the years is different among patients, as some of them remain relatively stable during adolescence, while others develop other psychiatric disorders, such as conduct disorders, substance use disorders or mood disorders.
Aim: The aim of our study is to analyse the ADHD patients admitted into a psychiatric inpatient unit in Romania during a period of one year and to determine their course over a 6-year period in terms of diagnostic stability and models of comorbidities.
Methods: The eligible sample consists of all the patients (age range 6-11) diagnosed with ADHD as a first-line diagnosis, out of a total of 3050 admissions in 2011, in the Child and Adolescent Psychiatry Department of an inpatient Psychiatric Hospital, in Bucharest, Romania. The ADHD and other psychiatric diagnoses were established based on ICD-10 criteria and confirmed by psychiatric structured interviews. Exclusion criteria were represented only by moderate to profound intellectual disability as psychiatric comorbidities. These less stringent exclusion criteria were deliberately chosen in order to appropriately asses a disorder that itself implies a high number of coexisting difficulties and thus maintaining the sample representativeness. All the subsequent admissions of the participants between January 2012 and December 2017 were tracked and analysed, with persistence of ADHD diagnosis, type and number of psychiatric comorbidities, number of admissions, substance use and school-related challenges as outcome variables. The age at diagnosis, gender, IQ level and comorbid conditions in 2011 were considered independent variables in a multinomial logistic regression model. The statistical significance level was set at $p<0.05$
Results: From the total number of admissions in 2011, 443 patients (male 74.9%, female 25.1%) with a first-line ADHD diagnosis were identified and included in the study. Preliminary results indicate that ADHD was highly-persistent in our sample and among the most frequent psychiatric comorbid disorders that were diagnosed throughout the 6-year study period were conduct disorders, oppositional defiant disorder and mood disorders. Moreover, the lower the IQ was at first admission, the greater was the number of comorbid conditions, number of following admissions and other accompanying challenges such as school dropout.
Conclusion: Our results suggest significant within-condition heterogeneity with respect to developmental course of ADHD, consistent with the evidence available in the current literature. These findings indicate the importance of a constant adequate assessment of ADHD from childhood to adolescence and adulthood, and subsequent adjustment of therapeutic interventions according to every individual clinical presentation

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Eur Neuropsychopharmacol. 2019;29:S435.

EFFECT OF STIMULANT MEDICATIONS ON INTELLIGENCE QUOTIENT SCORES IN A SPANISH SAMPLE OF CHILDREN AND ADOLESCENTS WITH ADHD.

Valdivielso MV, et al.

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder defined as developmentally inappropriate levels of hyperactivity, impulsivity and/or inattention. Available psychopharmacological treatments with good to moderate effect sizes include stimulants (methylphenidate and lisdexamphetamine) and non-stimulants medications (atomoxetine and alfa-agonist agent). Stimulant medication has been shown to be effective in improving cognitive performance but neuropsychological tests of executive function in this population have yielded inconsistent results [1,2]

Objective: The purpose of this study was to explore the intervention effect of methylphenidate on cognitive performance in a sample of children with ADHD and whether the effect is associated with age, sex, different subtypes of ADHD, and drug dosage.

Method: We included children and adolescent with ADHD treated with stimulants (methylphenidate or lisfexamphetamine) in our outpatient Clinic, evaluated with the K-SADS interview. They all were drug-na+»ve at baseline. We collected ADHD-RS-IV, CGI-S scores and neuropsychological testing (WISC-IV) at baseline and at follow up to evaluate clinical response and cognitive performance changes. Clinical response was defined as >30% reduction from baseline of total ADHD-RS score and CGI-S final score of 1 or 2 maintained for the at least 3 months. Differences in ADHD-RS-IV and CGI-S over time were analysed using twoΓ ÇÉtailed +ñΓÇÉtest. Correlations between different neuropsychological variables were performed, correlation coefficients Cohen were interpreted as small (r = 0.10), medium (r = 0.30) or large (r = 0.50). All these variables were examined in relation with inattention and hyperactivity symptoms. Correlations, multiple regressions, and logistic regressions analyses were used to investigate socio-demographic, clinical, neuropsychological variables. Two-tailed p values <.05 were considered statistically significant. A statistician supervised all analyses and were conducted using statistical package SPSS.

Results: We included 91 children and adolescents with ADHD, mean (SD) age of patients was 9.56 (2.5) years old; 64.5% male and 69.35% had clinical response to stimulant treatment. Total intelligence quotient (T-IQ) (mean (SD): 99.31 (12.91)) did not differ significantly (t-test, p > 0.1) neither between ADHD presentations (inattentive vs. combined) nor between age of onset (children vs. adolescents). 75.6% of children had a T-IQ-score between 85 and 100, and 10.9% had a T-IQ score higher than 116. Lower Working Memory scores were associated with early age of ADHD diagnosis (p<0.001). Despite the fact that there were no significant changes on the different WISC-IV subtests from baseline to follow-up visit, there were an increase of both Working Memory and Total Intelligent Quotient scores, especially in girls. There were no differences between both stimulant medications.

Conclusion: Stimulant medications can enhance cognitive performance in ADHD patients thus evaluating their IQ scores, although the effect size seems to be small, so the results should not be seen as an increase in intelligence

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Eur Neuropsychopharmacol. 2019;29:S145.

PSYCHIATRIC COMORBIDITIES IN HIGH FUNCTIONING AUTISM: POLYGENIC OVERLAP WITH MAJOR DEPRESSION AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Gonzàlez-Peas J, et al.

Background: In the clinical practice, overlap between Autism Spectrum Disorders (ASD) and other psychiatric disorders has been consistently described. Latest Genome Wide Association Studies (GWAS) have consolidated, from a biological point of view, these observations, with clear significant overlaps between Attention and Hyperactivity Disorder (ADHD) or Major Depression Disorder (MDD) and ASD common predisposing variation [1]. However, psychiatric comorbidities are particularly present in the DSM-extinct subtype Asperger Syndrome (DSM-5, APA 2013) [2]. In a previous study, our group described subsyndromal psychopathology in children and adolescents with High Functioning Autism spectrum disorders [3]. Aims: We wanted to test the hypotheses that co-occurrence of ASD and sub-syndromic symptomatology may be 1) partly due to shared common SNPs of susceptibility and 2) at some point specific to Asperger population. Using exome-based polygenic risk scores in a population of ASD trios we examined polygenic transmission

related to previously described comorbid disorders [3]: MDD, ADHD, Obsessive Compulsive Disorder (OCD) and Anxiety (ANX).
Methods: Our sample consisted of 241 ASD trios with a DSM-IV diagnosis of Asperger (ASP[MP1],16%), Childhood Autism (62%), Pervasive Developmental Disorder (18%) or Atypical Autism (4%). The ASD sample has been phenotypically characterized within project PI14/02103 (Spanish ISCIII) and has been exome- sequenced as part of the Autism Sequencing Consortium (NIMH). Sequencing data was imputed using Michigan Imputation Server. Biallelic variants with MAF>0.1% and imputation quality score > 0.9 were included. MDD, OCD, ADHD and ANX summary data from Psychiatric Genomic Consortium (PGC) were used as discovery samples. Polygenic scores were calculated in PLINK, considering an r2 = 0.1 and a window size of 500 kb, and trio-based polygenic transmission test (pTDT) were conducted following previously described procedures [4]. For each disorder, pTDT was calculated for the whole ASD to select adequate P-value threshold. Polygenic transmission was then studied in ASP and non-ASP sample. Two sample t-test was used to analyze transmission differences between ASP and non-ASP population across our sample.
Results: We first examined pTDT test for polygenic transmission and selected P<0.01 thresholds for for all disorders except OCD (P<0.2). In line with our previous clinical findings, we observed that polygenic risk for ADHD and MDD was significantly over-transmitted to affected children (P = 0.02 and P = 0.03, respectively) in the ASP sample, but not in the rest of our ASD population. Furthermore, this specificity is even clearer in the case of ADHD, in which the comparison between the average pTDT in ASP against non-ASP samples is statistically significant (two-sample t-test; P = 0.04). This is the first time that significant differences between Asperger and other types of ASD in relation to ADHD common genetic predisposing variation are described. Although there were higher OCD and ANX polygenic transmission in ASP than in non-ASD patients, no significant results were found.
Conclusions: Exome-based polygenic risk score for ADHD and MDD is significantly over-transmitted to children with ASP but not to other ASD subtypes. This genetic heterogeneity reinforces clinical observations and claims Asperger Syndrome to be considered a distinctive entity within ASD

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Eur Neuropsychopharmacol. 2019;29:S19.

S.14.02 DISTINCTIVE NEURAL RESPONSE TOWARDS CERTAIN AND CONDITIONAL MONETARY LOSS IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Van DJ, Moerkerke M, Sonuga-Barke E, et al.

The neural response towards cues signalling monetary gain and loss has been extensively studied through the Monetary Incentive Delay (MID) task [1]. Abnormalities in reward processing have been found in adolescents and adults with attention-deficit/hyperactivity disorder (ADHD). Anticipation of loss is often directly compared against anticipation of gain to represent the trade-off between positive and negative outcomes. In daily life situations, these events occur independently from each other and one can often avoid monetary loss. We used an adaptation of the MID functional Magnetic Resonance Imaging (fMRI) task to assess the differential brain activity to cues signalling certain, conditional and no monetary loss. Developmental changes in neural response were compared between children (n=20) and adolescents (n=19) with ADHD and typically developing matched controls (n=34). Participants started with Γé¼150 and were told that they could take home the remainder after 135 trials. The game was set that 4/5 of the start amount was lost. fMRI BOLD responses were acquired to compare anticipatory brain activation following the different cue types. Prospect of certain monetary loss altered the neural response in emotion-related brain regions towards the end of the task, while conditional loss provoked an increased motivational state that remained constant throughout the task. We provide some of the first evidence of a distinctive brain pattern between conditional and certain monetary loss in individuals with ADHD and typically developing controls. The identification of such contingencies can provide more insight how children and adolescents respond to monetary loss in daily life

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Eur Neuropsychopharmacol. 2019;29:S548-S549.

PLASMA POLY-UNSATURED FATTY ACIDS PROFILE IN CHILDREN WITH INATTENTIVE ADHD - PRELIMINARY RESULTS OF AN EFFICACY ITALIAN STUDY WITH OMEGA 3/6.

Sanna E, Romaniello R, Balia C, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a common child psychiatric disorder with a significant global functional impairment. Interest in the role of essential fatty acids (EFA) has increased during the last two decades in correlation with hypotheses that Omega-3/6 fatty acids seem to be deficient in ADHD individuals [1] and moderately improvements in several domains, including total symptoms, inattention [2] and learning disorders [3]. Actually, a small number of study have examined essential fatty acid profiles in plasma in children and adolescents with ADHD and controls and evidence for an association between treatment response and bloody fatty acid changes is limited. A recent randomized placebo-controlled study showed marked and long-lasting changes in the treatment responders compared to the non-responders in the ratio between n-6 and n-3 fatty acids [4]. Objectives: Whitin a multicentric study the efficacy of a specific Omega-3/6 combination supplement was evaluated in a population of Italian children and adolescents with predominantly Inattentive Type of ADHD (ADHD-I). The primary efficacy measure was the ADHD Rating Scale (ADHD-RS-IV) score. Among the secondary objectives of the study the average composition of total EFA in the whole blood and the levels of the major fatty acid (n-3, n-6 and n3/n6 ratio) were analysed.
Methods: The study was a randomised, double-blind, placebo-controlled efficacy trial of Omega-3/6 combination in mild/moderate ADHD-I children (6-12 y), conducted in 4 Italian sites (Cagliari, Roma, Pisa and Messina), and including a screening and baseline assessment, a double blind evaluation phase of Omega-3/6 supplement vs placebo (at 6 months) and a following open label treatment phase of further 6 months during which all subjects were on the Omega3/6 combination supplement. Essential fatty acid profiles in plasma were assessed at baseline and at 3, 6, 9 and 12 months collecting by a drop of blood from a fingertip. Data were analysed by Pearson's correlations using SPSS version 20.0 software Macintosh.
Results: One hundred and sixty drug na+»ve Italian children with predominantly Inattentive Type of ADHD (118 M; 42 F) were enrolled. Preliminary results suggested only a mild improvement in global functioning and in clinical symptoms, especially inattention, without significant differences between Omega-3/6 dietary supplementation and placebo. First analyses of blood level of fatty acids at baseline, currently limited to a subgroup of the total sample (n = 31) did not show a statistically significant correlation between the baseline values of n3, n6, and n3/n6 ratio and the improvement of clinical symptoms after 6 months.
Discussion: Our data do not show a correlation between the baseline levels of EFA, the severity of the clinical symptoms and the response to treatment. More reliable results will be obtained with measures of blood level of major fatty acids at baseline and at 6 and 12 months used as covariate in total sample

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Int Clin Psychopharmacol. 2019;34:57-64.

PHARMACOLOGICAL TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER COMORBID WITH AN ANXIETY DISORDER: A SYSTEMATIC REVIEW.

Villas-Boas CB, Chierrito D, Fernandez-Llimos F, et al.

The purpose of this study was to conduct a systematic review of the pharmacological options available to treat patients diagnosed with attention-deficit hyperactivity disorder and anxiety disorder, for generating evidence on the safest, most-effective and tolerable pharmacotherapy. To this end, a systematic search was performed in three electronic databases (Medline, Scopus and Directory of Open Access Journals; December 2017). Randomized, double-blind, parallel-design clinical trials evaluating the efficacy, safety or tolerability of therapies for attention-deficit hyperactivity disorder and anxiety disorder in children and adolescents or adults were considered. A total of 1960 articles were retrieved from the databases, of which five studies were included in the qualitative synthesis. Two of these studies evaluated the drug atomoxetine, another study evaluated desipramine, and the remaining two studies evaluated methylphenidate, with fluvoxamine being associated with methylphenidate in one of the trials. Owing to the high heterogeneity among studies, it was not possible to combine data for meta-analyses. Although only few studies have been evaluated in this systematic review, the results point to a more significant benefit of atomoxetine. This is probably because this drug was studied in a wider age range and evaluated by more specific scales for both

disorders. To further strengthen this evidence, randomized, controlled and multicenter clinical trials with larger sample sizes should be conducted

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Int J Environ Res Public Health. 2019;16.

EFFECT OF TAEKWONDO PRACTICE ON COGNITIVE FUNCTION IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kadri A, Slimani M, Bragazzi NL, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neuro-developmental/behavioral disorders among adolescents. Sport and physical activity seem to play a major role in the development of cognition, memory, selective attention and motor reaction time, especially among adolescents with ADHD. In this context, the objective of this study was to investigate the effects of a one-and-a-half-year-long Taekwondo (TKD) intervention on cognitive function in adolescents with ADHD. Two cognitive instruments, namely the Stroop and the Ruff 2 and 7 tests, were administered to assess attentional inhibitory control and sustained and selective visual attention, respectively. Comparisons between the TKD and control groups at baseline did not reveal significant differences. For post-test scores, there were statistically significant differences on the Stroop color block test (large effect size or ES = 1.26 [95% confidence interval or CI 0.30⁻2.22]), the color-word interference test (large ES = 2.16 [95% CI 1.10⁻3.26]), the interference test (large ES = 1.63 [95% CI 0.62⁻2.64]) and error (large ES = -2.20 [95% CI -3.31 to -1.10]). Similar trends were reported for the Ruff 2 and 7 automated detection trials (large ES = 2.78 [95% CI 1.55⁻4.01]), controlled search trials (large ES = 2.56 [95% CI 1.38⁻3.75]) and total speed (large ES = -2.90 [95% CI -4.15 to -1.64]). In conclusion, TKD practice increased selective attention in adolescents with ADHD. Practitioners should implement martial art programs in their general plans to favorably influence attention and health in adolescents with ADHD

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Int J Pediatr Otorhinolaryngol. 2019;120:89-92.

RELATIONSHIP BETWEEN OTORHINOLOGIC TRAUMA AND ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN CHILDREN.

***Karaya-ƒmurlu A, et al*.**

Objevtives: Otorhinologic trauma is an important condition at the ear, nose and throat (ENT) outpatient clinic in children. Attention deficit hyperactivity disorder (ADHD) has been identified as a potential risk factor that may contribute to the incidence of traumatic injuries. The aim of the study was to investigate whether there is an association between otorhinologic trauma and ADHD symptoms in children.

Methods: A prospective study was conducted between September 2017 and March 2018. Fifty-six pediatric patients admitted to the Ear Nose and Throat (ENT) outpatient clinic of a research and training hospital aged between 4 and 18 years were included. The control group consisted of 56 age- and gender-similar children without otorhinologic trauma. Conner's parent Rating Scale (CPRS) was used to evaluate the ADHD symptoms.

Results: The children with otorhinologic trauma had significantly higher mean scores in all subscales, including inattentiveness, hyperactivity, oppositional defiant disorder (ODD) ($p < 0.05$). Furthermore, analysis of the study group showed that the hyperactivity score in the subgroup with a history of repetitive injuries were significantly higher than those of the subgroup without a history of repetitive injuries ($p < 0.05$).

Conclusions: These findings suggest that patients admitted to the ENT outpatient clinic for otorhinologic trauma had a higher number of ADHD and ODD symptoms than those who did not have otorhinologic trauma. Psychiatric evaluation for ADHD and ODD should be considered for patients admitted to clinics with similar injuries, especially those who have a history of repetitive injuries

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J Adolesc. 2019;71:119-37.

EXPLORING HOW ADOLESCENTS WITH ADHD USE AND INTERACT WITH TECHNOLOGY.

Dawson AE, Wymbs BT, Evans SW, et al.

Introduction: The ubiquity of technology is reshaping the way teens express themselves and interact with peers. Considering that teens with attention-deficit/hyperactivity disorder (ADHD) experience a range of social impairments and that risk behaviors have the potential to be more widespread and damaging online, understanding how teens with ADHD use the Internet is important.

Methods: The current study included 58 teens (72.4% boys; 13Γ Çô16 years old) from the United States of America with ADHD. Study aims were to examine these teens' Internet use frequency, preferred online activities, Facebook interactions, and online risk behaviors (i.e., cyberbullying and sexting). Associations between online behaviors and offline symptoms and behaviors were explored to identify potential risk and protective factors.

Results: Findings suggested that teens with ADHD use technology in similar ways as do the general population of teens described in previous research but appeared at unique risk of cyberbullying behaviors. Offline risks were associated with online risk behaviors. Using Facebook was associated with online risks (e.g., weak online connections) and offline risks (e.g., poorer social skills and more internalizing symptoms).

Conclusions: Online social platforms permit the exploration of social behaviors via naturalistic observation. It is imperative researchers gain understanding of the increasingly prevalent online social worlds of teens. Such an understanding may enable researchers to formulate effective social interventions for teens with ADHD

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J Autism Dev Disord. 2019;49:468-80.

PSYCHOMETRIC PROPERTIES OF THE AUTISM SPECTRUM QUOTIENT: CHILDREN'S VERSION (AQ-CHILD).

Gomez R, Stavropoulos V, Vance A.

Confirmatory factor analysis (CFA) and exploratory and factor analysis (EFA) aimed to determine the optimum Autism Spectrum Quotient-Children (AQ-Child) model. Initial CFA of parent ratings of the AQ-Child for 404 clinic-referred children with ADHD, aged between 4 and 11 years, revealed mixed/moderate support for the implied AQ-Child five-factor model and the past statistically supported four-factor model (Auyeung et al., J Autism Dev Disord 38:1230-1240, 2008). Interestingly, EFA findings indicated most support for a four-factor model, with factors reflecting "mind-reading", "social skills", "attention to details", and "imagination". The items loading in these factors were different from those proposed originally for similar factors (Auyeung et al., J Autism Dev Disord 38:1230-1240, 2008). The factors in the model showed acceptable internal consistency-reliability and discriminant validity. Clinical and research implications are discussed

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J Child Adolesc Psychopharmacol. 2019;29:9-19.

COMPARATIVE EFFICACY OF METHYLPHENIDATE AND ATOMOXETINE ON EMOTIONAL AND BEHAVIORAL PROBLEMS IN YOUTHS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shih H-H, Shang C-Y, Gau SSF.

OBJECTIVE: Methylphenidate and atomoxetine are efficacious in reducing core symptoms of attention-deficit/hyperactivity disorder (ADHD), but little is known about their efficacy in improving emotional/behavioral problems among youths with ADHD.

METHODS: One hundred sixty drug-naïve youths with DSM-IV-defined ADHD, aged 7-16 years, were recruited and 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 parent-reported Child Behavior Checklist (CBCL), and the secondary efficacy measures included Youth Self Report (YSR) and Strengths and Difficulties Questionnaire (SDQ), which was based on the ratings of parents, teachers, and subjects.

RESULTS: For CBCL, both methylphenidate and atomoxetine groups showed significant improvement in all scores at weeks 8 and 24 except Somatic Complaints in the atomoxetine group. For SDQ, both treatment

groups showed significant improvements in the Hyperactive and Conduct subscales for parent ratings, and the Externalizing subscale for teacher ratings at week 24. Methylphenidate was associated with greater improvements in Aggressive Behavior and Somatic Complaints of CBCL and in Conduct subscale of self-reported SDQ at week 24 compared with atomoxetine.
CONCLUSIONS: Our findings provide evidence to support that both methylphenidate and atomoxetine were effective in improving a wide range of emotional/behavioral problems in youths with ADHD after 24 weeks of treatment, with greater improvement in aggressive behavior, somatic complaints, and conduct problems in the methylphenidate group

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J Child Adolesc Psychopharmacol. 2019;29:50-57.
PREVALENCE AND PREDICTORS OF MEDICATION USE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: EVIDENCE FROM A COMMUNITY-BASED LONGITUDINAL STUDY.
Efron D, Gulenc A, Sciberras E, et al.
Objectives: To determine, in a community-based sample of primary school-aged children meeting diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD), (1) the proportion of children with ADHD treated with medication; (2) predictors of medication use; and (3) the association between medication use and psychological service utilization.
Methods: Grade 1 children with ADHD were recruited through 43 schools in Melbourne, Australia, using a two-stage screening and case confirmation procedure. Parent report of medication treatment, clinician diagnosis, and psychological service use were collected at ages 7 and 10 years. Medication use was analyzed by ADHD subtype. Predictors of medication treatment examined included ADHD symptom severity and persistence, externalizing comorbidities, poor academic performance, and social disadvantage. Unadjusted and adjusted logistic regression were used to identify the predictors of medication status.
Results: One hundred seventy-nine children with ADHD were recruited. At baseline, 17.3% had been clinically diagnosed with ADHD, increasing to 37.7% at age 10 years. At baseline, 13.6% were taking ADHD medications, increasing to 25.6% at age 10. Children with the combined and hyperactive-impulsive subtypes were more likely to be taking medication than those with inattentive subtype (age 7: $p = 0.002$; age 10: $p = 0.03$). ADHD symptom severity (Conners 3 ADHD Index) at baseline was concurrently and prospectively associated with medication use at both ages (both $p = 0.01$), and ADHD symptom severity at age 10 was also associated with medication use at age 10 ($p = 0.01$). Baseline area-level disadvantage was associated with medication use at age 7 ($p = 0.04$). At 10 years, children receiving medication were more likely, compared with those who were not, to be receiving psychological services ($p = 0.001$).
Conclusions: In this study, only a minority of children meeting diagnostic criteria for ADHD were diagnosed clinically or treated with ADHD medication by age 10. The strongest predictors of medication treatment were ADHD symptom severity and area disadvantage

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J Child Adolesc Psychopharmacol. 2019;29:2-8.
EARLY-ONSET EFFICACY AND SAFETY PILOT STUDY OF AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION IN THE TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Childress AC, Kando JC, King TR, et al.
Objective: To determine whether amphetamine extended-release oral suspension (AMPH EROS) has an onset of effect at 30 minutes postdose in children with attention-deficit/hyperactivity disorder (ADHD).
Methods: This randomized, double-blind, two-treatment, two-sequence, placebo-controlled crossover pilot study enrolled subjects aged 6-12 years with ADHD and ADHD-Rating Scale-5 scores of ΓëÑ90th percentile for sex and age. An optimized dose of 5-20 mg/day of AMPH EROS was determined during a 1-week open-label dose optimization phase based on medication history, symptom control, and tolerability. Subjects completed a practice laboratory classroom then received 1 day of double-blind active drug or placebo each in random sequence during two double-blind laboratory classroom days. Subjects completed the first double-blind laboratory classroom, returned to open-label drug for 5 days, and then crossed over on day 6 during a

second double-blind laboratory classroom. Double-blind dose was fixed at AMPH EROS 15, 17.5, or 20 mg. The primary end point was change from predose in the Swanson, Kotkin, Agler, M-Flynn, Pelham-Combined (SKAMP-C) Rating Scale score at 30 minutes postdose on two double-blind days. The key secondary end points were change from predose in the SKAMP-C score at 3 hours postdose for AMPH EROS compared with placebo and change from baseline Permanent Product Measure of Performance (PERMP) scores at 30 minutes and 3 hours postdose compared with placebo. Safety assessments included vital signs and adverse events (AEs).
Results: Eighteen subjects were enrolled in the study (14 males and 4 females) with a mean age of 9 years. At both 30 minutes and 3 hours postdose, changes from baseline in SKAMP-C for AMPH EROS versus placebo were statistically significant ($p < 0.01$ and $p = 0.0002$, respectively). PERMP scores were not statistically significantly improved at 30 minutes postdose for AMPH EROS relative to the placebo group. PERMP scores were statistically significantly improved at 3 hours postdose for AMPH EROS relative to the placebo group (PERMP problems attempted treatment difference least-squares [LS] mean [SE] = 60.3 [12.93], $p = 0.0003$; PERMP problems correct treatment difference LS mean [SE] = 61.6 [13.16], $p = 0.0003$). AEs (>10%) during the open-label phase included upper respiratory tract infection, fatigue, upper abdominal pain, headache, decreased appetite, and affect lability.
Conclusions: AMPH EROS was effective in reducing ADHD symptoms at 30 minutes postdose as indicated by SKAMP-C score improvement, although improvements in PERMP scores at 30 minutes were not statistically significant. AEs were mild or moderate and consistent with those of other extended-release amphetamines

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J Child Adolesc Psychopharmacol. 2019;29:58-65.
USE OF NUTRITIONAL SUPPLEMENTS IN YOUTH WITH MEDICATED AND UNMEDICATED ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Scholle O, Jilani H, Riedel O, et al.
Objective: To find out whether use of nutritional supplements (NUS) differs between children and adolescents with attention-deficit/hyperactivity disorder (ADHD; medicated or unmedicated), compared with those without the disorder.
Methods: We used cross-sectional data from the population-based I.Family study conducted between 2013 and 2014 in eight European countries. Parents completed questionnaires and participated in interviews, for example, on health and medical history of their child. Data from 5067 children and adolescents aged 5-17 years were included. Exposures were medicated (with ADHD-approved medication) and unmedicated ADHD. The outcome was the use of NUS, measured by use of any or multiple different NUS. Multivariable logistic regression adjusted for sociodemographics and health determinants was used to find ADHD-depending differences.
Results: The study sample comprised 4490 children and adolescents without ADHD and 51 medicated and 76 unmedicated subjects with ADHD. Regarding the use of any NUS, no statistically significant differences were found between children and adolescents without ADHD (18%) and those with medicated (18%) or unmedicated ADHD (22%). However, discrepancies appear when considering multiple use of NUS, not reported for any medicated ADHD subject but remarkably often for unmedicated ADHD subjects (13%), resulting in an adjusted odds ratio of 2.6 (95% confidence interval, 1.2-5.6) when compared with those without ADHD (5%).
Conclusion: Children and adolescents who were not using medication for treating ADHD potentially took NUS as oral remedies. Given the potential for a delay of indicated treatments and for use of those NUS which have no proven effectiveness, pediatricians should actively explore whether NUS have been used to treat ADHD core symptoms, and families should be informed that the average effect size has to be considered small

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J Indian Assoc Child Adolesc Ment Health. 2019;15:121-38.

COGNITIVE TRAINING FOR SUBCLINICAL ATTENTION PROBLEM: A CASE STUDY.

Chakraborty S, Halder S.

Cognitive training entails the repeated exercise of a specific cognitive process over a period of time to improve performance on the trained task as well as on tasks not specifically trained. Studies have shown that cognitive training can remediate deficits in children with Attention Deficit Hyperactivity Disorder (ADHD) as they commonly present with inattention and working memory deficits. In this case study, index client N.S. 11 years, male presented with core inattention problems however not meeting the ADHD diagnostic criteria and that would not be manifested in academic functioning and in school and home behaviour. However, standardized neuropsychological assessment like Wechsler Intelligence Scale for Children (WISC) and Test of Everyday Attention-Children (TEA-Ch) showed the deficits. The client was trained with a flexible combination of cognitive tasks tailored to target the deficit areas. The cognitive tasks addressed the areas of working memory and attention that included selective attention, sustained attention, focused attention, response inhibition and switching. Over multiple sessions the client showed improvement in the neuropsychological test (TEA-Ch), thereby showing efficacy of the flexible approach of cognitive training combining different cognitive tasks as per the need with subclinical attention problems

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J Mol Neurosci. 2019.

IRON DEFICIENCY, COGNITIVE FUNCTIONS, AND NEUROBEHAVIORAL DISORDERS IN CHILDREN.

Pivina L, Semenova Y, Do+ƒa MD, et al.

More than 25% of the worldΓÇÖs population is affected by anemia, of which more than 50% suffers from iron deficiency anemia (IDA). Children below 7-áyears of age are the population group that is most vulnerable to iron deficiency. Iron is an essential element in brain metabolism. Iron deficiency can cause changes in neurotransmitter homeostasis, decrease myelin production, impair synaptogenesis, and decline the function of the basal ganglia. Therefore, IDA adversely affects cognitive functions and psychomotor development. Research has shown that iron deficiency is a frequent comorbidity in attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder. Iron deficiency may also induce or exacerbate deficiency of other essential nutrients, which may have a negative impact on the developing brain and other organs in infants. Many nations of the world have programs to control IDA based on the use of iron supplementation, intake of fortified food and drinks, improved food safety, and monitoring of dietary diversity. Based on the current recommendations of the World Health Organization on cost-effectiveness (WHO-CHOICE), iron fortification and iron supplementation programs can be considered cost-effective or even highly cost-effective in most countries of the world to averting cognitive impairment

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J Neural Transm. 2019.

THE ROLE OF PRE-, PERI-, AND POSTNATAL RISK FACTORS IN BIPOLAR DISORDER AND ADULT ADHD.

Tole F, Kopf J, et al.

Gene environment development interactions are suggested to play a crucial role in psychiatric disorders. However, it is not clear if there are specific risk gene interactions with particular pre-, peri-, and postnatal risk factors for distinct disorders, such as adult attention-deficit-/hyperactivity disorder (aADHD) and bipolar disorder (BD). In this pilot study, the first aim was to investigate retrospective self-reports of pre-, peri-, and postnatal complications and risk factors from 126 participants (aADHD, BD, and healthy controls) and their mothers. The second aim was to investigate possible interaction between the previously published common risk gene variants of ADHD in the ADGRL3 (=LPHN3) gene (rs2305339, rs1397548, rs734644, rs1397547, rs2271338, rs6551665, and rs2345039) and shared risk gene variants of aADHD and BD in the DGKH gene (DGKH rs994856/rs9525580/rs9525584 GAT haplotype) and pre-, peri-, and postnatal risk factors in comparison to a healthy control group. After correction for multiple comparison, the following pre-, peri-, and postnatal risk factors remained statistically significant (p Γëñ 0.0036) between healthy controls and ADHD and BD patients as one group: unplanned pregnancies, psychosocial stress of the mother during pregnancy,

mode of delivery, shared decision-making regarding medical procedures during the delivery, perinatal bonding, number of crybabies, and quality of mother child and father child relationship. There were no significant environment gene interactions. In our preliminary data, similar risk factors were found to be significantly associated with both disorders in comparison to healthy controls. However, larger and longitudinal studies and standardized and validated instruments to get a better understanding of the interaction of pre-, peri-, and postnatal complications and mental health in the offspring are needed

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J Paediatr Child Health. 2019;55:244.

MOTHER AND CHILD ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Isaacs D.

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Journal of Psychopathology. 2019;25:3-9.

RELIABILITY AND VALIDITY OF THE STRUCTURED CLINICAL INTERVIEW FOR DSM-5-CLINICIAN VERSION (SCID-5-CV) ATTENTION DEFICIT/HYPERACTIVITY DISORDER CRITERIA: PRELIMINARY EVIDENCE FROM A SAMPLE OF 217 ITALIAN ADOLESCENTS.

Somma A, Carlotta D, Boni F, et al.

Objectives The aim of this study was to evaluate the psychometric properties of the Italian translation of the Structured Clinical Interview for DSM-5 Clinician Version (SCID-5-CV) Attention Deficit Hyperactivity Disorder (ADHD) module in a community sample of male adolescents.

Methods 217 male adolescents with problem behavior/poor performance at school were administered the SCID-5-CV ADHD module by trained clinicians during school time. Participants received also the Italian translations of the Adult ADHD Self-Report Scale, the Wender Utah Rating Scale, and the Personality Diagnostic Questionnaire-4+ Conduct Disorder Scale. Official school behavior and subject grades were collected.

Results Our findings suggested that DSM-5 adult ADHD diagnostic criteria may be reliably assessed using the SCID-5-CV ADHD module, at least in a community sample of male adolescents with problem behavior/performance at school. More than 6% of the participants qualified for a DSM-5 ADHD diagnosis; this finding was consistent with the available literature and supported the usefulness of adult ADHD diagnosis. All convergent validity coefficients were large (i.e., ≥ .50). A confirmatory bi-factor model proved to be the best fitting model of the SCID-5-CV ADHD symptom items.

Conclusions We feel that our data provide first support to the reliability and validity of the SCID-5-CV ADHD module, at least among community male adolescents

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Medicine (Baltimore). 2019 Feb;98:e14483.

PREVALENCE OF BULLYING AND PERCEIVED HAPPINESS IN ADOLESCENTS WITH LEARNING DISABILITY, INTELLECTUAL DISABILITY, ADHD, AND AUTISM SPECTRUM DISORDER: IN THE TAIWAN BIRTH COHORT PILOT STUDY.

Lung FW, Shu BC, Chiang TL, et al.

Children with learning disability (LD), intellectual disability (ID), attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) reported higher risk of being bullied compared to their peers. Controlling for the co-morbidity of different diagnosis is important in investigating the frequency of bullying. Therefore, this study aimed to investigate the pathway relationship of adolescents' psychiatric diagnoses, including LD, ID, ADHD, ASD, with being bullied, their self-perceived psychological well-being (PWB) and social adaptation status (SAS) in 12-years-olds. The Taiwan Birth Cohort Pilot Study dataset (N = 1561) was used. The Chinese Oxford Happiness Questionnaire was used to measure PWB and SAS. Adolescent-reported rate of bullying was 25.4%, while only 2.8% of the parents reported knowing their child had been bullied. Boys reported higher rate of being bullied than girls. Adolescents with ADHD were not at higher risk of being bullied compared to their peers, nevertheless, they perceived lower level of SAS. Adolescents

diagnosed with ID and ASD reported 63% rate of bullying and those who have been bullied perceived lower level of happiness. Adolescents with ADHD reported lower level of SAS, for disruption of harmony is even less acceptable in the Asian culture. Adolescents with ID and ASD reported higher rate of bullying than their peers and perceived lower level of happiness. A gap was found between parent and adolescent-reported rate of bullying. Encouraging adolescents to seek adult protection and support to reduce the effect of bullying on the perceived level of happiness is important

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Medicine (Baltimore). 2019 Feb;98:e14483.

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Mol Psychiatry. 2019.

MAPPING ASSOCIATIONS BETWEEN POLYGENIC RISKS FOR CHILDHOOD NEUROPSYCHIATRIC DISORDERS, SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER, COGNITION, AND THE BRAIN.

Sudre G, Frederick J, Sharp W, et al.

There are now large-scale data on which common genetic variants confer risk for attention deficit hyperactivity disorder (ADHD). Here, we use mediation analyses to explore how cognitive and neural features might explain the association between common variant (polygenic) risk for ADHD and its core symptoms. In total, 544 participants participated (mean 21 years, 212 (39%) with ADHD), most with cognitive assessments, neuroanatomic imaging, and imaging of white matter tract microstructure. We found that polygenic risk for ADHD was associated with symptoms of hyperactivity-impulsivity but not inattention. This association was mediated across multiple PRS thresholds by white matter microstructure, specifically by axial diffusivity of the right corona radiata, (maximum indirect effect β = -0.034 (CI: -0.065 to -0.01), by thickness of the left dorsomedial prefrontal (β = -0.029; CI: -0.061 to -0.0047) and area of the right lateral temporal cortex (β = 0.024; CI: 0.0034-0.054). In addition, modest serial mediation was found, mapping a pathway from polygenic risk, to white matter microstructure of the anterior corona radiata, then cognition (working memory, focused attention), and finally to hyperactivity-impulsivity (working memory β = -0.014 (CI: -0.038 to -0.0026); focused attention β = -0.011 (CI: -0.033 to -0.0017). These mediation pathways were diagnostically specific and were not found for polygenic risk for ASD or schizophrenia. In conclusion, using a deeply phenotyped

cohort, we delineate a pathway from polygenic risk for ADHD to hyperactive-impulsive symptoms through white matter microstructure, cortical anatomy, and cognition

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Nan Fang Yi Ke Da Xue Xue Bao. 2019 Jan;39:30-34.

RESPONSE INHIBITION AND EMOTIONAL RESPONDING IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH COMORBID DISRUPTIVE, IMPULSE-CONTROL, AND CONDUCT DISORDERS.

Jiang X, Liu L, Ji H, et al.

OBJECTIVE: To characterize the traits of neuropsychological functioning deficits in patients with attention-deficit/ hyperactivity disorder (ADHD) with comorbid disruptive, impulse-control, and conduct disorders (DICCD).

METHODS: Twenty out-patients with ADHD, 20 with ADHD with comorbid DICCD, and 20 with DICCD, all aged 6-16 years, were enrolled in this study, with 20 healthy subjects matched for age, gender and IQ serving as the healthy controls. The patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Revision (DSM-5). All the subjects were assessed with Golden Stroop test and emotional Stroop test to evaluate their response inhibition and emotional responding.

RESULTS: In Golden Stroop test, the interference scores (IGs) of errors and reaction time both differed significantly among the groups (P < 0.05), and were the highest in patients with ADHD only. In emotional Stroop test, the mean reaction time (MRT) showed significant differences among the groups (P < 0.05); the MRT of positive- congruent trials in ADHD with comorbid DICCD group was shorter than that in ADHD group but longer than that in group DICCD; the MRT in the 3 case groups were all longer than that in the control group. The MRT of both positive-incongruent trials and negative-congruent trials in ADHD with comorbid DICCD group and DICCD group was shorter than that in ADHD group but longer than that in the control group. The MRT of negative- incongruent trials in DICCD group was shorter than that in ADHD group and ADHD with comorbid DICCD group but longer than that in the control group.

CONCLUSIONS: The response inhibition deficit and abnormal emotional responding are the core symptoms of ADHD. Bias emotional stimuli may render response inhibitory dysfunction in patients with DICCD with callous-unemotional traits of emotional responding disorder, especially in dealing with negative emotional trials, while the comorbidity of ADHD and DICCD tends to have the emotional response trait of DICCD

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NeuroImage Clin. 2019;21.

SEGREGATING SUSTAINED ATTENTION FROM RESPONSE INHIBITION IN ADHD: AN FMRI STUDY.

Hwang S, Meffert H, Parsley I, et al.

Background: The functional significance of the impairment shown by patients with ADHD on response inhibition tasks is unclear. Dysfunctional behavioral and BOLD responses to rare no-go cues might reflect disruption of response inhibition (mediating withholding the response) or selective attention (identifying the rare cue). However, a factorial go/no-go design (involving high and low frequency go and no-go stimuli) can disentangle these possibilities.

Methods: Eighty youths [22 female, mean age = 13.70 (SD = 2.21), mean IQ = 104.65 (SD = 13.00); 49 with diagnosed ADHD] completed the factorial go/no-go task while undergoing fMRI.

Results: There was a significant response type-by-ADHD symptom severity interaction within the left anterior insula cortex; increasing ADHD symptom severity was associated with decreased recruitment of this region to no-go cues irrespective of cue frequency. There was also a significant frequency-by-ADHD symptom severity interaction within the left superior frontal gyrus. ADHD symptom severity showed a quadratic relationship with responsiveness to low frequency cues (irrespective of whether these cues were go or no-go); within this region, at lower levels of symptom severity, increasing severity was associated with increased BOLD responses but at higher levels of symptom severity, decreasing BOLD responses.

Conclusion: The current study reveals two separable forms of dysfunction that together probably contribute to the impairments shown by patients with ADHD on go/no-go tasks

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Neuropsychology. 2019.

FACE PROCESSING IN AUTISM SPECTRUM DISORDER REEVALUATED THROUGH DIFFUSION MODELS.

Powell G, Jones CRG, Hedge C, et al.

Objective: Research using cognitive or perceptual tasks in autism spectrum disorder (ASD) often relies on mean reaction time (RT) and accuracy derived from alternative-forced choice paradigms. However, these measures can confound differences in task-related processing efficiency with caution (i.e., preference for speed or accuracy). We examined whether computational models of decision-making allow these components to be isolated.

Method: Using data from two face-processing tasks (face recognition and egocentric eye-gaze discrimination), we explored whether adolescents with ASD and wide-ranging intellectual ability differed from an age and IQ matched comparison group on model parameters that are thought to represent processing efficiency, caution, and perceptual encoding/motor output speed.

Results: We found evidence that autistic adolescents had lower processing efficiency and caution but did not differ from nonautistic adolescents in the time devoted to perceptual encoding/motor output. These results were more consistent across tasks when we only analyzed participants with IQ above 85. Cross-task correlations suggested that processing efficiency and caution parameters were relatively stable across individuals and tasks. Furthermore, logistic classification with model parameters improved discrimination between individuals with and without ASD relative to classification using mean RT and accuracy. Finally, previous research has found that ADHD symptoms are associated with lower processing efficiency, and we observed a similar relationship in our sample, but only for autistic adolescents.

Conclusions: Together, these results suggest that models of decision-making could provide both better discriminability between autistic and nonautistic individuals on cognitive tasks and also a more specific understanding of the underlying mechanisms driving these differences

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Pediatr Diabetes. 2019.

THE EFFECT OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND OTHER PSYCHIATRIC DISORDERS ON THE TREATMENT OF PEDIATRIC DIABETES MELLITUS.

Yazar A, et al.

Objective: Psychiatric diagnoses of patients with type 1 diabetes mellitus (T1DM), the severity of attention deficit/hyperactivity disorder (ADHD) symptoms of the patients and their primary caregivers, and the effects of these factors on treatment were investigated.

Methods: Sixty-one patients with T1DM were included in the study along with their parents. Psychiatric diagnoses of the patients were determined using a semistructured psychiatric interview, and their depression and ADHD symptom severities were evaluated with self-report scales. The ADHD symptom severities of the parents were evaluated using self-report scales. The relationships among the psychiatric symptoms and the hemoglobin A1c (HbA1c), fasting blood glucose (FBG), and postprandial blood glucose (PBG) levels of the patients were investigated.

Results: HbA1c levels were found to correlate with the hyperactivity levels of children and the number of diagnoses they had. FBG and PBG values of patients diagnosed with ADHD were found to be higher than in those who did not have ADHD. HbA1c, FBG, and PBG values of the patients who had any disruptive behavior disorder were found to be higher than in those who did not. ADHD total scores, gender (being female), having diagnoses of ADHD or depression were found to be predictive of HbA1c levels according to the regression analyses. No relationship between the clinical findings of the children and their parents' ADHD levels was found.

Conclusions: The findings of this study implicate that children with T1DM should be evaluated in terms of ADHD which could have negative effects on the treatment

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Pediatr Res. 2019.

EARLY SLEEP DEPRIVATION AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Tso W, Chan M, Ho FK, et al.

Background: This study aims to study prospectively specific sleep patterns and risk of ADHD after adjusting for potential confounders such as obstructive sleep apnoea (OSA) and methylphenidate use.

Methods: A population-representative sample of 514 Chinese preschool children was recruited when in kindergarten (K3). Parents reported on their socioeconomic status and children's sleep duration. The cohort was reassessed 3 years later when the children were in Grade 3 (P3). Parents reported on children's sleep patterns and ADHD symptoms. Information on OSA diagnosis and methylphenidate use was retrieved from health records.

Results: Among the 514 parentΓÇôchild dyads (mean [SD] age, 5.52 [0.33] years), 411 were reassessed (80.0% retention; 9.35 [0.33] years) at follow-up. There were no significant baseline differences between follow-up and drop-out groups. A gradient relationship was observed between probable ADHD in P3 and sleep duration in K3. The risk of probable ADHD was 15.5 per 100 for children with <8 h of sleep in K3, whereas it was 1.1 per 100 for children with 11-12 h of sleep in K3. The adjusted risk ratio was 14.19 (p = 0.02).

Conclusions: Sleep deprivation in early childhood is associated with higher risk of ADHD in middle childhood

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Pediatr Int. 2019;61:43-48.

D2-R TEST FOR JAPANESE ADOLESCENTS: CONCURRENT VALIDITY WITH THE ATTENTION DEFICIT-HYPERACTIVITY DISORDER RATING SCALE.

Yato Y, Hirose S, Wallon P, et al.

Background: The d2-R test is a cancellation test developed in Germany to measure concentration and attention. This study examined the validity of the d2-R test for Japanese adolescents in comparison with German standardized data.

Methods: Japanese junior high school students (n = 121; 61 girls, 60 boys) participated in this study. The students performance scores in the d2-R test were compared with their daily attentiveness and hyperactivity/impulsiveness assessments conducted by the teachers. The assessments were evaluated using the attention deficit hyperactivity disorder rating scale, fourth edition (ADHD-RS)-IV. The comparison with German counterparts was also made.

Results: Students who were rated as less attentive and more hyperactive/impulsive performed more slowly and committed more errors in the d2-R test. Although there were no sex differences in any of the d2-R parameters, male students were rated higher than female students in all of the ADHD-RS-IV scores. Japanese adolescents outscored German counterparts on speed, concentration, and carefulness.

Conclusion: The concurrent validity of the d2-R test is confirmed. It is an appropriate index to measure the sustained and focused attention of Japanese adolescents. The present research merits attention as the first investigation of the d2-R test conducted for Japanese adolescents

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PLoS ONE. 2019;14.

A NETWORK ANALYSIS APPROACH TO ADHD SYMPTOMS: MORE THAN THE SUM OF ITS PARTS.

Silk TJ, Malpas CB, Beare R, et al.

In interpreting attention-deficit/hyperactivity disorder (ADHD) symptoms, categorical and dimensional approaches are commonly used. Both employ binary symptom counts which give equal weighting, with little attention to the combinations and relative contributions of individual symptoms. Alternatively, symptoms can

be viewed as an interacting network, revealing the complex relationship between symptoms. Using a novel network modelling approach, this study explores the relationships between the 18 symptoms in the Diagnostic Statistical Manual (DSM-5) criteria and whether network measures are useful in predicting outcomes. Participants were from a community cohort, the ChildrenΓÇÖs Attention Project. DSM ADHD symptoms were recorded in a face-to-face structured parent interview for 146 medication na+»ve children with ADHD and 209 controls (aged 6-8 years). Analyses indicated that not all symptoms are equal. Frequencies of endorsement and configurations of symptoms varied, with certain symptoms playing a more important role within the ADHD symptom network. In total, 116,220 combinations of symptoms within a diagnosis of ADHD were identified, with 92% demonstrating a unique symptom configuration. Symptom association networks highlighted the relative importance of hyperactive/impulsive symptoms in the symptom network. In particular, the motoric-type symptoms as well as interrupts as a marker of impulsivity in the hyperactive domain, as well as loses things and does not follow instructions in the inattentive domain, had high measures of centrality. Centrality-measure weighted symptom counts showed significant association with clinical but not cognitive outcomes, however the relationships were not significantly stronger than symptom count alone. The finding may help to explain heterogeneity in the ADHD phenotype

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Postgrad Med. 2019.

A PROPOSED ANTI-MALADAPTIVE AGGRESSION AGENT CLASSIFICATION: IMPROVING OUR APPROACH TO TREATING IMPULSIVE AGGRESSION.

Robb AS, Schwabe S, Ceresoli-Borroni G, et al.

Proper drug categorization enables clinicians to readily identify the agents most appropriate for patients in need. Currently, patients with maladaptive aggression do not all always fall into a single existing diagnostic or treatment category. Such is the case for those with impulsive aggression (IA). IA is an associated feature of numerous neuropsychiatric disorders, and can be described as eruptive, aggressive behavior or a short fuse. Although agents from a broad spectrum of drug classes have been used to treat maladaptive aggression, few have been tested distinctly in patients with IA, and there is no drug specifically indicated by the US Food and Drug Administration (US FDA) for IA. Further, current treatments often fail to sufficiently treat IA symptomatology. These issues create an unclear and inadequate treatment path for patients. Here we will propose the establishment of a class of anti-maladaptive aggression agents to begin addressing this clinical issue. The development of such a class would unify the various drugs currently used to treat maladaptive aggression and streamline the treatment approach towards IA. As an important case example of the range of candidate drugs that could fit into a new anti-maladaptive aggression agent category, we will review an investigational IA pharmacotherapy. SPN-810 (extended-release molindone) is currently being investigated as a novel treatment for children with IA and ADHD. Based on these studies we will review how SPN-810 may be well suited for a new, anti-maladaptive aggression drug class and more precisely, a proposed subgroup of IA modulators. The goal of this review is to begin improving the identification of and therapeutic approach for maladaptive aggression as well as IA through more precise anti-maladaptive aggression agent categorization

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Psychoneuroendocrinology. 2019;103:212-18.

DEHYDROEPIANDROSTERONE SULFATE, FREE TESTOSTERONE, AND SEX HORMONE-BINDING GLOBULIN ON SUSCEPTIBILITY TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang L-J, Lee S-Y, Chou M-C, et al.

The neuroendocrine system may affect the pathophysiology of gender differences in attention deficit/hyperactivity disorder (ADHD). This study examines whether the relationships among dehydroepiandrosterone sulfate (DHEA-S), free testosterone, or sex hormone-binding globulin (SHBG) and ADHD presentations exhibit gender differences. A total of 113 boys and 35 girls with ADHD (all drug na+»ve) and 46 and 26 healthy control boys and girls, respectively, were recruited. Blood samples were obtained to measure the serum levels of DHEA-S, free testosterone, and SHBG in each child. The Swanson, Nolan, and

Pelham Scale for ADHD Version IV (SNAP-IV) was used to evaluate behavioral symptoms and the Wechsler Intelligence Scale for ChildrenΓÇôFourth Edition (WISC-IV) and the ConnersΓÇÖ Continuous Performance Test (CPT) were utilized to assess neurocognitive functions. Patients with ADHD had lower DHEA-S levels than male and female healthy control subjects, and no significant differences were observed in free testosterone and SHBG levels between the patients and the controls. DHEA-S levels were negatively correlated with children's impulsivity performance in the CPT. SHBG levels were negatively correlated with ADHD behavior symptoms among boys. Free testosterone levels were not significantly correlated with either ADHD clinical symptoms or neuropsychological functions. We propose that DHEA-S serves as a potential biomarker of ADHD and is consistently involved in the pathogenesis of ADHD in both boys and girls. SHBG may be involved in behaviors associated with ADHD in boys. Additional studies with basic scientific measures are warranted to elucidate the relationship between androgen hormones and clinical presentations of ADHD

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Scand J Psychol. 2019 Feb;60:26-35.

INCREMENTAL CLINICAL UTILITY OF CONTINUOUS PERFORMANCE TESTS IN CHILDHOOD A.

Tallberg P, Rastam M, Wenhov L, et al.

Despite extensive research on attention deficit hyperactivity disorder (ADHD), there are still uncertainties regarding the clinical utility of different ADHD assessment methods. This study aimed to examine the incremental clinical utility of Conners' continuous performance test (CPT) II and QbTest in diagnostic assessments and treatment monitoring of attention deficit hyperactivity disorder (ADHD). Retrospective data from child and adolescent psychiatric records of two populations were studied. The diagnostic clinical utility of Conners' CPT II and QbTest was analysed using receiver operator characteristics (ROC) and post-test probability in 80 children with and 38 without ADHD. Dose titrations of central stimulants in 56 children with ADHD were evaluated using QbTest and the Swanson, Nolan, Pelham, version IV (SNAP-IV) scale. Conners' CPT II, but not QbTest, had incremental clinical utility in diagnostic assessment of children with ADHD when teacher and parent ratings were inconclusive. QbTest proved useful in titration of central stimulant treatment when parent ratings were inconclusive. Continuous performance tests were found to be clinically useful when rating scales were inconclusive

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World Journal of Pediatrics. 2019.

WHAT SHOULD PROFESSIONALS DO FOR THE PARENTS OF CHILDREN WITH ADHD?

Mao S-J, Shen J.

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World Neurosurg. 2019 Feb;122:680-83.

IMPROVEMENT OF HYPOTHALAMIC HAMARTOMA-RELATED PSYCHIATRIC DISORDER AFTER STEREOTACTIC LASER ABLATION: CASE REPORT AND REVIEW OF LITERATURE.

Arocho-Quinones EV, Koop J, Lew SM.

BACKGROUND: Hypothalamic hamartomas (HHs) are nonneoplastic congenital malformations associated with refractory epilepsy and behavioral disorders. Improvement in behavioral functioning following resection of HHs has been reported. Stereotactic laser ablation (SLA), a minimally invasive technique, has been used for the treatment of HH-related epilepsy. We report the case of child with an HH, gelastic seizures, and severe psychiatric dysfunction who was successfully treated via SLA therapy.

CASE DESCRIPTION: The patient was an 11-year-old female with a history of central hypothyroidism, precocious puberty, and localization-related epilepsy thought to be secondary to an HH. She had a significant psychiatric history including attention deficit hyperactivity disorder, depressed mood, impulsivity, threatening behavior, and suicidal ideation requiring management with dexmethylphenidate, bupropion, and aripiprazole. Seizure onset occurred at age 7, and her semiology included nighttime hypermotor seizures and uncontrollable laughing spells thought to be gelastic seizures. Her hypermotor seizures were successfully

managed with oxcabazepine monotherapy, but she continued to have several weekly laughing spells and self-harming behavior. Her HH was successfully treated via SLA. Postoperatively, she remained neurologically intact and was discharged the next day. At her 6-month follow-up, she had a markedly improved affect and general mood. At 3 years postprocedure, she remains seizure free and has been weaned off her antiepileptic and antipsychotic medications.

CONCLUSIONS: Severe behavioral dysfunction in the setting of an HH may constitute an indication for surgical intervention. The outcome of this case suggests there may be a role for SLA in the management of HH-related psychiatric dysfunction, even in patients with good seizure control

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REVIEW

The evidence-based choice for antipsychotics in children and adolescents should be guaranteed

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Abstract

Purpose Drug use in the pediatric population still often features off-label prescriptions, particularly for psychotropic drugs. We reviewed the registration status, scientific evidence, and recommendations from the guidelines for antipsychotics used for psychiatric disorders in children.

Methods Antipsychotic drugs marketed in Italy, the United Kingdom (UK) and United States (US) were identified with the ATC Classification System. The licensing status and Summary of Product Characteristics (SPC) were taken from the national formularies. We analyzed reviews and guidelines on antipsychotics use in children and adolescents in the MEDLINE, EMBASE, and PsycINFO databases.

Results Out of 67 drugs, 19 were marketed with a pediatric license in at least one country: three in all the selected countries, and only paliperidone with the same indications. Haloperidol was the only antipsychotic authorized for autism in Italy and the UK, and as well as risperidone and aripiprazole in the US. Aripiprazole and paliperidone were licensed in all three countries for schizophrenia. Aripiprazole was licensed for bipolar disorders in all three countries. Haloperidol was licensed for Tourette syndrome in Italy and the UK, and pimozide and aripiprazole in the US.

We retrieved 21 pertinent reviews and 13 guidelines for the management of neuropsychiatric disorders in pediatrics. There was a complete overlap between the authorized therapeutic indications and the available scientific evidence for autism in the US, for conduct disorders and bipolar disorders in the UK, and for Tourette syndrome and tics in the UK and Italy.

Conclusions These results highlight the different regulatory processes that deny to many children and adolescents the most appropriate and rational antipsychotic therapy.

Keywords Adolescent · Antipsychotic agents · Child · Mental disorders · Off-label drug use

Introduction

Many marketed drugs lack the authorization for specific use for the pediatric population. Despite the approval of the European Regulation for pediatric drugs [1, 2], the impact of drug licensing is again lower than expected [3]. Then too, children are often prescribed drugs that have been tested mainly in adults but are used as unlicensed or off-label. Off-label drug usage refers to drugs prescribed outside their licensed indications with respect to dosage, age, indication, or route, and unlicensed drugs are those whose formulation is modified and are prepared extemporaneously, those that are imported or used before a license is granted, or are chemicals used for therapeutic purposes [4].

The purpose of off-label use is to benefit an individual patient. It is important to note that the term "off-label" does not imply improper, illegal, contraindicated, or investigational use [5, 6]. To approve a drug for sale and marketing, the regulatory authorities require substantial evidence of efficacy and safety. Requests by a sponsor to add a new indication to drug labeling must also be accompanied by additional evidence in support of that indication. If the regulatory authorities find that this evidence supports approval, the new indication is added to the product labeling. The absence of labeling for a

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specific age group or a specific disorder does not necessarily mean that the drug's use is improper for that age or disorder. It only means that the evidence required to allow inclusion in the label has not been submitted or approved by the regulatory authorities. Additionally, in no way does a lack of labeling signify that therapy is unsupported by clinical experience or data in children. It specifically means that evidence of drug efficacy and safety in the pediatric population has not been submitted to regulatory authorities for review or has not met the regulatory standards of "substantial evidence" for regulatory authorities' approval [5, 6].

In this a context between license, off-label use, physicians' attitudes and legal concern, producers' interests, and regulatory agencies strategies, the evidence-based use of drugs can be a source of inequality.

After stimulants, antipsychotics are the most prescribed drugs and between 32.3 and 93.2% of all prescriptions are off-label in children and adolescents [7, 8]. In Italy, a physician can prescribe drugs off-label if evidence of safety and efficacy exists, no authorized medication is available, and with the patients or parents give informed consent (law 94/98). The Italian Medicine Agency (AIFA) admits reimbursement by the National Health Service (NHS) which is public and universal, despite off-label prescription, for specific drugs and therapeutic indications reported in a list (law 648/96). The inclusion of a drug in this list is decided by an AIFA advisory committee (the one also involved in the approval of marketing authorization) on the basis of the available evidence: clozapine, olanzapine, and quietapine are not licensed for use in children and adolescents but can be reimbursed by the NHS.

In the US, recommendations have been elaborated by scientific societies or and agencies to regulate the off label prescriptions [6, 9]. Proper assessment of evidence for off-label use should involve as full and balanced a review as possible [9]. In the UK, doctors, nurses, and pharmacists may legally prescribe drugs off-label but there is no specific regulation as there is in Italy or the US [10].

Although physicians can prescribe drugs off-label, the scant availability of certain licensed drugs generates inequalities in access to therapy, since the prescription depends on the attitude and competence of the physician and his/her concern about medico-legal consequences, and therapies may have to be paid for out-of-pocket by parents. However, in some therapeutic areas lacking specific studies for the pediatric population, off-label use is the only therapeutic possibility with documented evidence of efficacy and safety.

Multiple factors can therefore influence off label use, such as different health care systems, drug regulatory agency activities, and professional attitudes.

Pharmaco-epidemiological studies demonstrate the off-label use of several antipsychotics in children [11–13] in most cases based exclusively on data from randomized controlled trials in adults [7, 12, 14].

We reviewed the registration status, scientific evidence, and recommendations from the guidelines for antipsychotics for psychiatric disorders in children in three high-income countries (Italy, the UK, and the US) with different drug policies and access medication [15].

Methods

Evaluation of licensing status

Antipsychotics were identified and classified according to the International Anatomic Therapeutical Chemical (ATC) classification system (N05A). A quantitative analysis was done to record the numbers of antipsychotic drugs available for neuropsychiatric disorders and those with a pediatric license in Italy, the UK, and the US. These three countries were selected on the basis of different health systems, regulatory situations, and patterns of psychotropic drug use in the pediatric population (low prevalence in Italy and high prevalence in the US).

The numbers of drugs marketed in all three countries were also considered. The licensing status and Summary of Product Characteristics (SPC) were obtained from the following national formularies: Codifa for Italy, Electronic Medicine Compendium for the UK, and Food and Drugs Administration for the US (FDA). The last date of search was June 2018. For the Italian situation, we also examined the list of off-label drugs that can be reimbursed by NHS.

Evaluation of available evidence (reviews and guidelines)

To review the evidence on safety and efficacy of antipsychotics in the pediatric population, we made a bibliographic research for systematic reviews and meta- analyses on antipsychotics in children aged up to 18 years in the MEDLINE, EMBASE, and PsycINFO (from 2015 to May 2018) databases. The Mesh search terms used in our search strategy were child/infant/newborn/adolescent, antipsychotic agents (OR the name of each active substance), limiting to human. To make the search more complete, the terms were searched for in the database dictionaries and through a free text search of the keywords in article titles and abstracts. All references retrieved were then analyzed using the software program Reference Manager V.12. The titles and abstracts were screened independently by two reviewers to assess the relevance of the studies. Contrasting results were reviewed by a third person.

We also searched for guidelines concerning the management of pediatric neuropsychiatry disorders in these databases and on the website of the National Institute for Clinical Excellence (NICE), the American Academy of Child and Adolescent Psychiatry (AACAP), the Italian National Health

Table 1 Therapeutic indications in pediatric populations

Drugs	Italy	UK	US
Paliperidone	• Schizophrenia in adolescents 15 years and older	• Schizophrenia in adolescents 15 years and older	• Schizophrenia in adolescents 12 years and older
Aripiprazole	• Manic episodes in bipolar I disorder in adolescents aged 13 years and older • Schizophrenia in adolescents 15 years and older	• Manic episodes in bipolar I disorder in adolescents aged 13 years and older • Schizophrenia in adolescents 15 years and older	• Bipolar mania—as monotherapy or as an adjunct to lithium or valproate in patients aged 10 years and older • Schizophrenia in adolescents aged 13 years and older • Irritability associated with autistic disorder in children aged 6 years and older • Tourette's disorder in children aged 6 years and older
Risperidone	• Short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors requires pharmacologic treatment	• Short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors requires pharmacologic treatment.	• Irritability associated with autistic disorder in children aged 5 years and older • Schizophrenia in adolescents aged 13 years and older • Bipolar mania in patients aged 10 years and older

Service (Istituto Superiore di Sanità, ISS), and the Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza (SINPIA).

Results

The 2018 ATC index reported 67 antipsychotic drugs, respectively 28 (42.0%), 29 (43.2%), and 23 (34.3%) of which were marketed in Italy, the UK and the US (Supplementary Table 1). Thirty-seven (60.0%) drugs were marketed in at least one of the countries and 15 (22.3%) in all three. In Italy, 43% had a pediatric license, in the UK 36.0%, and in the US 43.5% (Supplementary Table 1). Nineteen antipsychotics were marketed with a pediatric license in at least one country, three of these in all the three countries (paliperidone, aripirazole, and risperidone), but the indications were the same only for paliperidone (with some differences in the licensed age). Aripiprazole is not licensed for irritability associated with autistic disorder and Tourette's syndrome in children in Italy and the UK, while risperidone is licensed for irritability associated with autistic disorder in children, schizophrenia in adolescents, and bipolar mania only in the US (Table 1).

Wide differences were found in the age groups and diseases for which drugs were licensed. For autism in Italy and the UK, the only antipsychotic authorized was haloperidol in children aged ≥ 6 years old, while in the US, risperidone (≥ 5 years) and aripiprazole (≥ 6 years) were authorized (Table 2). Risperidone was licensed for conduct disorders in children aged ≥ 5 years old in Italy and in the UK. No drug was licensed in the US for conduct disorders. For schizophrenia, aripiprazole and paliperidone were licensed with similar age ranges in all three countries. Haloperidol, trifluoperazine, and clorpromazine were licensed in Italy and in the UK and phenothiazine derivatives only in Italy. Aripiprazole was licensed for bipolar disorders in all three countries with wide age ranges (10–13 years). Haloperidol (> 10 years) was licensed for Tourette syndrome in Italy and in the UK, and pimozide (> 12 years) and aripiprazole (> 6 years) in the US.

In all, 21 pertinent reviews were retrieved (Table 3) [16–31, 33–36]. They mainly concerned schizophrenia or psychosis (5), and bipolar disorders (4). Eight systematic reviews specifically regarded one drug (6 aripiprazole, 1 paliperidone, and 1 asenapine); 11 reviews included a meta-analysis. Theses concerned schizophrenia and psychosis (4), Tourette's syndrome and tics (3), conduct disorders (1), autism (2), and bipolar disorders (1).

Thirteen guidelines for management of neuro-psychiatric disorders in children were found (Supplementary materials section – Guideline): 4 regarded autism, 3 conduct disorders, 2 psychosis and schizophrenia, 2 Tourette syndrome and tic, 2 maladaptive aggression in youth, and 1 bipolar disorders. Table 3 summarizes the evidence in reviews and guidelines, and which drugs can be considered first choice according to them.

Table 2 Therapeutic indications in pediatric populations stratified by disease

Disease	Italy	UK	US
Autism	Haloperidol ≥ 6 years	Haloperidol ≥ 6 years	–
	–	–	Risperidone ≥ 5 years
	–	–	Aripiprazole ≥ 6 years
Conduct/behavior disorders	Risperidone ≥ 5 years	Risperidone ≥ 5 years	–
	Trifluoperazine	–	–
Schizophrenia and psychosis	Aripiprazole ≥ 15 years	Aripiprazole ≥ 15 years	Aripiprazole ≥ 13 years
	Paliperidone ≥ 15 years	Paliperidone ≥ 15 years	Paliperidone ≥ 12 years
	Haloperidol ≥ 13 years	Haloperidol ≥ 13 years	–
	Trifluoperazine	Trifluoperazine ≥ 6 years	–
	Clorpromazine ≥ 6 years	Clorpromazine ≥ 1 years	–
	Quetiapine ≥ 12 years*	–	Quetiapine ≥ 13 years
	Olanzapine ≥ 7 years*	–	Olanzapine ≥ 13 years
	–	Proclorperazine ≥ 12 years	Proclorperazine ≥ 2 years
	Promazine ≥ 12 years		
	Perfenazine ≥ 12 years		
	Periciazine		
	Clozapine ≥ 7 years*	–	–
	–	Sulpiride ≥ 14 years	–
	–	Pimozide ≥ 12 years	–
	–	–	Lurasidone ≥ 13 years
	–	–	Risperidone ≥ 13 years
Bipolar disorder	Aripiprazole ≥ 13 years	Aripiprazole ≥ 13 years	Aripiprazole ≥ 10 years
	Lithium ≥ 12 years	–	Lithium ≥ 12 years
	Quetiapine ≥ 12 years*	–	Quetiapine ≥ 10 years
	Olanzapine ≥ 7 years*	–	Olanzapine ≥ 13 years
	Ziprasidone ≥ 10 years	–	–
	–	–	Asenapine ≥ 10 years
	–	–	Lurasidone ≥ 10 years
	–	–	Risperidone ≥ 10 years
Tourette—disorders related to tic	–	–	Aripiprazole ≥ 6 years
	–	–	Pimozide ≥ 12 years
	Haloperidol ≥ 10 years	Haloperidol ≥ 10 years	–

*Not licensed but included in the list of off-label drugs that can be reimbursed by the Italian NHS

In the US, there was a full agreement between therapeutic indications and available scientific evidence for all diseases except conduct disorders. In Italy and in the UK, agreement exists only for schizophrenia and bipolar disorders, in part for Tourette syndrome and tics but not for autism. For schizophrenia and psychosis and bipolar disorders, therapeutic indications reflect the scientific evidence in all three countries (Tables 2 and 3).

Discussion

To the best of our knowledge, this is the first study comparing the licensing status of antipsychotic drugs in the pediatric population in three countries with current knowledge. Zhu et al. [37] compared the licensing status in China and in the US and described inconsistencies in the rates of unlicensed and off-label drugs when looking at the different labels: 74% of the antipsychotic prescriptions in China were unlicensed, but this percentage decreased to 22% if US regulatory decisions were applied.

Wide heterogeneity was found in our study too, concerning the national regulatory status for the same antipsychotic drug. Only 37 drugs were licensed in at least one country. This may reflect differences between countries in marketing opportunities for producers, or in the evaluation of available evidence for approval of drug licenses by regulatory authorities.

In all, 19 out of 67 drugs (29%) were licensed for use in children and/or adolescents in at least one country, with Italy

Table 3 Reviews and systematic reviews about medications in pediatric populations stratified by disease

Disease	Drugs*	Review and systematic review	Guidelines
Autism	Aripiprazole, risperidone	[16–20]	ISS, 2011 AACAP, 2014 NICE, 2013 (CG170) NICE, 2014 (QS51)
Conduct/behavior disorders	Risperidone, lithium	[16, 20–23]	Nice, 2013 (CG158) AACAP, 1997 CERT, 2012 TRAAY, 2004
Schizophrenia/psychosis	Clozapine, aripiprazole, quetiapine, risperidone, olanzapine, paliperidone, asenapine	[17, 24–29]	Nice, 2013 (CG155) AACAP, 2013 (All antipsychotics - not specified)
Bipolar disorders	Aripiprazole, lithium, risperidone, asenapine	[17, 25, 30–32]	Nice, 2014 (CG185) AACAP, 2007
Tourette syndrome and disorders related to TIC	Haloperidol, aripiprazole, pimozide, risperidone	[33–36]	ESSTS, 2011 AACAP, 2013

*Drugs for which consensus and/or solid evidence on safety and efficacy exists are reported

having the largest number of antipsychotics (N = 12) prescribable to patients under 18 years old.

The low proportion of pediatric RCTs for antipsychotics is probably due to the fact that most of these drugs were marketed in the 1960s–1970s, when there was no obligation to carry out such studies. A greater number of pediatric RCTs was performed for newer antipsychotics [11, 12].

Only three antipsychotics have a pediatric license in all three countries, though for paliperidone the therapeutic indications are similar, but differ in the licensed age. For risperidone and aripiprazole, their different licensed use is at least questionable, considering that both were initially registered in Europe and in the US by the same companies (Janssen for risperidone, and Otsuka Pharmaceutical for aripiprazole). The SPC of Abilify®, approved in Europe with a centralized authorization in 2004, still reports in the version updated at 9 April 2018 unlike the SPC approved in the US and supported by the literature and recognized by international guidelines, that the safety and efficacy of the drug for the treatment of irritability associated with autistic disorder and for tics associated with Tourette's syndrome in children and adolescents under 18 years have not been established [38, 39].

Two potential sources might explain the therapeutic conditions in an American and a European patient: the company was not willing to file a new application to extend the indications as new knowledge was gained, and/or the European Medicines Agency considered the existing evidence not sufficient to approve the new indications to start with and later did not update the work done. For practice and patients' health right, this is an important point: risperidone and aripiprazole are considered the first choice treatment for irritability in autism spectrum disorders. How and who must guarantee the most appropriate available treatment? Does producers' will still prevail over the (potential) action of a regulatory agency in the public interest? One example of the consequences of this situation is in Italy, where promazine, perphenazine, and periciazine are licensed for pediatric use in the treatment of psychosis, despite the lack of clinical trials evaluating their efficacy in the pediatric population. In fact, these drugs are not covered in the literature and the guidelines. Periciazine was among the psychotropic drugs most commonly prescribed to school-aged children in Italy, and the second antipsychotic in order of prescriptions [40], suggesting that in practice the risk of inappropriate (not evidence-based) use is high, not only for antipsychotics [41] but for many other drugs too in children and adolescents [42].

In the US, the FDA enacted a series of legislation in the late 1990s and early 2000s requiring pharmaceutical companies to gather efficacy and safety data on any new medications being developed that may at some stage in their life be used in children (0–17 years) and incentivized them to do so [43]. Following the FDA initiative, the European Commission developed the Pediatric Regulation [1], which established a system of obligations, rewards, and incentives to ensure that medicines are regularly researched, developed, and authorized to meet the therapeutic needs of children [43]. Despite this, the licensing status does not yet reflect the evidence on safety and effectiveness of drugs, and this affects children and adolescents' access to evidence-based therapies. Differences between Europe and the US also remain for antipsychotics marketed after 2007 (e.g., lurasidone and asenapine), however, suggesting that the impact of regulatory measures appears at the moment limited or scant.

Differences in licensing status are not exclusive to the pediatric age but also exist for adults, for example, the use of risperidone is not indicated for aggression in the elderly with Alzheimer's disease and aripiprazole is also indicated for major depressive disorder and bipolar mania.

A greater risk of adverse events was observed in association with off-label drug use [44]. It is possible that this is true also for the off-label use of psychotropic drugs.

A specific international formulary of psychotropic drugs for children and adolescents would be a useful response for a more rational prescribing of medicine for children and adolescents that scientific societies, regulatory agencies, and professionals could try to produce [45].

Looking at the different mental health disorders, only for schizophrenia and bipolar disorders are drugs with evidence of efficacy available in all the three countries, with aripiprazole (schizophrenia and bipolar disorder) and paliperidone (schizophrenia) as shared medications. Systematic reviews on the pharmacological treatment for psychosis did not find differences between antipsychotic drugs in terms of efficacy, with the exception of ziprasidone, which evidence recognized as low quality [28] and clozapine that was more effective than all the other antipsychotics [29]. For bipolar disorders, the majority of reviews suggest that aripiprazole was an effective in children and adults at 3 and 12 weeks of follow-up in a controlled experimental setting or in the real-world clinical practice, rarely causing hyperprolactinemia [31, 32].

The opposite was true for autism spectrum disorders (ASD) and Tourette syndrome. In the first case, only haloperidol is authorized for use in children with ASD in Italy and the UK. Despite placebo-controlled trials demonstrating its efficacy in reducing symptoms [46–48], this drug resulted less effective than risperidone in a RCT [49] and had worse tolerability profile [50].

The experts from the European Society for the Study of Tourette syndrome who drafted the guidelines in 2011 underlined that the best evidence from randomized clinical trials (RCTs) was available for haloperidol and pimozide, with pimozide probably more effective, with a more favorable adverse reaction profile than haloperidol [51]. Risperidone, clonidine, aripiprazole, and pimozide were rated as first-choice treatment by the expert group most likely because of better tolerability. In the last few years, several RCTs have been published on the efficacy of aripiprazole in tics and it appears to be promising for children [36].

More generally, the findings also raise some considerations as to whether guidelines always represent good quality evidence, and whether they are produced according to uniform principles [52, 53].

There is evidence that the on-label prescription of haloperidol may expose children to greater risks than the off-label use of other drugs such as aripiprazole or risperidone [43].

In conclusion, the finding emerging from the present evaluation is that different regulatory processes deny the most appropriate and rational antipsychotic therapy to many children and adolescents: a right to health denied. There is an urgent need for better long-term pharmaco-epidemiological, safety, and efficacy data on off-label prescribing in these groups. To date, there has been a far too narrow focus on short-term trials, with a lack of information on long-term and less frequency, but potentially serious adverse effects [52]. In pediatric settings, too little attention has been paid to the effects of commonly prescribed psychotropic medications on a child's development, and too little is known about the safety and effectiveness of common off-label prescribing [43].

If this can to some extent justify the defensive medicine choices of not prescribing off-label drugs (even with the patients' or parents' consent) [45], it is unacceptable when efficacy and safety evidence is available. Thus, more efforts are needed to update and maintain doctors' information on drug (and psychotropic) prescribing, conveying the message that the most important issue for the use of a medicine for a specific disease is the evidence based [5]. A common (at least European) pediatric formulary with evidence-based safety and efficacy information could be useful for improving the rational use of drugs for children and adolescents, harmonizing intercountry drug regulations and availability [54]. In addition, recommendations from high-quality RCTs and systematic reviews and effective knowledge translation strategies are essential to clinicians and policy makers in planning changes in practice that could ultimately improve patient- and system-related outcomes.

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Compliance with ethical standards

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

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Plasma Poly-Unsatured Fatty Acids profile in italian in children with inattentive ADHD. Preliminary results of an efficacy Italian study of Omega-3/6 dietary supplement.

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) treatment is based on a combined behavioural and pharmacological approach (1).

Recently, there has been a growing interest in alternative approaches, as dietary supplementation of polyunsaturated fatty acids (PUFAs) such as Ω3 and Ω6 fatty acids (FA). These ones are involved in different neural processes, oxidative stress and inflammation and play an unclear role in ADHD pathogenesis. ADHD individuals seem to have low plasma levels of Ω-3 and increased Ω6/3 ratio (2). Omega supplementation would seem effective in improving clinical symptoms and tolerability to methylphenidate, when prescribed as an add-on treatment (3).

OBJECTIVES

The primary objective was to evaluate the clinical efficacy and effects on essential FA plasma levels of an Omega-3/6 combination dietary supplement in a population of Italian children with Inattentive ADHD (ADHD-I).

METHODS

The study was a randomised, double-blind, multicentre, placebo-controlled efficacy trial of Omega-3/6 combination in children aged 6 to 12 with mild to moderate ADHD-I, according to DSM-IV criteria.

The study, conducted in 4 Italian sites, included three periods:

- a screening and baseline assessment;
- a double blind evaluation phase of Omega-3/6 supplement (two capsules per day of 279 mg EPA, 87 mg DHA, 30 mg GLA) vs placebo during the first 6 months;
- a phase II open label treatment period of further 6 months during which all subject were on the Omega-3/6 dietary supplement.

Clinical assessments have been performed at 5 time points: baseline, 3, 6, 9 and 12 months.

The primary efficacy measure was the ADHD Rating Scale (ADHD-RS-IV) score.

Blood levels of FA (Ω3, Ω6, Ω3/6 ratio) have been measured with specific clinical laboratory blood tests. Samples are obtained by collecting a drop of blood from a fingertip. Diet informations of the previous seven days before each applicable visit are collected.

Others secondary outcome measures were: C-GAS, CGI-I, CGI-S, CPRS, CTRS, CDRS-S, MASC, CHIP-CE-PRF and DCDQ.

STATISTICAL ANALYSIS

Statistical results have been performed by analysing the changes of scores from baseline visit over the three study periods in each arm of the study.

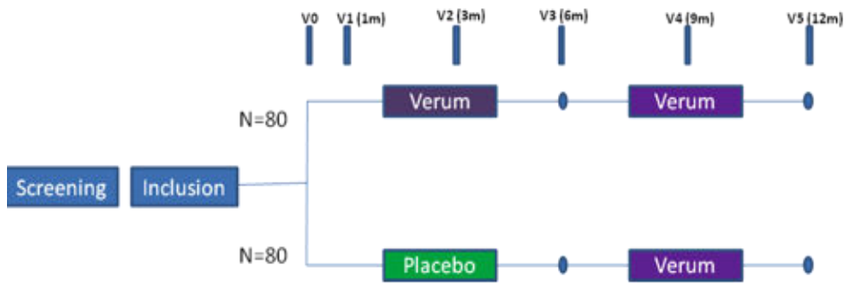
-The variation of factors within subjects has been analysed through ANOVA for repeated measures;

-The variation of the different scales and clinical measures in each arm has been analysed through Friedman test;

-The association between FA levels and scores for ADHD-RS has been analysed through Pearson's correlations.

RESULTS

Fig.1 Study Design Flow Chart



Tab.1 Recruiting Centers

	Male	Female	Total
Cagliari	22	13	35
Messina	35	5	40
Pisa	39	11	50
Roma	22	13	35
Total	118	42	160

Tab. 1 Number and gender of subjects recruited at each center. 160 drug naïve ADHD Italian children were enrolled. 45 patients did not complete the study (drop out 28%).

Fig.2 Mean and SD of ADHD-RS total score at 0, 6 and 12 months

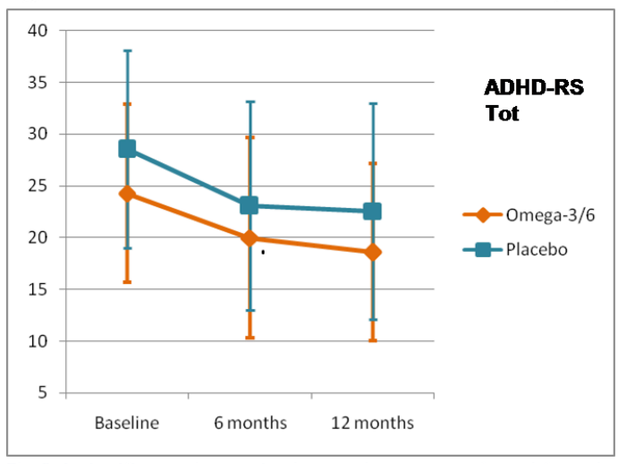


Fig.2 A significant change in the total score was found from baseline to the end of the study, although there was no significant difference between omega-3/6 and placebo groups.

Fig.3 Mean and SD of ADHD-RS Inattention score at 0, 6 and 12 months

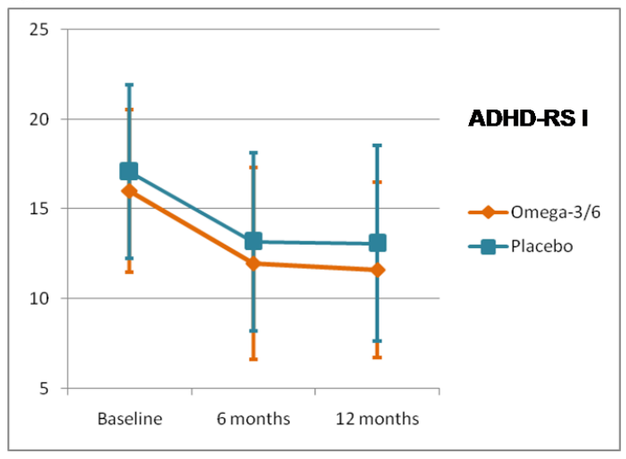


Fig.3 No significant differences were found in the change of the inattention score between omega-3/6 and placebo groups, although there was a significant change within each group.

Fig.4 Mean and SD of Omega 3 at 0, 6 and 12 months

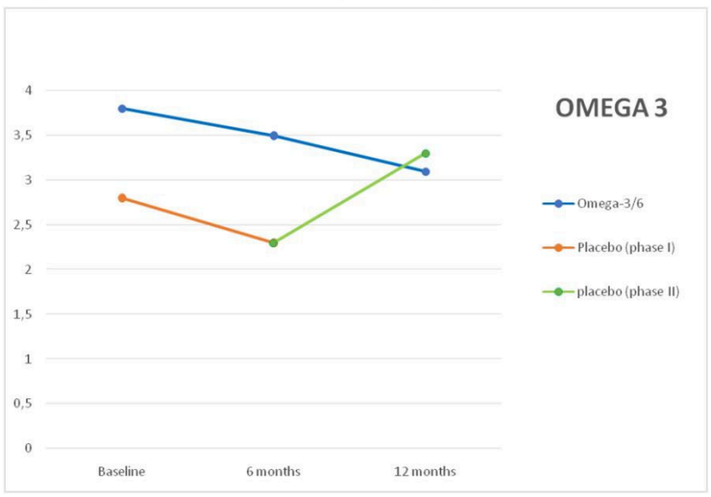


Fig. 4 No significant difference was found in blood level of Ω 3 within and between the two groups. Green line show the period of active treatment in placebo group. No significant difference also in blood level of Ω 6 FA.

Fig.5 Mean and SD of Omega 6/3 at 0, 6 and 12 months

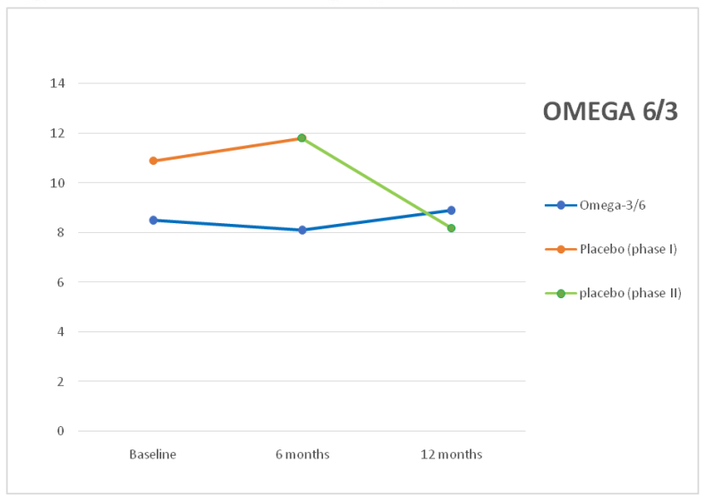


Fig. 6 No significant difference was found in blood level of FA within and between the two groups. Green line show the period of active treatment in placebo group.

Fig.6 Correlation ADHD-RS tot vs Ω6/3 at baseline

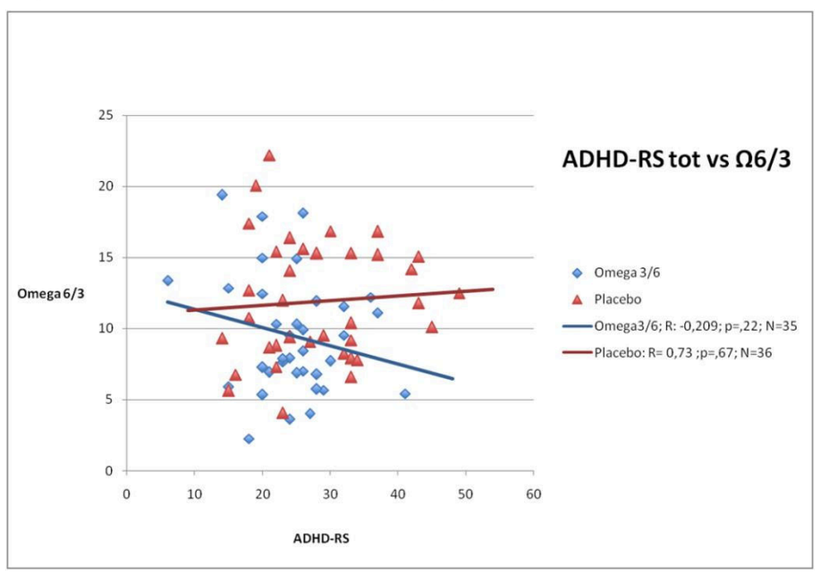
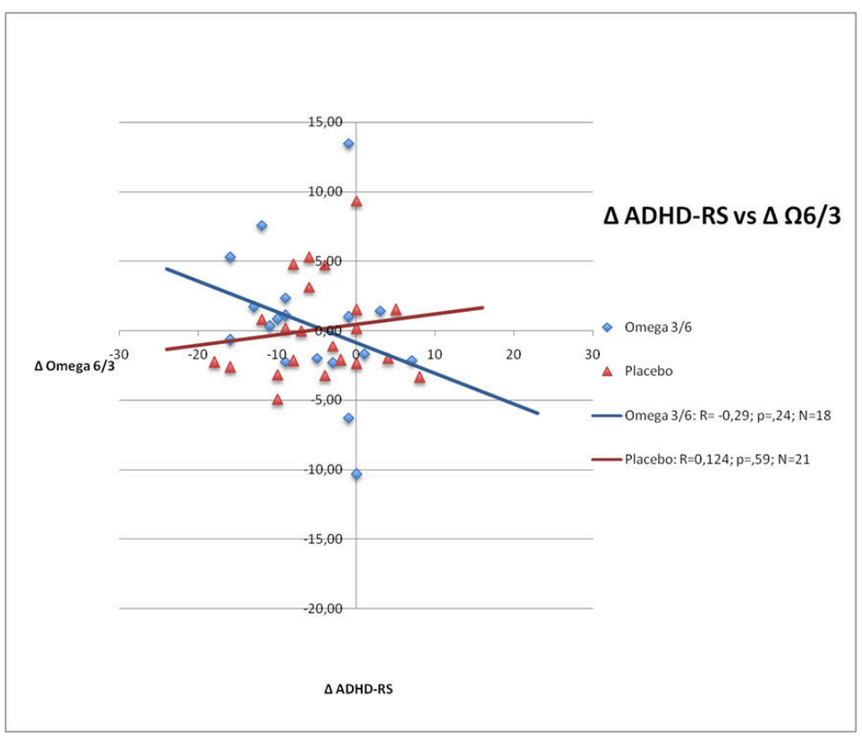


Fig. 6-7. No significant correlation was found between Ω6/3 ratio and clinical symptoms at baseline and between their variation after 6 months in the two groups. Similar results were found analysing correlation between FA and clinical symptons and their variations during the whole study period within and between the two groups.

Fig.7 Correlation Δ ADHD-RS tot vs Δ Ω6/3 at 6 months



CONCLUSIONS

- A mild improvement in global functioning and clinical symptoms (especially inattention) has been observed in all of the sample during the whole study period, without significant differences between the group treated with the Omega-3/6 dietary supplement and the placebo group.
- No significant changes in PUFA plasma levels were measured during the study. Basal levels of Ω6/Ω3 ratio in our sample were in the range of value reported in the literature, although a significant heterogeneity was found (4).
- Although the tissue ratio of these FA (Ω6/Ω3) seem to have adverse health effects in development of some psychiatric conditions (4), other clinical trials with Ω-3 and Ω-6 supplements as treatment for ADHD have shown controversial efficacy; most of them have analyzedΩ-3 and Ω-6 separately.
- No significant correlation between FA levels at baseline and clinical severity of ADHD symptoms was measured in the present study. A similar slight reduction in the rate of omega 6/3 and an increase of omega 3 level (although not statistically significant) was evidenced only during the first 6 months of active treatment. In our sample, Omega-3/6 dietary supplementation resulted not significantly related to changes in EFA blood levels nor to ADHD clinical and functional improvement, suggesting a possible role for other variables (for ex., western dietary pattern is rich in Ω6 and poor in Ω3 FA, with an increased risk of ADHD).
- The efficacy of fatty acids, although with low incidence of side effects, appears therefore mild and limited in short term.
- Further studies could be useful to clarify if omega 3/6 may be useful in management of ADHD and/ or as an add-on to standard pharmacological therapies by selecting patients who may benefit (for example, according to clinical symptoms, diet, optimal age and longer duration of PUFA treatment).

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Original article

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Reliability and validity of the Structured Clinical Interview for DSM-5-Clinician Version (SCID-5-CV) Attention Deficit/Hyperactivity Disorder Criteria: preliminary evidence from a sample of 217 Italian adolescents

Summary

Objectives

The aim of this study was to evaluate the psychometric properties of the Italian translation of the Structured Clinical Interview for DSM-5 Clinician Version (SCID-5-CV) Attention Deficit Hyperactivity Disorder (ADHD) module in a community sample of male adolescents.

Methods

217 male adolescents with problem behavior/poor performance at school were administered the SCID-5-CV ADHD module by trained clinicians during school time. Participants received also the Italian translations of the Adult ADHD Self-Report Scale, the Wender Utah Rating Scale, and the Personality Diagnostic Questionnaire-4+ Conduct Disorder Scale. Official school behavior and subject grades were collected.

Results

Our findings suggested that DSM-5 adult ADHD diagnostic criteria may be reliably assessed using the SCID-5-CV ADHD module, at least in a community sample of male adolescents with problem behavior/performance at school. More than 6% of the participants qualified for a DSM-5 ADHD diagnosis; this finding was consistent with the available literature and supported the usefulness of adult ADHD diagnosis. All convergent validity coefficients were large (i.e., ≥ .50). A confirmatory bi-factor model proved to be the best fitting model of the SCID-5-CV ADHD symptom items.

Conclusions

We feel that our data provide first support to the reliability and validity of the SCID-5-CV ADHD module, at least among community male adolescents.

Key words
SCID-5-CV • ADHD • Adolescence • Reliability • Validity

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Attention-deficit hyperactivity disorder (ADHD) is classified in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-5) as a childhood-onset neurodevelopmental disorder, defined by the presence of developmentally inappropriate and impairing levels of inattention, hyperactivity, and impulsivity [1]. Epidemiological studies showed that 5-6% of children meet diagnostic criteria for ADHD [2-4]; although the behavioral manifestations of the disorder are known to vary with subject's gender, the ADHD prevalence has been consistently found to be higher in boys than in girls [5], with a ratio of approximately 2:1 in children and 1.6:1 in adults [1].

Meta-analysis of follow-up studies of children with ADHD found that 15% of children retained the full diagnostic criteria by the age of 25 years, with a further 50% of those meeting subthreshold criteria with persistence of ADHD symptoms causing continued impairments [6]. Recently, this evidence has been consistently replicated in two follow-up studies showing high persistence of ADHD symptoms from childhood to young adulthood, with approximately 80% still meeting criteria for ADHD [7 8]. Moreover, Agnew-Blais and colleagues [9] documented both high persistence rate of childhood-onset ADHD into adulthood and late-onset ADHD.

These considerations lead the DSM-5 task force on ADHD to recognize the importance of diagnosing ADHD in adults, reducing from six to five criteria the number of criteria to meet the diagnostic threshold for ADHD diagnosis [1]. Moreover, an attempt to improve the criteria by including more age-appropriate descriptions has been included in DSM-5 [2].

The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview for making the major DSM-5 diagnoses [10]; it is administered by a clinician familiar with the DSM-5 classification and diagnostic criteria (American Psychiatric Association 2013). Work on revising the SCID for DSM-5 began in 2012; changes in the DSM-5 criteria sets [1] required the development of many new SCID questions, as well as adjustments to the SCID algorithm. Interestingly, the final version of the Structured Clinical Interview for DSM-5-Clinician Version (SCID-5-CV) [10] included an ADHD section. The ADHD presentation types (i.e., predominantly inattentive, predominantly hyperactive/impulsive, and combined) are included in the SCID-5-CV because they are required to determine the diagnostic code. Recently, the SCID-5-CV has been translated into Italian [11], using a backtranslation approach to ensure both translation accuracy and translation correspondence to the original US version [10]. One intriguing aspect of the SCID-5-CV is that its language and diagnostic coverage make it appropriate for use both with adults (age 18 and over) and adolescents [10]. Although the Diagnostic Interview for ADHD in Adults [12 13] represents the most widely used instrument for assessing ADHD in adults, the availability of an ADHD section in a general semi-structured interview for DSM-5 mental disorders may prove helpful to improve the assessment of ADHD in the transition from adolescence to adulthood and may be useful to increase clinician's awareness towards ADHD in adolescent and adult subjects.

Starting from these considerations, we aimed at testing the basic psychometric properties of the SCID-5-CV ADHD scale in a sample of male adolescents who were attending high school while showing problem behaviour according to their teachers' reports (e.g., poor school behaviour, truancy, high rates of failure, drug abuse, temper tantrums, anger outbursts etc.). We preferred relying on a community sample of adolescents because clinical samples are known to be poorly representative of the population of interest (the so-called Berkson's bias; Berkson, 1946) [14]. Male participants with poor school behaviour/performance were chosen as potential candidates for this study to maximize the likelihood to detect ADHD symptoms.

Methods

Participants

The sample was composed of male adolescents who were attending a vocational school in Northern Italy. Although 219 subjects originally agreed to participate in the study, 2 participants (0.9%) yielded incomplete questionnaires. The small number of participants with missing values prevented from missing value analysis. Participants' mean age was 17.63 years, *SD* = 1.50 years. All participants gave their informed assent to participate in the study; for participants of minor age, the written informed consent form was signed by their parents/legal guardians after detailed description of the study. To prevent linguistic bias, all participants were asked to be native Italian speaker. None of the participants received an incentive for participating in the study. After obtaining approval from the school principal, adolescents were contacted for their initial assent to participate in the study.

All participants were assessed anonymously by trained clinical psychologists during school time; an alphanumeric code was used to allow matching adolescent's graded with his/her corresponding test scores. All measures were administered individually in random order. SCID-5-CV ADHD was administered blind to self-reports and school grade scores. In the present study, time considerations allowed for testing only SCID-5-CV ADHD module.

Measures

Structured Clinician Interview for DSM-5-Clinician Version Attention-deficit/Hyperactivity Disorder Module (SCID-5-CV ADHD) [10]. The SCID-5-CV ADHD is a semi-structured interview for assessing DSM-5 ADHD criteria. It provides at least one question for each DSM-5 ADHD criteria and impairment and exclusion criteria are explicitly tested. The assessment for ADHD begins with two screening questions that are designed to determine whether or not to proceed with the full assessment of the 18 ADHD items; then, questions concerning the nine inattention symptoms and the nine hyperactive/impulsive symptoms are asked [10].

Adult ADHD Self-Report Scale (ASRS-6) [15]. The ASRS is a 6-item Likert-type screening measure designed to assess the presence of ADHD symptoms in adult popu-

lations. It showed adequate psychometric properties [15], also among Italian adolescents [16].

Wender Utah Rating Scale (WURS) [17]. The WURS is a self-report questionnaire designed to retrospectively assess the severity of ADHD symptoms during childhood. Adequate reliability and validity were reported for the WURS; moreover, it significantly predicted the treatment outcome of subjects with adult ADHD, and the WURS, together with the CAARS, showed the best psychometric properties among 14 scales for adult ADHD [18]. The Italian translation of the WURS showed adequate reliability and validity [19].

Personality Diagnostic Questionnaire-4+ (PDQ-4+) Conduct Disorder Scale [20]. The PDQ-4+ is a 99 true/false item self-report questionnaire designed to assess the diagnostic criteria of personality disorders (PDs) included in DSM-IV Axis II. It includes a scale for Conduct Disorder (CD) assessment. In the present study, participants were administered only the PDQ-4+ CD scale; the higher the total score, the higher the number of CD criteria reported by a given participant. The psychometric properties of the Italian translation of the PDQ-4+ were detailed elsewhere [21].

School grades were obtained from official school records.

Data analysis

Cronbach's α was used to evaluate the internal consistency reliability of SCID-5-CV ADHD criteria for the DSM-5 ADHD diagnosis, as well as for the two sub-subscales – namely, Inattention and Hyperactive/Impulsive; Cronbach's α values were expected to be adequate (i.e., > .70) [22].

The convergent validity of the SCID-5-CV ADHD scores (i.e., number of symptoms) was assessed by computing the Pearson r values with two self-report measures of ADHD, namely, the six-item version of the ASRS-6 and the WURS. To provide further evidence of the SCID-5-CV ADHD module validity, we computed correlations (i.e., Pearson r value) between the SCID-5-CV ADHD scores and the number of self-reported conduct disorder symptoms on the PDQ-4+ corresponding scale and with official school grades for participants' behaviour at school and subjects' performance, respectively.

The factor validity of the SCID-5-CV ADHD criteria was assessed using weighted least square mean and variance adjusted (WLSMV) confirmatory factor analysis (CFA); the following models were tested: a) a unidimensional model, with a single latent factor underlying the 18 SCID-5-CV ADHD items; b) a two-factor model, with SCID-5-CV Inattention items defining the Inattentive factor and SCID-5-CV Hyperactivity/Impulsivity items loading on the Hyperactive factor; a second-order ADHD factor was hypothesized to explain the correlation between the two first-order factors; c) a CFA bi-factor model, with all SCID-5-CV ADHD criteria loading on the general factor, and two specific factors corresponding to the Inattentive factor and the Hyperactive factor, respectively. We used several measures to identify model fit, including the χ^2 goodness-of-fit statistic, Browne and Cudeck's [23] root mean square error of approximation (RMSEA), the Tucker-Lewis index (TLI), and comparative fit index (CFI). Following Hu and Bentler's [24] suggestions, TLI and CFI values ≥ .95, RMSEA values close to .06, and SRSMR < .08 were considered as indicating good model fit, whereas TLI and CFI values of .90 and higher, and an RMSEA of .08 and lower were considered as suggestive of an adequate fit. In bi-factor models, observable indicators are thought to measure all the same latent dimension (i.e., the general factor), while specific factors are hypothesized to explain only residual covariation [25]. The reliability of the factors was assessed by computing omega-hierarchical and omega-specific coefficients [25].

Results

Participants were 217 male adolescents who were attending a vocational school in Northern Italy; participants' mean age was 17.63 years (*SD* = 1.50 years). Seventy-three (33.6%) participants previously experienced one or more school failures; 45 (20.7%) adolescents manifested severe behavior problem at school. Descriptive statistics, reliability (Cronbach α) coefficients, and Pearson r values for all measures used in the present study are listed in Table I.

Based on SCID-5-CV ADHD module, 14 (6.5%) participants met DSM-5 criteria for adult ADHD diagnosis. Participants who met DSM-5 criteria for adult ADHD diagnosis received on average significantly lower behavior (7.50 *vs* 8.14, t(215) = -2.28, p < .05, d = -0.31) and school (6.4 *vs* 6.8, t(215) = -2.03, p < .05, d = -0.28) grades than participants who did not meet DSM-5 criteria for ADHD. Previous school failures were not significantly associated with adult ADHD, t(215) = 0.74, p > .40, d = 0.10.

Goodness-of-fit indices for the CFA models of the SCID-5-CV ADHD module are listed in Table II. According to Hu and Bentler [24] the bifactor model was the besting model for SCID-5-CV ADHD symptom criteria. Standardized factor loadings and omega-hierarchical/-specific coefficients for the best-fitting model (i.e., confirmatory bi-factor model of SCID-5-CV ADHD criteria) are listed in Table III. The general omega coefficient value was .88; the general ADHD factor explained 81.0% of the SCID-5-CV ADHD criteria reliable score variance, whereas the Inattentive and Hyperactive/Impulsive specific factors explained 66.5% and 4.6% of the reliable score variance that was independent from the general ADHD factor, respectively.

TABLE I. *Structured clinical interview for DSM-5-Clinician Version Attention-Deficit/Hyperactivity Disorder Scale: descriptive statistics, internal consistency reliability (Cronbach α values are listed on the main diagonal), convergent validity (i.e., Pearson r) coefficients with the adult ADHD Self-Report Scale-6 Item Version and the Wender Utah Rating Scale Total Scores, and external validity (i.e., Pearson r) coefficients with the Personality Diagnostic Questionnaire-4+ Conduct Disorder Scale Score and School Grades (n = 217).*

	M	SD	1	2	3	4	5	6	7	8
1. SCID-5- CVADHD Total Score (number of Symptoms)	6.00	3.67	.85							
2. SCID-5- CVADHD Hyperactivity Score (number of symptoms)	2.64	2.22	--	.82						
3. SCID-5- CVADHD Inattentive Score (number of symptoms)	3.36	2.12	--	**.44**	.73					
4. ASRS-6 Total Score	8.42	4.39	**.55**	**.43**	**.49**	.74				
5. WURS Total Score	23.95	15.04	**.54**	**.50**	**.43**	**.57**	.91			
6. PDQ-4+ Conduct Disorder Total Score	2.24	2.28	**.37**	**.40**	**.22**	**.29**	**.50**	.73		
7. School Behavior Grade	8.10	1.02	**-.23**	-.11	**-.28**	-.17	**-.23**	-.20	--	
8. School Subjects Average Grade	6.77	0.79	-.07	-.01	-.11	-.11	-.14	-.16	**.36**	--

Note. SCID-5-CV ADHD: Structured Clinical Interview for DSM-5-Clinician Version Attention-Deficit/Hyperactivity Disorder Module; ASRS-6: Adult ADHD Self-Report Scale-6 Item Version; WURS: Wender Utah Rating Scale; PDQ-4+: Personality Diagnostic Questionnaire-4+. Since a total of 26 correlations were computed, the nominal significance level was corrected according to the Bonferroni procedure and set at p <.0019. Pearson r coefficients greater than |.21| are significant at Bonferroni-corrected nominal p-level. Bold highlights significant r coefficients.
--: Statistic not computed.

TABLE II. *Structured clinical interview for DSM-5 Clinician Version Attention Deficit Hyperactivity Disorder Module: confirmatory factor analysis models and confirmatory bifactor model Goodness-of-Fit indices (n = 217).*

Factor Models of SCID-5-CV ADHD Criteria	WLSMV $\chi 2$	*df*	RMSEA	RMSEA 90% CI	CFI	TLI
a) 1 factor	223.343***	135	.055	.042 - .067	.891	.876
b) 2 correlated factors with one second-order ADHD factor	191.788***	134	.045	.029 - .058	.928	.918
c) Confirmatory bifactor model: 1 general factor and 2 specific factors	140.068	116	.031	.000 - .048	.970	.961

Note. SCID-5-ADHD: Structured Clinical Interview for DSM-5 Clinician Version Attention Deficit Hyperactivity Disorder module; WLSMV: weighted least square mean and variance adjusted; $\chi 2$: WLSMV goodness-of-fit chi-square; df: degrees of freedom; TLI: Tucker-Lewis index; CFI: Comparative fit index; RMSEA: root mean square error of approximation; CI: Confidence interval for RMSEA.
** p < .05; ** p < .01; *** p < .001.*

Discussion

To our knowledge, the present study represents the first attempt at evaluating the psychometric properties of the ADHD module of the Italian translation of the SCID-5-CV in a sample of adolescents. Consistent with our hypotheses, our findings suggested that DSM-5 adult ADHD diagnostic criteria may be reliably assessed using the SCID-5-CV ADHD module, at least in a community sample of male adolescents with problem behavior/performance at school. These findings may be important for the assessment of ADHD; indeed, structured interviews (i.e., SCID-5-CV ADHD module) have been specifically designed to improve on the limitations of unstructured clinical interview. The SCID-5-CV ADHD module represents a user-friendly instrument which can be used to enhance the reliability and validity of ADHD diagnostic assessment, particularly in clinical settings. Moreover, the User's Guide for the SCID-5-CV [10 11] represents an important instrument for clinicians who seek to integrate time-tested interview questions corresponding to the DSM-5 criteria into their DSM-5 diagnostic assessment process. Indeed, the User's Guide provides comprehensive instructions on how to use the SCID-5-CV accurately, describes the rationale and usage of the SCID-5-CV, and discusses in detail how to interpret and apply the specific DSM-5 criteria for each ADHD criterion [10 11]. According to SCID-5-CV ADHD module assessment, the internal consistency reliability estimates of the DSM-

TABLE III. *Confirmatory bifactor model of SCID-5-CV ADHD criteria: standardized factor loadings and omega-hierarchical/-specific coefficients (n = 217).*

SCID-5-CV ADHD criteria	General ADHD factor λ	Inattentive specific factor λ	Hyperactiviy/impulsivity specific factor λ
H2. Missed details	.20*	.31**	---
H3. Had trouble staying focused	.49***	.35**	---
H4. Mind was elsewhere	.56***	.45***	---
H5. Started and dropped things	.10	.57***	---
H6. Had trouble organizing things	.16	.40***	---
H7. Avoided/disliked tasks	.33**	.50***	---
H8. Lost or misplaced things	.29**	.24	---
H9. Easily distracted by things	.37***	.31*	---
H10. Been very forgetful	.12	.53***	---
H12. Fidgeted/squirmed/tapped	.66***	---	-.60***
H13. Left seat	.66***	---	-.28
H14. Physically restless	.61***	---	-.61***
H15. Unable doing things quietly	.49***	---	.09
H16. Uncomfortable being still	.74***	---	-.43*
H17. Often talked too much	.43***	---	.14
H18. Finished people's sentences	.51***	---	.17
H19. Trouble waiting for "turn"	.37***	---	-.10
H20. Often interrupted	.88***	---	.45*
Omega-hierarchical/-specific	.71	.50	.04
Explained common variance	.60	.22	.18
Construct replicability (H index)	.90	.68	.64

Note. SCID-5-CV: Structured Clinical Interview for DSM-5 Clinician Version; ADHD: Attention Deficit Hyperactivity Disorder; λ: Standardized factor loading.
**p <.05; **p < .01; ***p <.001.*

5 ADHD criteria were adequate both for the full set of criteria and for the two sub-sets (i.e., Hyperactivity/Impulsivity and Inattentive). In our sample of community youngsters, 6.5% of the adolescents qualified for a DSM-5 diagnosis of ADHD. This finding was pretty consistent with prevalence estimates of adult ADHD in community samples [26], and further stressed the importance of assessing ADHD also in adolescence and later age [9]. Indeed, our school-based interview assessment prevented us from testing the inter-rater reliability of the SCID-5-CV ADHD module, as well as from administering the full interview. Although this method issue may represent a major limitation of our study, it should be observed that in our sample the SCID-5-CV ADHD scores (i.e., number of DSM-5 ADHD criteria met by each participant) showed significant associations with self-report measures of ADHD whose effect size would be considered large by conventional standards [27]. This finding could be hardly compatible with poor consistency of ADHD criteria ratings between independent interviewers. Interestingly, the number of ADHD symptoms (particularly, Hyperactivity/Impulsivity symptoms) based on SCID-5-CV assessment was significantly associated with the number of self-report CD criteria; this finding was consistent with previous longitudinal studies documenting that ADHD may represent a risk factor for antisocial behavior in adolescence/adulthood [9]. Consistent with our expectations, the association between SCID-5-CV ADHD symptoms and PDQ-4+ self-reports of CD was somewhat smaller than the convergent validity correlations with self-report measures of ADHD, further stressing the validity of the SCID-5-CV module as a measure of ADHD. Interestingly, our data suggested that the number of SCID-5-CV ADHD symptoms (as well as the WURS total score) was significantly associated with adolescents' current poor behavior at

school. Adolescents who qualified for a DSM-5 ADHD diagnosis based on the SCID-5-CV interview showed significantly poorer behavior at school and school performance than non-ADHD adolescents, although the effect size estimates for these differences were small. Of course, we do not mean not to say that poor academic performance in adolescence is always related to ADHD. Rather, we feel that our findings stress the importance of identifying ADHD in adolescence to prevent early drop-out from school [9 28].

Our WLSMV CFA results suggested that the tetrachoric correlations among the 18 SCID-5-CV ADHD symptom items are best explained by a bi-factor model hypothesizing a general ADHD factor, and two specific factors corresponding to the a priori DSM-5 Hyperactivity/Impulsivity and Inattentive dimensions. With the exception of three (16.7%) of SCID-5-CV ADHD symptom items, all other ADHD symptoms significantly loaded on the ADHD general factor, with an omega-hierarchical value that may be considered adequate by conventional standards [29]. When this general ADHD dimension was held constant, the majority of SCID-5-CV ADHD Inattentive symptom items showed positive, significant loadings on the Inattentive specific factor. Rather, none of the SCID-5-CV Hyperactivity/Impulsivity symptom item loaded positively and significantly on the Hyperactivity/Impulsivity specific factor.

In our study, the explained common variance and the omega-hierarchical coefficient values for the ADHD general factor were .60 and .71, respectively. Under these conditions, Reise and colleagues [30] suggested that the presence of some multidimensionality may not be severe enough to disqualify the interpretation of the instrument – i.e., the SCID-5-CV ADHD module – as primarily unidimensional. However, the Inattentive specific factor showed a non-trivial omega-specific value; moreover, the proportion of reliable score variance in the Inattentive factor sub-scale that was independent from the general ADHD factor was .665. In other terms, in our sample a non-negligible amount of reliable score variance in SCID-5-CV Inattentive symptoms was independent from the general ADHD factor; this finding was consistent with studies suggesting that attention problems are heterogeneous in nature and are not wholly captured by the inattention symptoms used to assess, diagnose, and treat ADHD [31 32].

Of course, our findings should be considered in the light of several limitations. The sample size was moderate and included only community male participants; this limits the generalizability of our findings clinical samples as well to samples including female adolescents and to community adult samples. We were not able to provide full assessment of DSM-5 mental disorder diagnoses included in the SCID-5-CV, thus not providing data on ADHD co-morbidity. As we mentioned above, we were not able to provide data on the inter-rater reliability of the SCID-5-CV ADHD criteria; however, the pattern of associations that we observed for the SCID-5-CV ADHD module was hardly compatible with poor rater agreement. Further studies on this topic are badly needed before accepting our conclusions. The reduced number of participants who met DSM-5 criteria for ADHD diagnosis prevented us from sub-typing the disorder. It might be claimed that relying on CFA for testing the latent structure of the SCID-5-CV ADHD symptom items may not be consistent with the categorical nature of the DSM-5 ADHD diagnosis. However, available evidence clearly supports the dimensional latent structure of ADHD [33].

Even keeping these limitations in mind, we feel that our data provides first support to the reliability and validity of the SCID-5-CV ADHD module, at least among community male adolescents.

Conflict of Interest

The authors have no conflict of interests.

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ARGENTO VIVO

Confesso che non seguo Sanremo, i suoi *gossip* e polemiche, né mi appassionano i retroscena delle canzoni o le vite dei cantanti (troppo vecchio? troppo *radical chic*?). Solo su indicazione di colleghi e conoscenti, molti fortemente critici, qualcuno quasi entusiasta, dopo molti giorni dalla conclusone del Festival ho cercato sul *web* i testi di "Argento vivo", scovando anche il video ufficiale del brano.
Ho guardato il video seguendo il testo, ignorando pressoché tutto degli Autori e degli interpreti: mi scuserete per questo approccio molto poco strutturalista[1], ma l'ho trovato una delle più accurate e poetiche descrizioni dell'ADHD in adolescenza, specie quando non "gestito" in maniera adeguata in età scolare e prescolare.
Ho trovato magistrale la descrizione della specifica percezione del tempo ("*E il tempo scorre di lato ma non lo guardo nemmeno, Nella testa girano pensieri che io non spengo, non interagiscono se li tocchi*") e di come ciò influisca sulla percezione delle figure adulte di riferimento ("*E parlano parlano, parlano, parlano, Mentre mio padre mi spiega perché è importante studiare, Mentre mia madre annega nelle sue stesse parole*): il video rallentato con frammenti di immagini, in apparenza non direttamente correlate, permette, a chi vuol farlo, di immedesimarsi in una percezione del tempo caratteristica e pressoché costante, anche se non sempre conosciuta o considerata: dovrebbe essere alla base di qualsiasi intervento educativo con i soggetti con ADHD.
Il brano descrive bene anche la percezione di perenne inadeguatezza già in età scolare che ("*Ma è una bugia, non si può imparare ad attraversare quel che sarò*"; "*Aula come cella, Zaino come palla al piede*"), specie quando i clinici non considerano con attenzione che l'ADHD si associa quasi costantemente a relativa insensibilità alle punizioni e aumentato bisogno di gratificazione[2].
Tutto ciò conduce, a 8-9 anni, ai comportamenti oppositivi e provocatori che, a loro volta ben presto evolvono i disturbi dell'umore e della condotta. La percezione dei mancati risultati di sviluppo sociale e nella difficoltà a essere compresi fanno sì che la rabbia diventi il sentimento predominante ("*Come se casa non fosse una gabbia anche lei e la famiglia non fossero i domiciliari, Ho sedici anni ma è già da più di dieci che vivo in un carcere; Ma è già più di dieci anni che ho smesso di credere che ci sia ancora qualcosa là fuori; E voi lasciatemi perdere, mi resta solo il rancore*").
Ho trovato molto adeguata anche la descrizione del contesto, specie italiano: interventi educativi focalizzati sul *parent training*, molto meno sul vissuto del bambino, ignorare che madri anch'esse ADHD possono trovarsi in seria difficoltà a implementare le strategie educative in età scolare, talvolta colpevolizzandole, spesso ignorando che appunto per la loro natura di ADHD possono essere un importante punto di forza per i figli adolescenti[3,4], attribuire "all'adolescenza", e non al disturbo, la demoralizzazione e violazione delle regole come quasi unica fonte di gratificazione ("*Questa prigione corregge e prepara a una vita che non esiste più da almeno 20 anni*").
L'ascolto (e soprattutto il video) mi ha infine stimolato alcune considerazioni sulla "cura" in Italia ("*Dottore, io così agitato, così sbagliato, con così poca attenzione, Ma mi avete curato*"), focalizzata soprattutto sugli interventi educativi, indipendentemente dalla loro relativa efficacia sui sintomi cardine del disturbo[5,6], dove la persistenza dopo dodici anni (doveva durare due anni, per garantire appropriatezza e sicurezza della prescrizione dei farmaci) di un inefficiente e inutilizzato Registro Nazionale[7] ha oggettivamente limitato fortemente l'adeguato utilizzo di terapie altamente efficaci e sicure[8], inducendo l'uso tardivo e spesso di utilità limitata di categorie di farmaci sicuramente gravate da effetti indesiderati molto maggiori[9].
Se "Argento vivo" contribuirà a riaprire in Italia un dibattito sulla psicopatologia dello sviluppo e sulle corrette modalità di gestione clinica e di prevenzione delle conseguenze a lungo termine di uno dei più diffusi e meno considerati disturbi dell'età evolutiva, non potrò che ricredermi e augurare, mio malgrado, lunga vita al Festival della Canzone Italiana.

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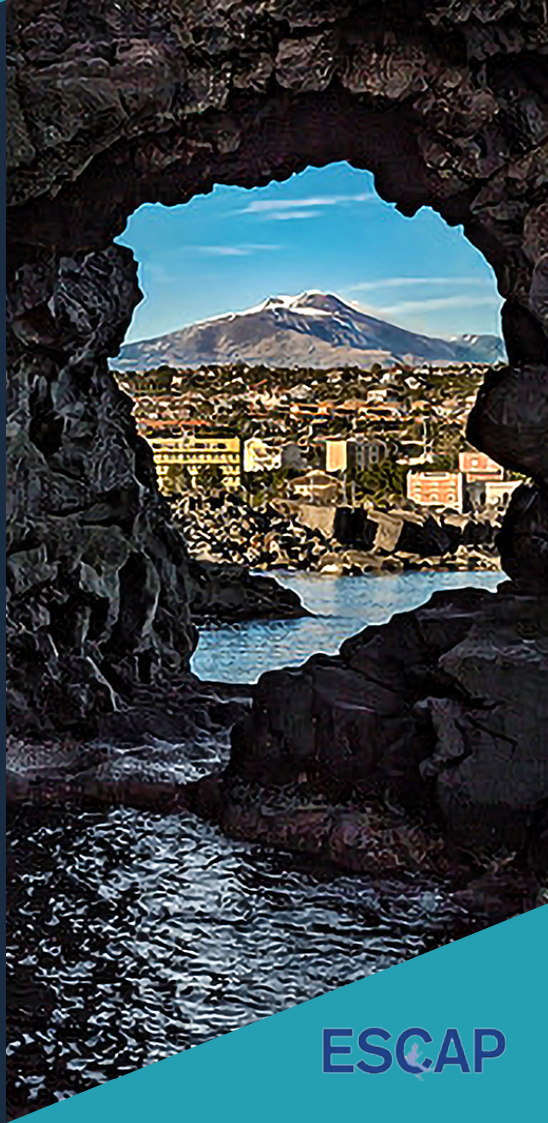

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