NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

BIBLIOGRAFIA ADHD LUGLIO 2019

Acta Medica Nagasakiensia. 2019;62:77-86.

EFFICACY OF A GROUP PSYCHOEDUCATION PROGRAM FOCUSING ON THE ATTITUDES TOWARDS MEDICATION OF CHILDREN AND ADOLESCENTS WITH ADHD AND THEIR PARENTS: A PILOT STUDY.

Nagae M, Tokunaga A, Morifuji K, et al .

Introduction: The Group Psychoeducation Program focuses on improving the attitudes towards medication of parents and their children/adolescents (G-PAM) with attention deficit hyperactivity disorder (ADHD). Aim: We evaluated the program's effectiveness at improving children's attitudes and identified what aspects required improvement.

Method: This non-randomized, pragmatic evaluation had a comparative before-after design. The G-PAM comprised five 90-minute sessions. We assessed knowledge of psychopharmacology and employed several instruments including the Southampton ADHD Medication Behavior and Attitude Scale (SAMBA), Child Adherence Questionnaire (CAQ), and a Client Satisfaction Questionnaire, among others.

Results: The intervention group consisted of 15 families (17 children) who participated in the program in 3 groups. The control group consisted of 24 families (24 children). Children in the intervention group showed improved treatment knowledge, a decreased SAMBA score for resistance to medication, and an increased CAQ score for attitude toward medication. Parents showed an increased SAMBA score for perceived psychosocial benefits of medication. Both children and parents reported high satisfaction levels.

Discussion: The current psychoeducation program provides a new approach to improve the attitudes and behaviors towards medication of children/adolescents with ADHD and their parents in clinical settings

……..

……..

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.

Am J Med Genet Part B Neuropsychiatr Genet. 2013;162:419-30.

POLYGENIC TRANSMISSION AND COMPLEX NEURO DEVELOPMENTAL NETWORK FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER: GENOME-WIDE ASSOCIATION STUDY OF BOTH COMMON AND RARE VARIANTS.

Yang L, Neale BM, Liu L, et al.

Attention-deficit hyperactivity disorder (ADHD) is a complex polygenic disorder. This study aimed to discover common and rare DNA variants associated with ADHD in a large homogeneous Han Chinese ADHD case-control sample. The sample comprised 1,040 cases and 963 controls. All cases met DSM-IV ADHD diagnostic criteria. We used the Affymetrix6.0 array to assay both single nucleotide polymorphisms (SNPs) and copy number variants (CNVs). Genome-wide association analyses were performed using PLINK. SNP-heritability and SNP-genetic correlations with ADHD in Caucasians were estimated with genome-wide complex trait analysis (GCTA). Pathway analyses were performed using the Interval enRICHment Test (INRICH), the Disease Association Protein-Protein Link Evaluator (DAPPLE), and the Genomic Regions Enrichment of Annotations Tool (GREAT). We did not find genome-wide significance for single SNPs but did find an increased burden of large, rare CNVs in the ADHD sample (P=0.038). SNP-heritability was estimated to be 0.42 (standard error, 0.13, P=0.0017) and the SNP-genetic correlation with European Ancestry ADHD samples was 0.39 (SE 0.15, P=0.0072). The INRICH, DAPPLE, and GREAT analyses implicated several gene ontology cellular components, including neuron projections and synaptic components, which are consistent with a neurodevelopmental pathophysiology for ADHD. This study suggested the genetic architecture of ADHD comprises both common and rare variants. Some common causal variants are likely to be shared between Han Chinese and Caucasians

……..

Appl Neuropsychol Child. 2019 Jul;8:231-45.

OVERDIAGNOSIS OF ADHD IN BOYS: STEREOTYPE IMPACT ON NEUROPSYCHOLOGICAL ASSESSMENT.

Fresson M, Meulemans T, Dardenne B, et al.

There is vigorous debate regarding the possibility that ADHD is overdiagnosed in boys. We investigated the impact of the gender stereotype depicting boys as inattentive and impulsive on neuropsychological assessment (observation of psychology students and child's cognitive performance). In experiment 1, after the stereotype was activated, psychology students rated a 'boy,' a 'girl,' or a 'child' on a behavioral assessment scale. In experiment 2, 103 children (boys and girls) completed neuropsychological tasks under stereotype threat or neutral conditions. The gender stereotype led psychology students to assess a child's behaviors more negatively if they thought the child was a boy. Boys' performance on one cognitive score declined following stereotype threat. Regression path analyses suggested moderation by stigma consciousness. Additionally, there were mediating and suppressing (through stereotype endorsement) effects. Our results suggest that the gender stereotype might contribute to the overdiagnosis of ADHD in boys

……..

Appl Neuropsychol Child. 2019 Jul;8:246-52.

CONTINUOUS PERFORMANCE TEST IN CHILDREN WITH INTELLECTUAL DISABILITY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Celeste PM, Esteban VP, Mariana L, et al.

Data regarding clinical and neuropsychological features of attention deficit in children with lower cognitive ability is still scarce. The objective was to analyze the response patterns on the Continuous Performance Test II in children with Intellectual Disability and Attention Defficit Hyperactivity Disorder (ADHD). This is a cross-sectional study, in which patients were divided into 2 groups: one group with ADHD and Full IQ > 80 and another group with ADHD + Full IQ score < 80. They were afterwards administered the CPT II (Continuous Performance Test). A total of 215 children were included in the study, 57% of them with ADHD IQ > 80 and 43% with ADHD + Lower Intellectual Performance (LIP). Patients with ADHD and Lower Intellectual Performance presented more omissions error, slower reaction time and greater variability in the performance as the tests progresses, as well as worse stimulus detection and discrimination capacity. The

results observed supply new information for the proper understanding of the functioning of attention processes in a poorly studied population

……..

Arch Dis Child. 2019;104.

CONSIDERATION OF GUANFACINE FOR ADDITION TO THE ADHD PATHWAY FOLLOWING REVIEW OF EFFECTIVENESS.

Webb L.

Background Intuniv (guanfacine hydrochloride) is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. In June 2016 the decision by All Wales Medicines Strategy Group (AWMSG) was that cost effectiveness had not been proven making it difficult to add the drug to our local prescribing formulary. Initially Individual Patient Funding Requests (IPFR) were submitted but this was not a sustainable approach. Following discussion at Women and Children's Clinical Board Medicines Management Group it was agreed that a Non Formulary request could be used if each was approved by the Community Child Health Clinical Director and Directorate Pharmacist and both stimulants and atomoxetine had been tried unless contraindicated. This would allow us to gain much needed experience of using the drug and allow us to evaluate where it should sit within the treatment pathway.
Aim To review the effectiveness of guanfacine in all children and young people for whom an IPFR or Non Formulary Form had been approved over 12 months May 2017 - April 2018 Methods Children and young people were identified from the IPFR and Non Formulary forms. The forms provided information on reasons for considering guanfacine, clinician and patient identifiers, other data, date, reason and age at initiation was collected from medical notes and electronic clinical system (PARIS). The maintenance dose, any side effects and assessment of effect as well as reason and date stopped, if relevant were recorded.
Results 22 children and young people were reviewed consisting of 6 IPFR's and 16 non formulary forms. 100% of patients had previously taken stimulants and atomoxetine. 5 patients never started guanfacine. 17 patient's notes were reviewed. Average age at initiation was 13 (range 8-17). 9 (53%) patients have continued on guanfacine and the average maintenance dose was 3 mg daily (range 1-4 mg). 6 (35%) had a good response, 1 (6%) had some benefit, 2 (12%) limited benefit but better than no medication. 8 (47%) patients stopped treatment. 4 (24%) stopped due to increased challenging behaviour/anger/character changes, 1 (6%) borderline BP and dizziness, 1(6%) no response, 1 (6%) substance misuse and non-compliance, 1 (6%) vomiting, 76% were requested by CAMHS clinicians, 24% requested by community paediatricians.
Conclusion Guanfacine is an effective alternative treatment for some ADHD patients with a different mode of action and different side effect profile. A small number of patients would benefit from its inclusion in the Formulary. The children and young people on guanfacine had already had stimulants and atomoxetine unless contraindicated; historically the alternative for them has been non pharmacological interventions. Half of the patients on guanfacine received benefit. An Implementation Planning Document (IPD) has been submitted to the Clinical Board requesting addition to the formulary as a Hospital Only (HO) medicine and inclusion in the ADHD pathway. AWMSG are not due to review guanfacine

……..

Assessment. 2019 Jul;26:799-810.

BIFACTOR MODELS OF ATTENTION DEFICIT/HYPERACTIVITY SYMPTOMATOLOGY IN ADOLESCENTS: CRITERION VALIDITY AND IMPLICATIONS FOR CLINICAL PRACTICE.

Willoughby MT, Fabiano GA, Schatz NK, et al.

This study evaluated the fit and criterion validity of a bifactor model for 18 DSM-IV attention deficit/hyperactivity disorder (ADHD) symptoms, along with nine supplementary symptoms that represented the manifestation of inattention and hyperactivity–impulsivity in adolescence and early adulthood. Participants included N = 172 adolescents who were diagnosed with combined type ADHD and who were enrolled in a treatment study. A bifactor model provided reasonably good fit to combined parent- and teacher-reported DSM symptoms and supplemental items at baseline prior to treatment. Across models, the general factor was characterized by high reliability (? = .93, .95), while specific inattentive and hyperactive–impulsive

factors were characterized by poor reliability (? = .30-.50). With respect to criterion validity, the general ADHD and specific inattentive factors were uniquely associated with home and school impairment (R^2 = .13-.29) but not adolescent risk-tasking behavior. Results are discussed with respect to the ways in which bifactor models of ADHD inform the diagnostic criteria for ADHD

……..

Assessment. 2019 Jul;26:811-24.

PSYCHOMETRIC VALIDATION OF THE REVISED CHILD ANXIETY AND DEPRESSION SCALES–PARENT VERSION (RCADS-P) IN CHILDREN EVALUATED FOR ADHD.

Becker SP, Schindler DN, Luebbe AM, et al.

Children with attention-deficit/hyperactivity disorder (ADHD) frequently experience comorbid internalizing symptoms. The Revised Child Anxiety and Depression Scales–Parent Version (RCADS-P) is a frequently used measure of anxiety and depression in children, though its psychometric properties remain unexamined in children referred for ADHD specifically. The present study evaluated the RCADS-P in 372 children (age 7-12 years; 68% male) referred for evaluation at an ADHD specialty clinic (89% met criteria for ADHD). In addition to the RCADS-P, parents completed the Vanderbilt ADHD Diagnostic Rating Scale and Child Behavior Checklist and were administered the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children semistructured diagnostic interview. Teacher ratings were available for approximately half of the sample. Factor structure, reliability, convergent/discriminant validity, and sensitivity/specificity were examined. Results supported the six-factor structure of the RCADS-P. The RCADS-P demonstrated adequate internal consistency as well as convergent and discriminant validity with other parent ratings and, to a somewhat lesser extent, teacher ratings. Children with an internalizing diagnosis had higher RCADS-P scores than children without an internalizing diagnosis. Finally, the RCADS-P had good-to-excellent diagnostic efficiency, and a total sum score of 25 had excellent sensitivity and fair specificity. Findings provide psychometric support for the RCADS-P in children with ADHD

……..

Assessment. 2019 Jul;26:825-38.

FACTOR STRUCTURE AND CONVERGENT VALIDITY OF THE STRESS INDEX FOR PARENTS OF ADOLESCENTS (SIPA) IN ADOLESCENTS WITH ADHD.

Eadeh HM, Langberg JM, Molitor SJ, et al.

Parenting stress is common in families with an adolescent with attention-deficit/hyperactivity disorder (ADHD). The Stress Index for Parents of Adolescents (SIPA) was developed to assess parenting stress but has not been validated outside of the original development work. This study examined the factor structure and sources of convergent validity of the SIPA in a sample of adolescents diagnosed with ADHD (Mage = 12.3, N = 327) and their caregivers. Three first-order models, two bifactor models, and one higher order model were evaluated; none met overall model fit criteria but the first-order nine-factor model displayed the best fit. Convergent validity was also assessed and the SIPA adolescent domain was moderately correlated with measures of family impairment and conflict after accounting for ADHD symptom severity. Implications of these findings for use of the SIPA in ADHD samples are discussed along with directions for future research focused on parent stress and ADHD

……..

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2019.

EFFECTS OF MATERNAL PSYCHOPATHOLOGY AND EDUCATION LEVEL ON NEUROCOGNITIVE DEVELOPMENT IN INFANTS OF ADOLESCENT MOTHERS LIVING IN POVERTY IN BRAZIL.

Shephard E, Fatori D, Mauro LR, et al.

Background: Adolescent motherhood remains common in developing countries and is associated with risk factors that adversely impact infant neurodevelopment, including poverty, low maternal education, and

increased maternal psychopathology. Yet, no published work has assessed how these factors affect early brain development in developing countries.
Methods: This pilot study examined effects of maternal psychopathology and education on early neurocognitive development in a sample of adolescent mothers (N = 50, final n = 31) and their infants living in poverty in Sao Paulo, Brazil. Maternal symptoms of anxiety, depression, and attention-deficit/hyperactivity disorder and education level were assessed during pregnancy. Infant neurocognitive development was assessed at 6 months of age, with oscillatory power and functional connectivity in the theta (4-6 Hz), alpha (6-9 Hz), and gamma (30-50 Hz) frequencies derived from resting-state electroencephalography; temperament (negative affect, attention, and regulation); and cognitive, language, and motor skills. Cluster-based permutation testing and graph-theoretical methods were used to identify alterations in oscillatory power and connectivity that were associated with maternal psychopathology and education. Correlations between power and connectivity alterations were examined in relation to infants' overt cognitive behavioral abilities.
Results: Increased maternal anxiety and lower maternal education were associated with weaker oscillatory connectivity in alpha-range networks. Infants with the weakest connectivity in the alpha network associated with maternal anxiety also showed the lowest cognitive ability. Greater maternal anxiety and attention-deficit/hyperactivity disorder were associated with increased absolute and relative theta power.
Conclusions: Our findings highlight the importance of addressing maternal psychopathology and improving education in poor adolescent mothers to prevent negative effects on infant neurodevelopment

……..

BMC Psychiatry. 2019 Jun;19.
ASSOCIATIONS OF PERSONALITY TRAITS WITH INTERNET ADDICTION IN CHINESE MEDICAL STUDENTS: THE MEDIATING ROLE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS.
Shi M, Du TJ.
Background: Internet addiction (IA) has emerged as a public health concern, particularly among adolescents and young adults. However, few studies have been conducted in medical students. This multi-center study aimed to investigate the prevalence of IA in Chinese medical students, to examine the associations of big five personality traits with IA in the population, and to explore the possible mediating role of attention-deficit/hyperactivity disorder (ADHD) symptoms in the relationship.
Methods: Self-reported questionnaires, including Internet Addiction Test (IAT), Big Five Inventory (BFI), Adult ADHD Self-Report Scale-V1.1 (ASRS-V1.1) Screener, and socio-demographic section were distributed to clinical students at 3 medical schools in China. A total of 1264 students became the final subjects.
Results: The overall prevalence of IA among Chinese medical students was 44.7% (IAT > 30), and 9.2% of the students demonstrated moderate or severe IA (IAT = 50). After adjustment for covariates, while conscientiousness and agreeableness were negatively associated with IA, neuroticism was positively associated with it. ADHD symptoms mediated the associations of conscientiousness, agreeableness and neuroticism with IA.
Conclusion: The prevalence of IA among Chinese medical students is high. Both personality traits and ADHD symptoms should be considered when tailored intervention strategies are designed to prevent and reduce IA in medical students

……..

Brain Imaging Behav. 2019;13:879-92.
IDENTIFYING DISEASE-RELATED SUBNETWORK CONNECTOME BIOMARKERS BY SPARSE HYPERGRAPH LEARNING.
Zu C, Gao Y, Munsell B, et al.
The functional brain network has gained increased attention in the neuroscience community because of its ability to reveal the underlying architecture of human brain. In general, majority work of functional network connectivity is built based on the correlations between discrete-time-series signals that link only two different brain regions. However, these simple region-to-region connectivity models do not capture complex connectivity patterns between three or more brain regions that form a connectivity subnetwork, or subnetwork

for short. To overcome this current limitation, a hypergraph learning-based method is proposed to identify subnetwork differences between two different cohorts. To achieve our goal, a hypergraph is constructed, where each vertex represents a subject and also a hyperedge encodes a subnetwork with similar functional connectivity patterns between different subjects. Unlike previous learning-based methods, our approach is designed to jointly optimize the weights for all hyperedges such that the learned representation is in consensus with the distribution of phenotype data, i.e. clinical labels. In order to suppress the spurious subnetwork biomarkers, we further enforce a sparsity constraint on the hyperedge weights, where a larger hyperedge weight indicates the subnetwork with the capability of identifying the disorder condition. We apply our hypergraph learning-based method to identify subnetwork biomarkers in Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD). A comprehensive quantitative and qualitative analysis is performed, and the results show that our approach can correctly classify ASD and ADHD subjects from normal controls with 87.65 and 65.08% accuracies, respectively

……..

Brain Imaging Behav. 2019.

EFFECTS OF COMPUTERIZED COGNITIVE TRAINING AS ADD-ON TREATMENT TO STIMULANTS IN ADHD: A PILOT FMRI STUDY.

de OR, V, Rosa FA, et al.

The neurofunctional effects of Cognitive training (CT) are poorly understood. Our main objective was to assess fMRI brain activation patterns in children with ADHD who received CT as an add-on treatment to stimulant medication. We included twenty children with ADHD from a clinical trial of stimulant medication and CT (10 in medication + CT and 10 in medication + non-active training). Between-group differences were assessed in performance and in brain activation during 3 fMRI paradigms of working memory (N-back: 0-back, 1-back, 2-back, 3-back), sustained attention (Sustained Attention Task - SAT: 2-ás, 5-ás and 8-ás delays) and inhibitory control (Go/No-Go). We found significant group x time x condition interactions in working memory (WM) and sustained attention on brain activation. In N-back, decreases were observed in the BOLD signal change from baseline to endpoint with increasing WM load in the right insula, right putamen, left thalamus and left pallidum in the CT compared to the non-active group; in SAT - increases in the BOLD signal change from baseline to endpoint with increasing delays were observed in bilateral precuneus, right insula, bilateral associative visual cortex and angular gyrus, right middle temporal, precentral, postcentral, superior frontal and middle frontal gyri in the CT compared to the non-active group. CT in ADHD was associated with changes in activation in task-relevant parietal and striato-limbic regions of sustained attention and working memory. Changes in brain activity may precede behavioral performance modifications in working memory and sustained attention, but not in inhibitory control

……..

Brain Imaging Behav. 2019.

EXPLORING CHARACTERISTIC FEATURES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: FINDINGS FROM MULTI-MODAL MRI AND CANDIDATE GENETIC DATA.

Yoo JH, Kim JI, Kim B-N, et al.

The current study examined whether machine learning features best distinguishing attention-deficit/hyperactivity disorder (ADHD) from typically developing children (TDC) can explain clinical phenotypes using multi-modal neuroimaging and genetic data. Cortical morphology, diffusivity scalars, resting-state functional connectivity and polygenic risk score (PS) from norepinephrine, dopamine and glutamate genes were extracted from 47 ADHD and 47 matched TDC. Using random forests, classification accuracy was measured for each uni- and multi-modal model. The optimal model was used to explain symptom severity or task performance and its robustness was validated in the independent dataset including 18 ADHD and 18 TDC. The model consisting of cortical thickness and volume features achieved the best accuracy of 85.1%. Morphological changes across insula, sensory/motor, and inferior frontal cortex were also found as key predictors. Those explained 18.0% of ADHD rating scale, while dynamic regional homogeneity within default network explained 6.4% of the omission errors in continuous performance test. Ensemble of PS to optimal

model showed minor effect on accuracy. Validation analysis achieved accuracy of 69.4%. Current findings suggest that structural deformities relevant to salience detection, sensory processing, and response inhibition may be robust classifiers and symptom predictors of ADHD. Altered local functional connectivity across default network predicted attentional lapse. However, further investigation is needed to clarify roles of genetic predisposition

……..

Clin Psychol Sci. 2019 Jul;7:856-72.

COGNITIVE MODELING SUGGESTS THAT ATTENTIONAL FAILURES DRIVE LONGER STOP-SIGNAL REACTION TIME ESTIMATES IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Weigard A, Heathcote A, Matzke D, et al.

Mean stop-signal reaction time (SSRT) is frequently employed as a measure of response inhibition in cognitive neuroscience research on attention deficit/hyperactivity disorder (ADHD). However, this measurement model is limited by two factors that may bias SSRT estimation in this population: (a) excessive skew in 'go' RT distributions and (b) trigger failures, or instances in which individuals fail to trigger an inhibition process in response to the stop signal. We used a Bayesian parametric approach that allows unbiased estimation of the shape of entire SSRT distributions and the probability of trigger failures to clarify mechanisms of stop-signal task deficits in ADHD. Children with ADHD displayed greater positive skew than their peers in both go RT and SSRT distributions. However, they also displayed more frequent trigger failures, which appeared to drive ADHD-related stopping difficulties. Results suggest that performance on the stop-signal task among children with ADHD reflects impairments in early attentional processes, rather than inefficiency in the stop process

……..

CNS Spectr. 2019.

EFFECTIVE USE OF ATOMOXETINE TO TREAT SIX INPATIENT YOUTHS WITH DISRUPTIVE MOOD DYSREGULATION DISORDER WITHOUT ATTENTION DEFICIT DISORDER.

Benarous X, Ferrafiat V, Zammit J, et al.

……..

Dev Cognitive Neurosci. 2019;38.

ABNORMAL ALPHA MODULATION IN RESPONSE TO HUMAN EYE GAZE PREDICTS INATTENTION SEVERITY IN CHILDREN WITH ADHD.

Guo J, Luo X, Wang E, et al.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by problems in directing and sustaining attention. Recent behavioral studies indicated that children with ADHD are more likely to fail to show the orienting effect in response to human eye gaze. The present study aimed to identify the neurophysiological bases of attention deficits directed by social human eye gaze in children with ADHD, focusing on the relationship between alpha modulations and ADHD symptoms. The electroencephalography data were recorded from 8ΓÇô13-year-old children (typically developing (TD): n = 24; ADHD: n = 21) while they performed a cued visuospatial covert attention task. The cues were designed as human eyes that might gaze to the left or right visual field. The results revealed that TD children showed a significant alpha lateralization in response to the gaze of human eyes, whereas children with ADHD showed an inverse pattern of alpha modulation in the left parieto-occipital area. Importantly, the abnormal alpha modulation in the left hemisphere predicted inattentive symptom severity and behavioral accuracy in children with ADHD. These results suggest that the dysfunction of alpha modulation in the left hemisphere in response to social cues might be a potential neurophysiologic marker of attention deficit in children with ADHD

……..

Encephale. 2019.

CAN ADHD HAVE AN ADULTHOOD ONSET?

Ilario C, Alt A, Bader M, et al .

ADHD is the most common psychiatric disorder of childhood. It is considered to be a neurodevelopmental disorder that may persist from chilhood into adulthood. In childood it is associated with several outcomes such as inattention, hyperactivity and impulsivity. Symptoms may change as a person gets older with an increased risk of developing psychiatric comorbidities such as depression, anxiety and substance addiction. However, recent studies diverge from the traditional perspective. These authors hypothesized that ADHD may appear in adulthood, not as a continuation of child ADHD, but some limitations have to be considered. Firstly, ADHD often goes unrecognized throughout childhood. Secondly, families may help the children to develop compensation strategies and adaptative behaviors. The purpose of this report is to better investigate these different and innovative clinical results and understand if adult ADHD could really be considered as a distinct, different pathology, as a late-onset disorder. We conducted a brief review of literature and included the most recent scientific longitudinal follow-up cohort studies. We conclude that, while adult ADHD is still considered a continuation from childhood, many questions of late-onset ADHD remain and further research is necessary to better understand and explain the etiology, the development, the clinical impact, and the psychotherapeutic and pharmacologic treatment of this late-onset disorder

……..

Erciyes Medical Journal. 2019;41:91-95.

EVALUATION OF SUPAR LEVELS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER ETIOPATHOGENESIS.

Irmak A, et al.

Objective: Although a strong inflammatory basis has been demonstrated, the pathophysiology of attention deficit hyperactivity disorder (ADHD) has not been defined clearly. The aim of the present study was to investigate whether soluble urokinase plasminogen activator receptor (suPAR), one of the inflammatory disruptors, plays a role in the etiology of ADHD.

Materials and Methods: The study population comprised 50 patients aged 7-13 years, diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, without any chronic or other psychiatric disease, and 25 healthy controls. Parents of the children in the study group completed the Conners' Parent Rating Scale-Revised Short, and teachers completed the Conners' Teacher Rating Scale-Revised Short. Enzyme-linked immunosorbent assay kits were used to measure suPAR levels in plasma samples.

Results: The mean plasma suPAR level of patients with ADHD was 2.92-¦1.74 ng/ml, the suPAR level of the controls was 2.54-¦1.05 ng/ml, and there was no significant difference in suPAR levels between ADHD and controls (Z=0.084, p=0.933). No correlation was found between plasma suPAR levels and ADHD severity as assessed by Conners' parent and teacher scales.

Conclusion: The role of inflammatory systems and mediators in ADHD was emphasized in many studies, and many important data on ADHD etiopathology were obtained. However, we found no significant relationship between ADHD and suPAR levels. Further research is needed with large samples

……..

Eur Arch Psychiatry Clin Neurosci. 2019.

GRAY MATTER VOLUME AND MICRORNA LEVELS IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang L-J, Li S-C, Kuo H-C, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder often characterized by gray matter (GM) volume reductions. MicroRNAs, which participate in regulating gene expression, potentially influence neurodevelopment. This study aimed to explore whether differential GM volume is associated with differential miRNA levels in ADHD patients. We recruited a total of 30 drug-na+»ve patients with ADHD (mean age 10.6-áyears) and 25 healthy controls (mean age 10.6-áyears) that underwent a single session of 3.0-T whole brain structural MRI scanning. RNA samples from the participants' white blood cells were collected to identify the t values of three miRNAs (miR-30e-5p, miR-126-5p, and miR-140-3p) using the real-

time quantitative reverse transcription polymerase chain reaction. In comparison to the control group, ADHD patients demonstrated a significantly lower GM volume in the cingulate gyrus, left middle temporal gyrus, right middle occipital gyrus, left fusiform gyrus, and significantly higher +öCt values of miR-30e-5p, miR-126-5p, and miR-140-3p. In the ADHD group, the GM volume of cingulate gyrus and left fusiform gyrus was negatively correlated with the t values of miR-30e-5p, miR-140-3p. The GM volume of left fusiform gyrus was negatively correlated to ADHD behavioral symptoms. Using structural equation modeling (SEM), we observed that the effect of miR-140-3p on hyperactivity/impulsivity symptoms was mediated by left fusiform gyrus. Our findings support that GM volume reduction and miRNA increases may be biomarkers for ADHD in children and adolescents. Expression levels of miRNAs may affect the development of brain structures and further participate in the pathophysiology of ADHD

……..

Eur Child Adolesc Psychiatry. 2019.

MATERNAL SERUM C-REACTIVE PROTEIN (CRP) AND OFFSPRING ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Chudal R, Brown AS, Gyllenberg D, et al.

Exposure to infection and inflammation during the fetal period are associated with offspring neuropsychiatric disorders. Few previous studies have examined this association with ADHD with mixed findings. This study aims to examine the association between early gestational maternal C-reactive protein (CRP), prospectively assayed in stored maternal sera and the risk of ADHD in offspring. This study is based on the Finnish Prenatal studies of ADHD (FIPS-ADHD) with a nested caseΓÇôcontrol design. It includes all singleton-born children in Finland between January 1, 1998 and December 31, 1999 and diagnosed with ADHD. A total of 1079 cases and equal number of controls were matched on date of birth, sex and place of birth. Maternal CRP levels were assessed using a latex immunoassay from archived maternal serum specimens, collected during the first and early second trimester of pregnancy. Elevated maternal CRP when analyzed as a continuous variable was not associated with offspring ADHD (OR 1.05, 95% CI 0.96ΓÇô1.15). No significant associations were seen in the highest quintile of CRP (OR 1.18, 95% CI 0.88ΓÇô1.58). The results were similar in both sexes as well as among ADHD cases with or without comorbid ASD or conduct disorder. In this first study examining CRP, a biomarker for inflammation, during early pregnancy in relation to offspring ADHD, we report no significant associations. The lack of any association, when considered with positive findings seen in ASD and schizophrenia, and negative findings in bipolar disorder suggests different pathways linking maternal immune activation and development of various neuropsychiatric disorders

……..

Eur Child Adolesc Psychiatry. 2019;28:923-32.

MATERNAL POSTNATAL MENTAL HEALTH AND OFFSPRING SYMPTOMS OF ADHD AT 8□9 YEARS: PATHWAYS VIA PARENTING BEHAVIOR.

Mulraney M, Giallo R, Efron D, et al.

Exposure to maternal mental health problems during pregnancy and the first year of life has been associated with the development of ADHD. One pathway through which maternal mental health may influence children's outcomes is via its effects on parenting. This study aimed to investigate the mediating role of parenting behavior in the pathway between maternal postnatal distress and later symptoms of ADHD in the child. Biological mothers living with their children participating in the Longitudinal Study of Australian Children with data available from waves 1 (child age 3-12 months) and 5 (child age 8-9 years) were included in the current study (n = 3456). Postnatal distress was assessed by parent report at wave 1. Parenting warmth, hostility and consistency were assessed by parent report at wave 5. ADHD status at wave 5 was ascertained by parent report of the child having a diagnosis of ADHD/ADD or by elevated ADHD symptoms by both parent and teacher report. There was evidence of an indirect pathway from maternal postnatal distress to child ADHD at age 8-9 years via parenting hostility, but not through parenting warmth or consistency, even after accounting for concurrent maternal mental health. Our findings highlight the importance of early identification

and intervention for maternal postnatal distress, as treatment may prevent mothers from developing hostile parenting practices and also disrupt the pathway to ADHD in their offspring

……..

Eur Neuropsychopharmacol. 2019.

BEREITSCHAFTSPOTENTIAL AND LATERALIZED READINESS POTENTIAL IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: ALTERED MOTOR SYSTEM ACTIVATION AND EFFECTS OF METHYLPHENIDATE.

Jarczok TA, Haase R, Bluschke A, et al.

Attention deficit hyperactivity disorder (ADHD) has been linked to abnormal functioning of cortical motor areas such as the supplementary motor area, the premotor cortex and primary motor cortex (MI). The Bereitschaftspotential (BP) and lateralized readiness potential (LRP) are movement-related potentials generated by cortical motor areas. We hypothesized that the BP and LRP would be altered in children with ADHD. A group of 17 children with ADHD (mean age: 11.5 -¦ 1.9 years) and a control group of 16 typically developing children (mean age: 12.2 -¦ 2.0 years) performed movements at self-chosen irregular intervals while a 64-channel DC-EEG was registered. BP and LRP were calculated from the EEG. The ADHD group had significantly lower and on average positive BP amplitudes at Cz. In agreement with age-dependent maturation effects the LRP had a positive polarity in both groups, but lower amplitudes were found in the ADHD group without medication. The control group showed a mid-central negativity and a positivity over motor areas contra-lateral to the side of movement, whereas no negativity over Cz and a more diffuse positivity was found in the ADHD group. LRP group differences diminished after MPH administration as indicated by an interaction between group and time of measurement/medication. The cortical motor system shows altered functioning during movement preparation and initiation in children affected by ADHD. Positive Bereitschaftspotential polarities may represent delayed cortical maturation. Group differences of LRP were pharmacologically modulated by the catecholaminergic agent MPH

……..

Front Behav Neurosci. 2019;13.

INVESTIGATION ON THE ATTENTION DEFICIT HYPERACTIVITY DISORDER EFFECT ON INFATUATION AND IMPULSIVITY IN ADOLESCENTS.

Soares LS, Costa DDS, Malloy-Diniz LF, et al.

Introduction: In this study, we proposed to investigate the association between infatuation/passionate love and impulsivity in a context of potential high impulsivity: adolescents with attention deficit and hyperactivity/impulsivity (ADHD) diagnosis compared with typically developing adolescents.

Methods: Impulsivity was understood as an exploratory and a sensation seeking behavior, a trend to engage in novel and exciting activities, and was evaluated using the UPPS Impulsive Behavior Scale. Eighty-one adolescents from 13-to-18 years old with and without ADHD diagnosis were compared regarding infatuation intensity, behavioral impulsivity, and social and educational profiles.

Results: After correlation analysis, we found association between higher scores on the infatuation intensity with fewer years of formal education, heightened urgency and sensation seeking. On the other hand, using the generalized equation model, we showed that the association of passionate love with behavioral urgency and sensation seeking did not change in the presence of the ADHD diagnosis.

Conclusion: The understanding of the relationship of impulsivity with infatuation might help to clarify why some population groups show an increased risk for many negative social outcomes

……..

Front Human Neurosci. 2019;13.

CROSS-DOMAIN ASSOCIATIONS BETWEEN MOTOR ABILITY, INDEPENDENT EXPLORATION, AND LARGE-SCALE SPATIAL NAVIGATION; ATTENTION DEFICIT HYPERACTIVITY DISORDER, WILLIAMS SYNDROME, AND TYPICAL DEVELOPMENT.

Farran EK, Bowler A, Karmiloff-Smith A, et al.

In typical infants, the achievement of independent locomotion has a positive impact on the development of both small-scale and large-scale spatial cognition. Here we investigated whether this association between the motor and spatial domain: (1) persists into childhood and (2) is detrimental to the development of spatial cognition in individuals with motor deficits, namely, individuals with attention deficit hyperactivity disorder (ADHD) and individuals with Williams syndrome (WS). Despite evidence of a co-occurring motor impairment in many individuals with ADHD, little is known about the developmental consequences of this impairment. Individuals with WS demonstrate impaired motor and spatial competence, yet the relationship between these two impairments is unknown. Typically developing (TD) children (N = 71), individuals with ADHD (N = 51), and individuals with WS (N = 20) completed a battery of motor tasks, a measure of independent exploration, and a virtual reality spatial navigation task. Retrospective motor milestone data were collected for the ADHD and WS groups. Results demonstrated a relationship between fine motor ability and spatial navigation in the TD group, which could reflect the developmental impact of the ability to manually manipulate objects, on spatial knowledge. In contrast, no relationships between the motor and spatial domains were observed for the ADHD or WS groups. Indeed, while there was evidence of motor impairment in both groups, only the WS group demonstrated an impairment in large-scale spatial navigation. The motor-spatial relationship in the TD, but not the ADHD and WS groups, suggests that aspects of spatial cognition can develop via a developmental pathway which bypasses input from the motor domain

……

Front Psychiatry. 2019;10.

REDUCED PREFRONTAL GYRIFICATION IN CARRIERS OF THE DOPAMINE D4 RECEPTOR 7-REPEAT ALLELE WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A PRELIMINARY REPORT.

Palaniyappan L, Batty MJ, Liddle PF, et al.

Objective: Structural and functional abnormalities have been noted in the prefrontal cortex of individuals with neurodevelopmental disorders such as attention deficit/hyperactivity disorder (ADHD). Cortical thickness and gyrification, both of which have been reported as abnormal in the prefrontal cortex in ADHD, are thought to be modulated by genetic influences during neural development. This study aimed to investigate the effects of a polymorphism of the dopamine DRD4 gene (the 7-repeat (7R) risk allele) on thickness and gyrification as distinct parameters of prefrontal cortical structure in children with ADHD.

Method: Structural images and genetic samples were obtained from 49 children aged 9-15 years (25 with ADHD and 24 matched controls), and measures of cortical thickness and gyrification for inferior, middle, and superior frontal cortex were calculated.

Results: A significant interaction between diagnosis and genotype on prefrontal gyrification was observed, largely driven by reduced inferior frontal gyrification in patients who carried the DRD4 7R allele. Furthermore, inferior frontal gyrification-but not thickness-related to everyday executive functioning in 7R allele carriers across groups.

Conclusions: Prefrontal gyrification is reduced in children with ADHD who also carry the DRD4 7R allele, and it relates to critical functional skills in the executive domain in carriers of the risk allele. More broadly, these effects highlight the importance of considering precise neurodevelopmental mechanisms through which risk alleles influence cortical neurogenesis and migration

……

Front Psychiatry. 2019;10.

CORRELATIONS OF INTERNET ADDICTION SEVERITY WITH REINFORCEMENT SENSITIVITY AND FRUSTRATION INTOLERANCE IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE MODERATING EFFECT OF MEDICATIONS.

Lu W-H, Chou W-J, Hsiao RC, et al.

Background: Deviations in reinforcement sensitivity and frustration-related reactions have been proposed as components of the biopsychosocial mechanisms, which explained the high vulnerability to internet addiction (IA) among individuals with attention-deficit/hyperactivity disorder (ADHD). There is currently limited knowledge on the relationship of IA symptoms with reinforcement sensitivity and frustration intolerance, as well as factors moderating those correlations in this population.

Objective: The aims of this study were (1) to examine the associations of IA symptoms severity with reinforcement sensitivity and frustration intolerance and (2) identify the moderators of these associations among adolescents diagnosed with ADHD in Taiwan.

Methods: A total of 300 adolescents aged between 11 and 18 years who had been diagnosed with ADHD participated in this study. Their levels of IA severity, reinforcement sensitivity, and frustration intolerance were assessed using the Chen Internet Addiction Scale, behavioral inhibition system (BIS) and behavioral approach system (BAS), and Frustration Discomfort Scale, respectively. The associations of IA severity with reinforcement sensitivity and frustration intolerance were examined using multiple regression analysis. Possible moderators, including medications for ADHD, were tested using the standard criteria.

Results: Higher fun seeking on the BAS (p = .003) and higher frustration intolerance (p = .003) were associated with more severe IA symptoms. Receiving medication for treating ADHD moderated the association between fun seeking on the BAS and severity of IA symptoms. Conclusion: Fun seeking on the BAS and frustration intolerance should be considered as targets in prevention and intervention programs for IA among adolescents with ADHD

……..

Front Psychiatry. 2019;10.

DISRUPTED RESTING FRONTAL□ÇÔPARIETAL ATTENTION NETWORK TOPOLOGY IS ASSOCIATED WITH A CLINICAL MEASURE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang Y, Tao F, Zuo C, et al.

Purpose: Although alterations in resting-state functional connectivity between brain regions have been reported in children with attention-deficit/hyperactivity disorder (ADHD), the spatial organization of these changes remains largely unknown. Here, we studied frontalparietal attention network topology in children with ADHD, and related topology to a clinical measure of disease progression.

Methods: Resting-state fMRI scans were obtained from New York University Child Study Center, including 119 children with ADHD (male n = 89; female n = 30) and 69 typically developing controls (male n = 33; female n = 36). We characterized frontal parietal functional networks using standard graph analysis (clustering coefficient and shortest path length) and the construction of a minimum spanning tree, a novel approach that allows a unique and unbiased characterization of brain networks.

Results: Clustering coefficient and path length in the frontal parietal attention network were similar in children with ADHD and typically developing controls; however, diameter was greater and leaf number, tree hierarchy, and kappa were lower in children with ADHD, and were significantly correlated with ADHD symptom score. There were significant alterations in nodal eccentricity in children with ADHD, involving prefrontal and occipital cortex regions, which are compatible with the results of previous ADHD studies.

Conclusions: Our results indicate the tendency to deviate from a more centralized organization (star-like topology) towards a more decentralized organization (line-like topology) in the frontal parietal attention network of children with ADHD. This represents a more random network that is associated with impaired global efficiency and network decentralization. These changes appear to reflect clinically relevant phenomena and hold promise as markers of disease progression

……..

Front Psychiatry. 2019;10.

POTENTIAL NEGATIVE EFFECTS OF DEXTROMETHORPHAN AS AN ADD-ON THERAPY TO METHYLPHENIDATE IN CHILDREN WITH ADHD.

Chuang W-C, Yeh C-B, Wang S-C, et al.

Objectives: Methylphenidate (MPH) is highly effective in controlling the symptoms of attention-deficit/hyperactivity disorder (ADHD), but some children with ADHD either do not respond to, or do not tolerate, treatment. Dextromethorphan (DM) is a neuroprotective agent which has been used in the treatment of neuropsychiatric disorders. This clinical trial had examined the effect of DM on the use of MPH in the children with ADHD.

Methods: This randomized double-blind clinical trial had evaluated 44 male outpatients, aged between 6 and 12 years, with a diagnosis of ADHD. The study subjects were randomly assigned into one of the two groups: receiving MPH alone (15-60 mg per day) or MPH plus DM (30-60 mg per day) for 8 weeks. Assessments, comprising the Chinese version of the Child Behavior Checklist (CBCL-C) scale and the Swanson, Nolan and Pelham Questionnaire (SNAP)-IV rating tests conducted by parents and the serum cytokines measured by microarray and enzyme-linked immunosorband assay (ELISA), were compared between groups at baseline and at 8 weeks after the medication was started.

Results: There were a significant decrease at the mean scores of both CBCL-C and SNAP-IV scales after 8 weeks of treatment, but no significant differences between MPH and MPH+DM groups. Compared with the MPH-only group, the mean scores of some psychometric parameters reported on the CBCL-C and SNAP-IV scales regarding time effects as well as the attention problems on the CBCL-C scale regarding group effect were significantly higher in the DM+MPH group. Although there were no significant differences in the levels of various serum cytokines between groups, the subjects in the DM-MPH group had relatively fewer and lower levels of adverse effects. Significant interactions were found between the withdrawn/depression item reported on the CBCL-C scale and tumor necrosis factor +¦ (TNF-+¦) (p = 0.027), as well as between thought problems item on the CBCL-C and TNF-+¦ (p = 0.028) in subjects who had received DM+MPH treatment.

Conclusion: Following the trial, DM+MPH was not superior to MPH alone for the treatment of children with ADHD, yet DM may potentially have negative effects on ADHD symptoms when combined with MPH.

Clinical Trial Registration: Clinicaltrials.gov, trial number: NCT01787136

……..

Guncel Pediatri. 2019;17:71-84.

CHARACTERISTICS OF EPILEPSY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER COMORBIDITY IN CHILDREN: A RETROSPECTIVE ANALYSIS.

Arslan EA, et al.

INTRODUCTION: Epilepsy is often accompanied by attention deficit hyperactivity disorder (ADHD). There are different opinions about reasons. The effect of epilepsy features was not studied in ADHD before or after epilepsy. We aimed to obtain clues about this comorbidity in children.

METHODS: Data of forty-four (33 males, 11 girls) consecutive epilepsy patients with ADHD were retrospectively reviewed. The binary subgroups were statistically compared.

RESULTS: ADHD was diagnosed before epilepsy in 11 (25%) and after epilepsy in 33 (75%) patients. The mean age was 11.5-¦2.7, the first and last seizure ages were 5.2-¦3 and 9.5-¦2.8, antiepileptic drug (AED) starting and ADHD ages were 6.6-¦3.4 and 8.4-¦2 years respectively. In patients with ADHD after epilepsy, AED and first seizure ages were younger (p=0.004 and p=0.002, respectively). Gender, epilepsy type, ADHD age, electroencephalography and brain magnetic resonance imaging findings were similar. There was a shorter interval time between ADHD and epilepsy in patients with a first seizure age >5 and AED age >6.5 years (p=0.013 and p=0.000). EEG abnormalities were more frequent in patients with >1.5 years time interval between epilepsy and ADHD (p=0.044). The ages of last seizure and AED starting ages were positively correlated with ADHD age (r=0.389, r=0.434, p<0.05).

DISCUSSION and CONCLUSION: We found similar ADHD ages in patients with ADHD before or after epilepsy. However, AEDs need was observed in two separate periods, early childhood and school age. The similarity of other features suggests that common pathogenetic mechanisms may play a role in this comorbidity

……..

Health Economics Review. 2019;9.

COST EFFECTIVENESS OF OPTIMAL TREATMENT OF ADHD IN ISRAEL: A SUGGESTION FOR NATIONAL POLICY.

Ornoy A, Spivak A.

Objectives: There are well known behavioral complications of ADHD at adulthood such as learning difficulties resulting in lower education attainments; increased rate of car and other accidents; substance abuse; misconduct and imprisonment. These complications can be prevented or alleviated by effective treatment. In this study we calculated the economic burden of ADHD among adults in Israel and the cost of diagnosing and treating ADHD from childhood to adulthood. We then obtained the cost-benefit ratio of the treatment.

Methods: The data were calculated using accepted estimations of prevalence and cost for the Israeli population assuming a prevalence of 4% among adults which is based on the ADHD prevalence among school age children.

Results: The estimated cost per person with ADHD due to lower education attainment, higher involvement in crime and car accidents and more drug abuse is 289,969 USD and the estimated cost for optimal treatment is 41,667 USD. Hence, the benefit cost ratio is 7.02 and, assuming only 50% success of treatment, it is 3.51, still a very high cost benefit ratio.

Conclusions: Since early diagnosis and appropriate treatment of ADHD is very effective in reducing the various symptoms and complications at adulthood thus enabling a better education and higher income, it seems important to diagnose and offer comprehensive treatment to children with ADHD. Moreover, it seems equally important to continue treatment at adulthood

……..

Int J Clin Health Psychol. 2019 May;19:141-49.

INTERRATER AGREEMENT ON BEHAVIORAL EXECUTIVE FUNCTION MEASURES IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Krieger V, Amador-Campos JA, Peró-Cebollero M.

Background/Objective: Though most children with Attention Deficit Hyperactivity Disorder (ADHD) show difficulties in behavioral measures of executive functions (EF), few studies have examined interrater agreement in these measures.

Objective: To analyze the agreement between parents, teachers and self-reports of behavioral EF in adolescents with ADHD and controls.

Method: A sample of 118 adolescents (75 with ADHD and 43 controls) was rated by parents, teachers and the adolescents themselves using the Comprehensive Executive Function Inventory. The intraclass correlation coefficient (ICC) and Bland and Altman methods were used to evaluate agreement.

Results: The ICC between parents, teachers and self-report was poor or moderate in the group with ADHD; in the control group the agreement was fair to good. The Bland and Altman graphs show that, in the control group, most of the scores are below to the clinical cut-off point, while in the group with ADHD they are above.

Conclusions: Agreement between all raters was low. Parents, teachers and adolescents agreed on the absence of deficits in behavioral EF in the control group, and on the presence of deficits in the group with ADHD, although they did not agree on the frequency of these deficits

……..

Int J Dev Neurosci. 2019;78:1-6.

FUNCTIONAL NETWORK CONNECTIVITY CHANGES IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A RESTING-STATE FMRI STUDY.

Jiang K, Yi Y, Li L, et al.

The study aimed to investigate the pathologic mechanism of functional brain regions in attention-deficit hyperactivity disorder (ADHD) patients through making comparisons of normal and ADHD children from the perspective of the network nodes of brain network and the intensity of functional connection between bilateral of hemispheres by resting-state functional magnetic resonance imaging (fMRI). Thirty-five ADHD and forty-two children were examined by resting-state functional magnetic resonance imaging (fMRI) scans. Data analysis was done via the degree centrality (DC) and voxel-mirrored homotopic connectivity (VMHC) approaches. Compared with healthy subjects, the ADHD group exhibited significantly decreased DC values in the right posterior cingulate gyrus, left medial superior frontal gyrus, right inferior parietal gyrus, right middle frontal gyrus, left superior frontal gyrus and right superior frontal gyrus. Children with ADHD also exhibited some areas with increased DC values compared with healthy children. These regions included the cerebellar anterior lobe, right middle occipital cortex, left middle cingulate gyrus and right middle cingulate gyrus. VMHC analysis all revealed positive activation in a range of brain regions when comparing ADHD and normal children, suggesting that the VMHC scores of children with ADHD were higher in the bilateral superior frontal lobe, bilateral middle occipital lobe, and bilateral cerebellar anterior lobes. This work provides a new approach for examining the neural mechanisms underlying ADHD, demonstrating that the DC and VMHC methods enabled more comprehensive analysis that can be cross-checked

……..

Int J Environ Res Public Health. 2019;16.

PARENTING STRESS AND BROADER PHENOTYPE IN PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER, DYSLEXIA OR TYPICAL DEVELOPMENT.

Bonifacci P, Massi L, Pignataro V, et al.

In the present study parenting stress and the broader phenotype are investigated in two highly common developmental disorders, namely Attention Deficit Hyperactivity Disorder (ADHD) and specific reading impairment (dyslexia). Within a total sample of 130 parents, 27 were parents of children with ADHD (P-ADHD), 38 were parents of children with a diagnosis of dyslexia (P-DYS) and the other 65 participants were parents of children with typical development (P-TD). A battery of cognitive tasks was administered which included verbal and non-verbal Intellectual Quotient (IQ), reading speed (passage and nonwords), verbal fluency and the Attention Network Task (ANT). Reading history, symptoms of ADHD in adults and parenting stress were measured through questionnaires. Group differences evidenced that the P-DYS group had lower scores in the reading tasks, in the verbal fluency task and in the reading history questionnaire. Conversely, the P-ADHD group had more transversal cognitive weaknesses (IQ, reading tasks, verbal fluency) and the highest scores in parenting stress and ADHD symptoms, together with poor reading history. The groups did not differ in the ANT task. Parenting stress was predicted, on the whole sample, by lower socioeconomic status (SES) and number of family members and higher ADHD symptoms. Implications for research and clinical settings are discussed

……..

Int J Psychiatry Clin Pract. 2019.

COMORBIDITY BETWEEN ADHD AND ANXIETY DISORDERS ACROSS THE LIFESPAN.

D'Agati E, Curatolo P, Mazzone L.

Objectives: Attention deficit/hyperactivity disorder (ADHD) and anxiety disorders are among the most common psychiatric disorders with a 25% comorbidity rate with each other. In this study, we overview the comorbidity between ADHD and anxiety disorders in a longitudinal perspective across the lifespan and we discuss possible therapeutic strategies.

Methods: A literature search was performed using PubMed to identify clinical studies assessing comorbidity between ADHD and anxiety disorders from childhood to adulthood.

Results: Anxiety disorders may substantially change the presentation, the prognosis, and the treatment of ADHD itself. In childhood, the presence of generalised anxiety disorder, could prevent the typical inhibitory dysfunction present in ADHD, in adolescence may increase the deficit of working memory, and in adulthood may enhance the presence of sleep problems. Individuals with comorbid ADHD and anxiety disorders would benefit from adjunctive psychosocial or adjunctive pharmacotherapy interventions to cognitive behavioural treatment.
Conclusions: The management of individuals with comorbid ADHD and anxiety disorders could be challenging for clinicians, and assessing the developmental course is crucial in order to shed light on individualised treatment.Keypoints The comorbidity between ADHD and anxiety disorders changes the clinical presentation, the prognosis and treatment of patients with ADHD across lifespan. ADHD and anxiety disorders shared common neurobiological dysfunctions but have also different neurobiological abnormalities suggesting that they are different diagnoses. These patients are less likely to benefit from cognitive behavioural treatment strategies alone and often need adjunctive pharmacological treatments. Studies that evaluated the response to MPH reported conflicting results. These patients could respond less well and get more unpleasant arousal side-effects, but these findings need to be confirmed. For his unique mechanism of action, low dose aripiprazole treatment in adolescents and adults with this comorbid condition could be an intriguing avenue of exploration

……..

Iran J Child Neurol. 2019;13:75-82.

EFFECT OF NEUROFEEDBACK ON PERCEPTUAL ORGANIZATION, VISUAL AND AUDITORY MEMORY IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Nesayan A, Asadi GR, Moin N.

Objectives Neurofeedback is a noninvasive treatment that changes brain activity in children with attention-deficit/hyperactivity disorder and thereby improves performance in these children. We examined the effect of neurofeedback on perceptual organization, visual and auditory memory in children with attention-deficit/hyperactivity disorder.
Materials & Methods This study was quasi-experimental with pre-test, post-test design, and control group. The sample included 20 children with attention-deficit/ hyperactivity disorder were selected through convenience sampling in Khorramabad, central Iran in 2017. The sample was divided into control and experimental groups. Pre-test included Rey-Osterrieth complex figure and Wechsler digit span. Rey-Osterrieth complex figure test was used to measure perceptual organization and visual memory. Wechsler digit span was used to measure auditory memory. After conducting pre-test, the experimental group participated in neurofeedback training sessions. Theta/Beta protocol was applied for all participants. The control group did not receive any intervention. Then post-test was conducted on two groups.
Results Neurofeedback training significantly improved visual memory ($P<0.001$) but neurofeedback training had no significant effect on the perceptual organization ($P>0.05$). Moreover, neurofeedback training enhanced auditory short-term memory and auditory working memory ($P<0.05$).
Conclusion Neurofeedback improved neurocognitive abilities in children with attention-deficit/hyperactivity disorder

……..

J Urol. 2019 Aug;202:198.

RE: CHILDREN WITH NOCTURNAL ENURESIS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SEPARATE ENTITY?

Canning DA.

……..

J Burn Care Res. 2019;40:S101.

THE ROLE OF DRUG-GENE TESTING IN PEDIATRIC BURNS WITH ADHD.

Fields AL, Braun LC, Fowler L, et al.

Introduction: Drug-gene testing is used to detect how genes impact a patient's response to drugs. Its use may improve outcomes of psychopharmacological therapy by using genotype, phenotype and drug metabolism information to improve the safety and effectiveness of psychotropic medications, analgesics and medications used to treat ADHD. The tests give recommendations about which drugs are most effective and safest to prescribe. The resulting report categorizes medications into 3 possible color-coded groupings: Use as Directed; Moderate Gene-Drug Interaction; or Significant Gene-Drug Monitoring. Application of this test in the medical management of the pediatric burn population was evaluated.

Methods: A retrospective, IRB-approved chart review was performed for pediatric burn patients who underwent drug-gene testing from 2015-2017. Collected demographic data included age, gender, % total body surface area (TBSA) burn, behavioral diagnoses and decisional factor to testing. The test results and the outcomes of the testing also were tracked. Statistical procedures included the Wilcoxon rank sum test and ¤ç2 tests.

Results: Drug-gene tests were obtained on 23 patients. Fourteen were male, with mean age 8.9 years (range 4-16 years) and with a mean burn TBSA of 48.4%. Fifteen of the 23 patients had at least one psychological and/or behavioral diagnosis prior to the burn injury, with 9 patients having an ADHD diagnosis. Six of nine (67%) patients with an ADHD diagnosis also had concurrent psychological diagnoses. Of those children diagnosed with ADHD, 7/9 (78%) were male. Patients with ADHD required significantly more medication and dose changes after the test than did children without an ADHD diagnosis. Males, regardless of previous diagnoses, required significantly more medication changes before the drug-gene test than did females and were more likely to require a dose change (11/14 males vs 1/9 females), despite no burn size difference between sexes (Table 1).

Conclusions: Earlier drug gene testing may be prudent for patients with ADHD and/or those with multiple psychological/ behavioral diagnoses, especially for males. Applicability of Research to Practice: There may be a role for drug-gene testing in pediatric burn care, specifically in patient populations known to require frequent drug and dose changes to maintain adequate pain/anxiety control. (Table Presented)

……..

J Clin Exp Neuropsychol. 2019 Jul;41:445-59.

A NOVEL UNSTRUCTURED PERFORMANCE-BASED TASK OF EXECUTIVE FUNCTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ledochowski J, Andrade BF, Toplak ME.

Objective: Executive functions (EFs) have been assessed with performance-based measures and rating scales. Research has shown a lack of association between these two methods. One factor that might contribute to this difference is the structure provided on performance-based measures that is not provided on rating scales. This study examined the role of structure on self-directed task completion, an aspect of EF, using a novel unstructured performance-based task (UPT).

Method: Children aged 8–12 years (38 attention-deficit/hyperactivity disorder, ADHD; 42 typically developing) and their caregivers participated. We compared performance on the UPT, performance-based measures of EF (Stroop test and Trail-Making Test), and a rating scale to assess EF (Barkley Deficits in Executive Functioning Scale–Children and Adolescents, BDEFS–CA).

Results: Group differences were found across all measures. Significant associations emerged between the UPT and Stroop test, Trail-Making Test, and BDEFS–CA, but no significant associations were found between the Stroop test or Trail-Making Test and the BDEFS–CA. In regression analyses, performance-based tasks and the rating scale both uniquely predicted UPT performance. The UPT was a significant predictor of group status when entered with performance-based tasks, but the UPT did not enter as a significant predictor when entered with the rating scale.

Conclusion: The UPT is a promising measure to assess self-directed task completion in children with ADHD

……..

J Clin Psychiatry. 2019;80.

A 9-YEAR FOLLOW-UP OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN A POPULATION SAMPLE .

Lecendreux M, Silverstein M, Konofal E, et al.

Background: Prior follow-up studies of attention-deficit/hyperactivity disorder (ADHD) have mostly been from North America. They have provided a good deal of information about ADHD, but whether these results generalize to population samples and to other countries is not certain. Most prior studies have also not assessed predictors of possible new onsets of ADHD in non-ADHD youth or the validity of subthreshold forms of the disorder.

Methods: 1,012 families were recruited at baseline, when a telephone interview assessed a child in the 6-12 years age range. The interview covered symptoms of ADHD, conduct disorder, and oppositional defiant disorder as well as family living situation, school performance, sleep disturbance, eating habits, use of supplemental iron, and history of ADHD treatment. Nine years later, the persistence of ADHD and its impairments and the emergence of new conditions were assessed. DSM-5 diagnostic criteria were used to diagnose ADHD.

Results: 492 of the 1,012 participants seen at baseline were followed up 9 years later, at a mean age of 18 years. At follow-up, 16.7% of the children diagnosed with ADHD at baseline met full criteria for ADHD and 11.1% met criteria for subthreshold ADHD, yielding a persistence rate of 27.8%. Among children not diagnosed with ADHD at baseline, 1.1% met criteria for ADHD at follow-up. The persistence of ADHD and new onsets of ADHD were predicted by several baseline clinical features and by a family history of ADHD.

Conclusions: We replicated predictors of the persistence of ADHD found in prior studies and provide new data about predictors of new ADHD onsets in the population. Our findings about subthreshold ADHD support a dimensional conceptualization of the disorder, highlighting the potential clinical utility of a subthreshold diagnostic category. This study also contributes to the ongoing debate regarding adult-onset ADHD

……..

J Clin Psychiatry. 2019;80.

COAGGREGATION OF MAJOR PSYCHIATRIC DISORDERS IN FIRST-DEGREE RELATIVES OF INDIVIDUALS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A NATIONWIDE POPULATION-BASED STUDY.

Chen M-H, Pan T-L, Huang K-L, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable mental illness that is easily passed from one generation to the next. Studies have shown that first-degree relatives (FDRs; ie, parents, offspring, and siblings) of individuals with ADHD had a higher risk of also having ADHD. However, the familial coaggregation of ADHD with other major psychiatric disorders, specifically schizophrenia (ICD-9-CM code 295), bipolar disorder (ICD-9-CM cods 296 except codes 296.2, 296.3, 296.9, and 296.82), major depressive disorder (ICD-9-CM codes 296.2 and 296.3), and autism spectrum disorder (ASD; ICD-9-CM code 299), remains unclear.

Methods: Among the entire Taiwanese population in 2010, there were 220,966 parents of children with ADHD (ICD-9-CM code 314), 174,460 siblings of children with ADHD, and 5,875 children of parents with ADHD. Matched control individuals who did not have FDRs with ADHD (1:4) were selected based on age, sex, and their relation to family members.

Results: FDRs (parents, offspring, siblings, and twins) of ADHD-diagnosed individuals had higher relative risks (95% CI) of major psychiatric disorders than the controls: 1.69 (1.60-1.79) for schizophrenia, 2.21 (2.10-2.32) for bipolar disorder, 2.08 (2.02-2.13) for major depressive disorder, 4.14 (3.90-4.39) for ASD, and 6.87 (6.73-7.01) for ADHD.

Discussion: These results show that ADHD coaggregated with other major psychiatric disorders, specifically schizophrenia, bipolar disorder, major depressive disorder, and ASD, within families. The results suggest that public health officials and psychiatrists should closely monitor and follow the mental health of FDRs of ADHD-diagnosed individuals, such as parents and siblings of children with ADHD

……..

J Clin Psychiatry. 2019;80.

SEX AND PUBERTAL STATUS MODERATE THE ASSOCIATION BETWEEN ADHD AND DEPRESSION SYMPTOMS: AN EXAMINATION FROM PREADOLESCENCE THROUGH LATE ADOLESCENCE.

Babinski DE, Waschbusch DA, Waxmonsky JG.

Objective: This study examines the effects of sex and pubertal status on the association between attention-deficit/hyperactivity disorder (ADHD) and depression symptoms in preadolescence through late adolescence.

Methods: Participants were 472 youth from the Multimodal Treatment Study of Children With ADHD. The study sample included 308 youth with DSM-IV ADHD, recruited from 1993 through 1996, and 164 comparison youth who were recruited approximately 2 years later. Self-reported depression symptoms from the Children's Depression Inventory and pubertal status from the Tanner Self-Report Scale were collected, along with combined parent-teacher reports of ADHD. Regression analyses examined the impact of ADHD, sex, pubertal status, and their interactions on total depression symptoms and related subscales (ie, negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem) in preadolescence. Next, path models examined associations between ADHD, sex, and pubertal status on depression symptoms into middle and late adolescence.

Results: In preadolescence, significant ADHD sex puberty interactions emerged for total depression symptoms and anhedonia (P<.05). Higher levels of ADHD severity were associated with higher levels of depression in early maturing girls and later maturing boys. Effects appear to be driven by anhedonia. Longitudinal effects emerged showing that total depression symptoms and anhedonia in preadolescence predicted levels of each respective outcome into late adolescence.

Conclusions: Sex and pubertal status meaningfully impact the association between ADHD and depression symptoms in youth and should be considered in future work and treatment

……..

J Clin Psychopharmacol. 2019;39:409-10.

GUANFACINE TREATMENT OF SLEEPWALKING.

Ye L, Andrew W, Lippmann S.

……..

J Clin Psychopharmacol. 2019;39:386-92.

ADVERSE DRUG REACTIONS RELATED TO MOOD AND EMOTION IN PEDIATRIC PATIENTS TREATED FOR ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A COMPARATIVE ANALYSIS OF THE US FOOD AND DRUG ADMINISTRATION ADVERSE EVENT REPORTING SYSTEM DATABASE.

Pozzi M, Carnovale C, Mazhar F, et al.

Background Attention deficit/hyperactivity disorder (ADHD) can be comorbid with frequent anxiety and mood disorders, as well as emotional symptoms (anxiety, irritability, mood lability). These may also be triggered by drugs and appear as adverse drug reactions (ADRs).

Methods We mined data from the US Food and Drug Administration Adverse Event Reporting System pharmacovigilance database, focused on methylphenidate, atomoxetine, amphetamine, lisdexamfetamine, and their derivatives. We collected reports of ADRs connected with mood or emotional symptoms in pediatric patients, excluding drug abuse/accidents. Reporting odds ratios (RORs) were calculated and compared between drug classes and children/adolescents.

Results We collected 6176 ADRs of interest of which 59% occurred in children. Atomoxetine accounted for 50.7% of reports, methylphenidate for 32.5%, lisdexamfetamine for 14.2%, and amphetamine for 2.6%. Irritability, anxiety, obsessive thoughts, depressed mood, and euphoria scored significant RORs for all drugs, overall with an increasing risk from methylphenidate to atomoxetine, lisdexamfetamine, and amphetamine. Apathy regarded mostly atomoxetine, and crying regarded all drugs except methylphenidate. Several age-based differences were found. Notably, affect lability hit only adolescents. All drugs scored significant self-injury RORs, except lisdexamfetamine in adolescents, with an increasing risk from methylphenidate to lisdexamfetamine, atomoxetine, and amphetamine. For suicidality, all drugs had significant RORs in children,

and methylphenidate was better than atomoxetine and lisdexamfetamine. In adolescents, only methylphenidate and atomoxetine scored significant RORs.
Conclusions We conclude that real-world data from the US Food and Drug Administration Adverse Event Reporting System are consistent with previous evidence from meta-analyses. They support a hierarchy of drug safety for several ADRs (except self-injury/suicidality) with methylphenidate as safest, followed by atomoxetine, lisdexamfetamine, and amphetamine last. Self-injury and suicidality RORs were overall higher in children

……..

J Neurol Neurosurg Psychiatry. 2019;90:A10.

MISSED DIAGNOSIS OF ADHD IN CHILDREN REFERRED TO A TIC DISORDER CLINIC.

Hisham IN, Stern JS, Simmons H.

Aim To examine whether Attention Deficit Hyperactive Disorder (ADHD), a common comorbid disorder in Tourette's Syndrome (TS) patients, is often missed by physicians referring to a Tic Disorder Clinic.
Method Referral letters and first clinic attendance reports for 119 new patients aged between 4-17 that attended a national tic disorder clinic between 2015-2017 were analysed to see how many new diagnoses of ADHD were made at first consultation that were not included in the referral letters. Other variables that were noted for each patient included age, sex, if referrer had a suspicion of ADHD (rather than established or firm diagnosis), medication for ADHD and the main treatment target decided at the tic disorder clinic.
Results Out of 119 patients 13 (11%) already had a diagnosis of ADHD, which is in line with the prevalence of comorbid ADHD in the general population but not with the known increased prevalence in patients with TS (up to 80% in some studies). The assessment at the Tic Disorder Clinic found 46 cases of ADHD (38%). Referrals were from pediatricians (51%), general practitioners (35%) and from mental health services (10%).
Conclusions As the prevalence of comorbid ADHD is high in Tourette's patients and this can sometimes be obscured by the presentation of the tic disorder, referrers should have a low threshold for suspecting and managing ADHD in cases where specialist input for tics is awaited. It is likely that CAMHS referrals were under-represented in the sample and it may be expected that prior ADHD diagnoses would be more likely from that source

……..

J Pediatr. 2019.

FACTORS ASSOCIATED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER MEDICATION USE IN COMMUNITY CARE SETTINGS.

Kamimura-Nishimura KI, Epstein JN, Froehlich TE, et al.

Objectives: To examine patient- and provider-level factors associated with receiving attention-deficit/hyperactivity disorder (ADHD) medication treatment in a community care setting. We hypothesized that the likelihood of ADHD medication receipt would be lower in groups with specific patient sociodemographic (eg, female sex, race other than white) and clinical (eg, comorbid conditions) characteristics as well as physician characteristics (eg, older age, more years since completing training).
Study design: A retrospective cohort study was conducted with 577 children (mean age, 7.8 years; 70% male) presenting for ADHD to 50 community-based practices. The bivariate relationship between each patient- and physician-level predictor and whether the child was prescribed ADHD medication was assessed. A multivariable model predicting ADHD medication prescription was conducted using predictors with significant (P <.05) bivariate associations.
Results: Sixty-nine percent of children were prescribed ADHD medication in the year after initial presentation for ADHD-related concerns. Eleven of 31 predictors demonstrated a significant (P <.05) bivariate relationship with medication prescription. In the multivariable model, being male (OR, 1.34; 95% CI, 1.01-1.78; P =.02), living in a neighborhood with higher medical expenditures (OR, 1.11 for every $100 increase; 95% CI, 1.03-1.21; P =.005), and higher scores on parent inattention ratings (OR, 1.06; 95% CI, 1.03-1.10; P <.0001) increased the likelihood of ADHD medication prescription.

Conclusions: We found that some children, based on sociodemographic and clinical characteristics, are less likely to receive an ADHD medication prescription. An important next step will be to examine the source and reasons for these disparities in an effort to develop strategies for minimizing treatment barriers

……..

J Psychiatr Pract. 2018;24:323-30.

DIAGNOSIS AND USE OF PSYCHOTHERAPY AMONG CHILDREN AND ADOLESCENTS PRESCRIBED ANTIPSYCHOTICS.

Vanbronkhorst SB, Roberts DE, Edwards EM, et al.

To examine the diagnoses, demographics, and prevalence of psychotherapy use among children and adolescents prescribed antipsychotics by psychiatric providers in a community setting. Methods: Medical records from 1127 children aged 0 to 17 years who were prescribed antipsychotics in 2014-2015 at Pine Rest Christian Mental Health Services (PRCMHS) outpatient network were analyzed. Antipsychotics, diagnosis codes, demographics, and number of psychotherapy sessions during this time frame were analyzed using ¤ç2 and logistic regression analyses. Results: During this year, 50.8% of the patients attended psychotherapy, and 35.6% attended 5 or more sessions of psychotherapy. The most prevalent primary diagnosis was bipolar disorder (37.1%), followed by attention-deficit/hyperactivity disorder (19.7%). Females being treated with antipsychotics were significantly more likely to attend psychotherapy than their male peers (55.7% vs. 47.9%, P=0.01). In the fully adjusted models, patients with diagnoses of bipolar disorder or disorders first diagnosed in infancy, childhood, or adolescence were less than half as likely to attend psychotherapy as patients with depressive disorders, with adjusted odds ratios of 0.41 and 0.42, respectively. Conclusions: Approximately half of the child and adolescent patients prescribed antipsychotics in this community sample did not attend psychotherapy, and 39% of the patients did not have a diagnosis of bipolar disorder, psychotic disorder, or autistic disorder

……..

J Psychopathol Behav Assess. 2019.

DISTINGUISHING SCT SYMPTOMS FROM ADHD IN CHILDREN: INTERNAL AND EXTERNAL VALIDITY IN TURKISH CULTURE.

Flrat S, et al.

In this study, our aim was to evaluate the internal and external validity of Sluggish Cognitive Tempo (SCT) and to determine if it is an independent factor from Attention Deficit Hyperactivity Disorder (ADHD) in Turkish children, like in other cultures. Two hundred sixty-one children (6Γçô12-áyears of age) who applied to Ankara University Child and Adolescent Psychiatry outpatient clinics and diagnosed with ADHD recruited the study. All children were evaluated with the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version which is a semi-structured diagnostic interview (K-SADS-PL) for ADHD diagnosis. Child Behavior Checklist for ages 6-18, The Barkley's Child SCT Ratings Scale, SNAP-IV Parent and Teacher Scale, and Sociodemographic Information Form were enrolled by the parents and teachers of the children. Our results demonstrated that SCT symptoms formed two distinct but interrelated factors (Sluggish and Daydreaming) separate from those for ADHD. Due to regression analyses, higher levels of SCT predicted higher levels of ADHD-IN (Inattentive) and internalizing symptoms including anxiety-depression, social problems, and social withdrawal. These findings distinguished SCT cases from ADHD-IN in Turkish children. Results also indicated that ADHD- IN symptoms are risk factors for lower academic achievement while SCT symptoms haven't such an effect. Our study is the first which demonstrates SCT's construct validity relative to ADHD-IN by parental and teacher ratings in Turkey. Similar findings with Turkish children to the findings with children from other cultures would increase our confidence in the transcultural generalizability of SCT's internal-external validity

……..

J Can Acad Child Adolesc Psychiatry. 2019;28:30-41.

EXPLORING THE DECISIONAL NEEDS OF PARENTS WITH CHILDREN WITH ADHD AND DISRUPTIVE AND AGGRESSIVE BEHAVIOUR.

Nosratmirshekarlou E, Andrade BF, Jette N, et al.

Objective: The aim of this qualitative study was to explore the decisional needs of parents of children with ADHD and disruptive and aggressive behaviour to inform the creation of a patient decision aid.

Method: A one-day meeting of researchers, community advocacy partners, and 11 parents of children (age range eight to 21) with aggressive and disruptive behaviour associated with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder or Conduct Disorder was held. This meeting consisted of a two-hour educational session on the assessment and management of aggressive and disruptive behaviour in children and patient decision aids, followed by two concurrent focus groups to determine the decisional needs of parents. NVivo11 software was used for the organization of the data.

Results: The results outline the broad themes and subthemes that emerged from the thematic analysis. These themes and subthemes include (a) decisional needs treatment options and where to begin, availability, effectiveness of different treatment options, side effects, time, depth of information provided; (b) decision aid formats, and (c) accessibility language, involvement of children, and dissemination.

Conclusion: The themes generated from the focus groups suggest that a patient decision aid for parents with children with ADHD and disruptive and aggressive behaviour should follow the general recommendations for best practices for the creation of patient decision aids. Specific information on the regional availability of non-medical treatments will be especially helpful for parents to navigate services and service providers. Consideration should be given as to how the concept of values clarification is introduced to families

……..

Laryngo- Rhino- Otologie. 2018;97:S294.

FOREIGN BODIES DURING CHILDHOOD-EPIDEMIOLOGY AND CORRELATION ANALYSIS WITH HYPERKINETIC DISORDERS.

Schuldt T, et al.

Introduction: Children and infants present reaularly with foreian bodies in nose and ear in the emeraency room. Due to the risk of aspiration and serious inflammation an immediate treatment is necessary. In this study, we analyze the epidemioloaical characteristics in children with foreian body. The focus is on hyperkinetic disorders.

Methods: In collaboration with the AOK Nordost health insurance company, all cases of policy holders treated with the diaanoses T16 (foreian body in ear); T17 (foreian body in nasal sinus); T17.1 (foreian body in nostril) and F90.x (Hyperkinetic disorders) within the period January 2006 to March 2015 were included. Treatment date of the foreian body removal, aae at treatment, sex, date of first diaanosis of a hyperkinetic disorder and possible recurrent treatments for foreian bodies were analyzed.

Results: In the evaluation period, 12887 children (m: 6609/f:6278) were treated with a foreian body in nose or ear. In 1815 cases (14,1%), a hyperkinetic disorder was present as well. The mean aae of all children at time of foreian body removal was 5,91 years. Boys were with a mean aae of 5,70 years younaer than airls with a mean aae of 6,14 years. The initial diaanosis of a hyperkinetic disorder was made at a mean aae of 6,26 years.

Conclusions: The prevalence of hyperkinetic disorders in our examination aroup is with a rate of 14,1% much hiaher than in the standard population with a rate of 2 percent. Especially children presentina with recurrent foreian bodies, a possible hyperkinetic disorder should be kept in mind

……..

Nervenarzt. 2019.

DAY CARE/INPATIENT PSYCHIATRIC TREATMENT OF MINORS AND ADULTS WITH HYPERKINETIC DISORDER IN GERMAN PSYCHIATRIC HOSPITALS: BASIC CONDITIONS, DIAGNOSES AND COMORBIDITIES.

Belz M, Wiltfang J, et al.

Background: Hyperkinetic disorders (HKD, ICD-10 F90.ΓÇæ) have increasingly been the focus of research literature in recent years. Empirical studies analyzing the care situation in psychiatric clinics are so far primarily available for few health insurances. This study analyzed German sample from 2015 consisting of inpatient as well as day care psychiatric treatment cases from all statutory health insurances focusing on the care situation and differentiating between minor vs. adult patients with the main diagnosis HKD.
Material and methods: The study was based on the treatment relevant indicators in psychiatry and psychosomatics (VIPP) database, which contains data according to -º21-áof the Hospital Remuneration Act (KHEntgG). total of 896 treatment cases with the diagnosis of HKD from the year 2015, based on anonymized routine records from 41-ápsychiatric clinics, were analyzed.
Results: The basic conditions for inpatient/day care psychiatric treatment significantly differed between minor vs. adult patients. Minors travelled greater distances to the treatment site, received more therapy units and stayed longer in the psychiatric clinic than adults. Significant differences were also found between the subgroups concerning the main diagnoses according to ICD-10 coding as well as comorbid mental disorders.
Conclusion: Due to greater distances from their residence to psychiatric hospital for minors, extension of capacities with a focus on child and youth psychiatry seems to be a-áreasonable conclusion. Simultaneously, the intensity of treatment seems to be lower for adult patients, despite greatly increased number of secondary diagnoses and thus anticipated psychological stress. Transition difficulties from child and youth psychiatry to adult psychiatry may be possible explanation for this discrepancy

……..

Network Neuroscience. 2017;2:200-17.

ADHD AND ATTENTIONAL CONTROL: IMPAIRED SEGREGATION OF TASK POSITIVE AND TASK NEGATIVE BRAIN NETWORKS.

Mills BD, Miranda-Dominguez O, Mills KL, et al.

In children with attention deficit hyperactivity disorder (ADHD) difficulty maintaining task focus may relate to the coordinated, negatively correlated activity between brain networks that support the initiation and maintenance of task sets (task positive networks) and networks that mediate internally directed processes (i.e., the default mode network). Here, resting-state functional connectivity MRI between these networks was examined in ADHD, across development, and in relation to attention. Children with ADHD had reduced negative connectivity between task positive and task negative networks (p = 0.002). Connectivity continues to become more negative between these networks throughout development (7ΓÇô15 years of age) in children with ADHD (p = 0.005). Regardless of group status, females had increased negative connectivity (p = 0.003). In regards to attentional performance, the ADHD group had poorer signal detection (dΓÇ¦) on the continuous performance task (CPT) (p < 0.0001), more so on easy than difficult dΓÇ¦ trials (p < 0.0001). The reduced negative connectivity in children with ADHD also relates to their attention, where increased negative connectivity is related to better performance on the dΓÇ¦ measure of the CPT (p = 0.008). These results highlight and further strengthen prior reports underscoring the role of segregated system integrity in ADHD

……..

NeuroImage Clin. 2019;23.

THE REINFORCING VALUE OF DELAY ESCAPE IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER: AN ELECTROPHYSIOLOGICAL STUDY.

Chronaki G, Benikos N, Soltesz F, et al.

The delay aversion hypothesis argues that the tendency for impulsive choice (preference for smaller sooner over larger later rewards) is motivated by the escape of negative affective states associated with delay. This model predicts that individuals with ADHD find the imposition of delay before an outcome or event especially aversive and its escape reinforcing. Consistent with this, fMRI studies show that ADHD is associated with

amygdala hyper-sensitivity to cues of delay. However, evidence that delay escape is reinforcing is lacking. Here we extend fMRI research by using electrophysiological methods to study the reinforcing properties of delay-escape in ADHD. Thirty controls and 25 adolescents with ADHD aged 10-15 years performed the Escape Delay Incentive (EDI) task- in which pre-target cues indicated three conditions: i) CERTAIN DELAY: delay would follow a response irrespective of response speed ii) CONDITIONAL DELAY: delay would only follow if the response was too slow and iii) NO DELAY: delay would follow the response whatever the speed. We focused on the Contingent Negative Variation (CNV), a cue-evoked marker of motivated response preparation, across two time windows (CNV1 and CNV2). We took measures of parent, teacher and self-rated ADHD symptoms, task performance (RT) and self-rated delay aversion. We isolated CNV components and compared these between ADHD and controls. Adolescents with ADHD displayed a larger CNV2 to the CONDITIONAL DELAY than the CERTAIN DELAY cues compared to controls. However, this effect was not mirrored at the performance level and was unrelated to self-reported delay aversion. Our study provides the first ERP evidence that delay escape differentially reinforcers neural activation of attention preparation in ADHD cases. Future studies should examine the impact of varying cognitive load on task EDI performance

……..

Neurologia. 2019.

NEUROLOGICAL MANIFESTATIONS OF NEUROFIBROMATOSIS TYPE 1: OUR EXPERIENCE.

Sínchez Marco SB, et al.

Introduction: Neurofibromatosis type 1 (NF1) is a progressive multisystem disorder following an autosomal dominant inheritance pattern that presents with multiple neurological manifestations.

Methods: We reviewed medical histories of patients with NF1 followed up at our hospital's paediatric neurology department from May 1990 to 31 December 2018. We collected data on neurological symptoms.

Results: A total of 128 patients with NF1 were identified. Mean age (SD) at NF1 diagnosis was 4.43 (3.38) years (range, 0.5-14.5 years). There was a slight female predominance (53.1%). Macrocephaly (head circumference over 2 SDs above average for age) was present in 37.5% of cases. Attention-deficit/hyperactivity disorder was recorded in 28.9% of patients (37): combined type in 20 patients, predominantly inattentive in 15, and predominantly impulsive/hyperactive in 2. Other manifestations included headache (18.6%), cognitive impairment (7.8%), motor deficit (6.2%), and epilepsy (4.68%). Brain MRI was performed in 85 patients, revealing T2-weighted hyperintensities in the basal ganglia and/or cerebellum in 60 patients (70.5%), Chiari malformation type 1 in 4 cases, and arachnoid cysts in 3. Optic nerve gliomas were identified by MRI in 22 patients (25.8%). Other MRI findings included plexiform neurofibromas (9.3%) and central nervous system gliomas (3.1%).

Conclusions: The neurological manifestations identified in our sample are consistent with those reported in the literature. Effective transfer strategies from paediatric neurology departments and subsequent clinical follow-up by adult neurology departments are needed to prevent loss to follow-up in adulthood

……..

Neuropsychiatr Dis Treat. 2019;15:1517-23.

A VIRTUAL REALITY APPLICATION FOR ASSESSMENT FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN SCHOOL-AGED CHILDREN.

Fang Y, Han D, Luo H.

Background and objective: The development of objective assessment tools for attention deficit hyperactivity disorder (ADHD) has become a hot research topic in recent years. This study was conducted to explore the feasibility and availability of virtual reality (VR) for evaluating symptoms of ADHD.

Methods: School-aged children were recruited. The children with ADHD or without ADHD were assigned into the ADHD group or Control group, respectively. They were all evaluated using the Conners' Parent Rating Scale (CPRS), Child Behavior Checklist (CBCL), Integrated Visual and Auditory Continuous Performance Test (IVA-CPT), and a VR test.

Results: The correct items, incorrect items, and the accuracy rate of the VR test of the children with ADHD were significantly different with those of the children in the Control group. The correct items, incorrect items,

total time, and accuracy of the VR test were significantly correlated with the scores of IVA-CPT (auditory attention and visual attention), CPRS (impulsion/hyperactivity and ADHD index), and CBCL (attention problems and social problems), respectively.
Discussion: The results supported the discriminant validity of the VR test for evaluating ADHD in school-age children suffering from learning problems. The VR test results are associated with the commonly used clinical measurements results. A VR test is interesting for children and therefore it attracts them to complete the test; whilst at the same time, it can also effectively evaluate ADHD symptoms

……..

Neuropsychiatr Dis Treat. 2019;15:663-67.

EFFECTS OF MELATONIN IN CHILDREN WITH ATTENTIONDEFICIT/ HYPERACTIVITY DISORDER WITH SLEEP DISORDERS AFTER METHYLPHENIDATE TREATMENT.

Masi G, Fantozzi P, Villafranca A, et al.

Purpose: Methylphenidate (MPH), the first-line medication in children with attention-deficit/ hyperactivity disorder (ADHD), is associated with increased risk of sleep disorders. Melatonin has both hypnotic and chronobiotic properties that influence circadian rhythm sleep disorders. This study explores the effectiveness of melatonin in children with ADHD who developed sleep problems after starting MPH.
Patients and methods: This study, based on a clinical database, included 74 children (69 males, mean age 11.6±2.2 years) naturalistically treated with MPH (mean dosage 33.5±13.5 mg/d). The severity of sleep disorder (sleep onset delay) was recorded at baseline and after a follow-up of at least 4 weeks using a seven-point Likert scale according to the Clinical Global Impression Severity score. Effectiveness of melatonin on sleep (mean dosage 1.85±0.84 mg/d) after 4 weeks was assessed using a seven-point Likert scale according to the Clinical Global Impression Improvement (CGI-I) score, and patients who scored 1 (very much improved) or 2 (much improved) were considered responders.
Results: Clinical severity of sleep disorders was 3.41±0.70 at the baseline and 2.13±1.05 after the follow-up (P,0.001). According to the CGI-I score, 45 patients (60.8%) responded to the treatment with melatonin. Gender and age (children younger and older than 12 years) did not affect the response to melatonin on sleep. Patients with or without comorbidities did not differ according to sleep response. Specific comorbidities with disruptive behavior disorders (oppositional defiant disorder or conduct disorder), affective (mood and anxiety) disorders and learning disabilities did not affect the efficacy of melatonin on sleep. Treatment was well tolerated, and no side effects related to melatonin were reported.
Conclusion: In children with ADHD with sleep problems after receiving MPH treatment, melatonin may be an effective and safe treatment, irrespective of gender, age and comorbidities

……..

Neuropsychiatr Dis Treat. 2019;15:1547-55.

THE EFFECT OF STIMULANTS ON IRRITABILITY IN AUTISM COMORBID WITH ADHD: A SYSTEMATIC REVIEW.

Ghanizadeh A, Molla M, Olango GJ.

Introduction: While there is a very high rate of comorbidity of autism and ADHD, there are controversies about prescribing stimulants in children with autism. This is a systematic review about the effect of stimulants on irritability in children with both autism and ADHD.
Methods: A systematic review was conducted to study the possible effect of stimulants on irritability in autism and ADHD using the databases of PubMed, Scopus, EMBASE, and ScienceDirect in September 2018. Eligible clinical trials of stimulants in the treatment of Autism and ADHD without restriction of language were included. The primary outcome was irritability score. The full texts of relevant articles were studied, and their references were scanned for any possible related article.
Results: Out of 1,315 citations, there were 26 relevant articles. Of the relevant articles, 16 were not interventional studies and were excluded. There were 10 interventional studies. None of them considered irritability as a main outcome. Also, none of them studied the effect of stimulants on irritability in autism plus ADHD. Current uncontrolled evidence about the association of stimulants with irritability is controversial.

Conclusion: The current evidence is not enough to support or discourage the effect of stimulants on irritability in children and adolescents with both autism and ADHD. Well-designed controlled clinical trials need to be conducted for this ignored research area

……..

Neuropsychologia. 2019;131:342-52.

A SUPERIOR ABILITY TO SUPPRESS FAST INAPPROPRIATE RESPONSES IN CHILDREN WITH TOURETTE SYNDROME IS FURTHER IMPROVED BY PROSPECT OF REWARD.

Maigaard K, Nejad AB, Andersen KW, et al.

In children with Tourette syndrome (TS), tics are often attributed to deficient self-control by health-care professionals, parents, and peers. In this behavioural study, we examined response inhibition in TS using a modified Simon task which probes the ability to solve the response conflict between a new non-spatial rule and a highly-overlearned spatial stimulus-response mapping rule. We applied a distributional analysis to the behavioural data, which grouped the trials according to the individual distribution of reaction times in four time bins. Distributional analyses enabled us to probe the children's ability to control fast, impulsive, responses, which corresponded to the trials in the fastest time bin. Additionally, we tested whether the ability to suppress inappropriate action tendencies can be improved further by the prospect of a reward. Forty-one clinically well-characterized medication-na+»ve children with TS, 20 children with attention-deficit/hyperactivity disorder (ADHD), and 43 typically developing children performed a Simon task during alternating epochs with and without a prospect of reward. We applied repeated measures ANCOVAs to estimate how the prospect of reward modulated reaction times and response accuracy, while taking into account the distribution of the reaction times across trials. We found between-group differences in accuracy when subjects responded relatively fast. The TS group responded more accurately than typically developing control children when resolving the response conflict introduced by the Simon task. The opposite pattern was found in children with ADHD. Prospect of reward improved accuracy rates in all groups. Although the Tourette group performed with superior accuracy in the fast trials, it was still possible for them to benefit from prospect of reward in fast trials. The findings corroborate the notion that children with TS have an enhanced capacity to inhibit fast inappropriate response tendencies. This ability can be improved further by offering a prospect of reward which might be useful during non-pharmacological therapeutic interventions

……..

No To Hattatsu. 2019;51:S223.

STRUCTURAL CLASSIFICATION FEATURE IN CHILDREN WITH ADHD USING MACHINE LEARNING APPROACH.

Mizuno Y, Jung M, Fujisawa T, et al.

[**Introduction**] We have been reporting the abnormalities of brain structure, function, and network in children with ADHD using MRI (Neuroimage Clin 2013, World J Biol Psychiatry 2015, Sci Rep 2017). However, diagnostic application of MRI in ADHD has not been fully investigated yet. Here we challenge this notion by identifying classification feature of cortical thickness and surface area between children with ADHD and typical development (TD) controls using machine learning approach.

[**Methods**] Thirty-nine children with ADHD and thirty-four age- and IQ-matched TD controls (7-15 years) underwent high-resolution T1-weighted anatomical MRI. To investigate cortical thickness and surface area, FreeSurfer was used, and they served as features that were input into the classification analyses using support vector machine-recursive feature elimination (SVM-RFE). Additionally, to examine the classifier's generalization capability, the performance of the classifier was tested using samples from the ADHD-200 database (83 children with ADHD and 115 TD).

[**Results**] A classification analysis revealed 16 cortical thickness and 11 surface area features, predominantly observed in the frontal cortex, and each accuracy was 79% and 74%. Furthermore, their classifier from the ADHD-200 dataset also achieved an accuracy of 73% and 69%, respectively.

[**Conclusion**] The present study revealed diagnostic structural feature in children with ADHD. It may lead to neuroscientific diagnosis application of ADHD

……..

No To Hattatsu. 2019;51:S223.

INDIVIDUAL CLASSIFICATION OF ADHD WITH AND WITHOUT ASD USING FNIRS ON EFFECT OF METHYLPHE-NIDATE.

Ikeda T, Monden Y, Tokuda T, et al .

[**Introduction**] ADHD and ASD, often comorbid, present with performance and brain dysfunction in response inhibition, though the shared vs disorder-specific dysfunctions remain unknown. While we previously revealed group-level effects of Methylphenidate (MPH) on inhibitory brain activation (ADHD with vs without ASD), here we explore individual differentiation using fNIRS and behavior parameters.

[**Method**] We compared age and sex matched ADHD children with and without ASD, whose ADHD-Rating Scale (RS) scores improved significantly after 1 mo. of MPH ($p = 0.001$). We performed independent two-sample t-tests on group-level pre-/post-MPH contrasts for behavior (reaction time (RT) commission errors) and OxyHb (fNIRS) data for Go/No-go tasks. We set cut-off values for parameters with significant differences in group comparisons for more accurate classification.

[**Result**] MPH led to significant neural response differences between groups (rPFC: $p = 0.005$, ES = 0.87). It reduced RT for ADHD without ASD ($p = 0.001$), but not with ASD ($p = 0.198$). At an optimal cut-off value for individual classification, we differentiated between ADHD with and without ASD at a sensitivity of 72% and specificity of 81% for OxyHb, 63% and 23% for RT and 91% and 62% for both combined.

[**Discussion**] Combined neural and behavioral analysis achieved high accuracy for individual classification, suggesting that this novel method could provide a biomarker for the distinct impulsivity-control pathologies in ADHD with and without ASD

……..

Pediatric Obesity. 2019.

THE INFLUENCE OF PRESCHOOLERS' EMOTIONAL AND BEHAVIOURAL PROBLEMS ON OBESITY TREATMENT OUTCOMES: SECONDARY FINDINGS FROM A RANDOMIZED CONTROLLED TRIAL.

Eiffener E, Eli K, Ek A, et al.

Background: Few studies have explored the influence of preschoolers' behavioural problems on obesity treatment. Objectives: To assess emotional and behavioural problems before and after an obesity intervention and examine relationships between changes in child behaviour and changes in weight status.

Method: The study included 77 children (4-6 years old, 53% girls, mean body mass index [BMI] z-score of 3.0 [SD 0.6]) who participated in the More and Less Study, a randomized controlled trial. Families were randomized to a parenting program or to standard treatment. The children's heights and weights (BMI z-score, primary outcome) were measured at baseline and 12 months post baseline. Parents rated their children's behaviours (secondary outcome) on the Child Behavior Checklist (CBCL) for ages 1.5 to 5 years, a questionnaire that measures psychosocial health and functioning, encompassing emotional and behavioural problems. Changes in child behaviour during treatment were examined through paired samples t tests; the influence of child behaviour on treatment effects was examined through linear regressions.

Results: Child emotional and behavioural problems significantly improved after obesity treatment. Lower scores were found for Emotional Reactivity, Sleep Problems, Affective Problems, Aggressive Behaviour, Externalizing Behaviours, Oppositional Defiant Problems, and Total Problems. Child behaviour significantly affected obesity treatment results: Attention Problems and attention deficit hyperactivity disorder (ADHD) at baseline contributed to increasing BMI z-scores, whereas Oppositional Defiant Problems, Externalizing Behaviours, and a higher number of behavioural problems predicted decreasing BMI z-scores.

Conclusions: Child behaviours at baseline influenced treatment results. Child emotional and behavioural problems improved post treatment. The results suggest that obesity treatment may help in reducing emotional distress among preschoolers

……..

Pediatrics. 2019;143.

TRAFFIC CRASHES, VIOLATIONS, AND SUSPENSIONS AMONG YOUNG DRIVERS WITH ADHD.

Curry AE, Yerys BE, Metzger KB, et al.

OBJECTIVES: To compare monthly rates of specific types of crashes, violations, and license suspensions over the first years of licensure for drivers with and without attention-deficit/ hyperactivity disorder (ADHD).

METHODS: We identified patients of New Jersey primary care locations of the Children's Hospital of Philadelphia who were born in 1987-1997, were New Jersey residents, had their last primary care visit at age $12 years, and acquired a driver's license (N = 14 936). Electronic health records were linked to New Jersey's licensing, crash, and violation databases. ADHD diagnosis was based on International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic codes. We calculated monthly per-driver rates of crashes (at fault, alcohol related, nighttime, and with peers), violations, and suspensions. Adjusted rate ratios were estimated by using repeated-measures Poisson regression.

RESULTS: Crash rates were higher for drivers with ADHD regardless of licensing age and, in particular, during the first month of licensure (adjusted rate ratio: 1.62 [95% confidence interval: 1.1822.23]). They also experienced higher rates of specific crash types: their 4-year rate of alcohol-related crashes was 2.1 times that of drivers without ADHD. Finally, drivers with ADHD had higher rates of moving violations (for speeding, seat belt nonuse, and electronic equipment use) and suspensions. In the first year of driving, the rate of alcohol and/ or drug violations was 3.6 times higher for adolescents with ADHD.

CONCLUSIONS: Adolescents with ADHD are at particularly high crash risk in their initial months of licensure, and engagement in preventable risky driving behaviors may contribute to this elevated risk. Comprehensive preventive approaches that extend beyond current recommendations are critically needed

……

PLoS ONE. 2019;14.

LATENT RESTING-STATE NETWORK DYNAMICS IN BOYS AND GIRLS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Scofield JE, Johnson JD, Wood PK, et al.

Neuroimaging studies of subjects with ADHD typically show altered functional connectivity in prefrontal, striatal, and several temporal brain regions. While the majority of studies have focused on connectivity that is averaged over time, we investigated the temporal dynamics of brain network changes in resting-state fMRI. Using the ADHD-200 consortium, we characterized the time course of latent state changes using Hidden Markov Modeling, and compared state changes between boys and girls with ADHD along with typically developing controls. Sex differences were found in latent state switching, with boys dwelling longer in a given state than girls, and concurrently having fewer overall state transitions. These sex differences were found in children with ADHD and in typically developing controls. Children with ADHD were also found to be more variable in terms of state transitions than controls. These findings add to the growing literature on neural sex differences and may be related to the sex difference in focal versus diffuse attention

……

Psychiatr Pol. 2019;53:419-32.

GENERAL HEALTH, SENSE OF COHERENCE AND COPING STYLES IN PARENTS PARTICIPATING IN WORKSHOPS FOR PARENTS OF HYPERACTIVE CHILDREN.

Pisula A, Bryäska A, Wjtowicz S, et al.

Aim. The assessment of changes in the general health, sense of coherence and stress coping styles in parents of children and adolescents with ADHD, participating in 12-week Workshops for Parents of Hyperactive Children.

Material. The experimental group included 186 mothers and 139 fathers (parents of 199 children); the reference group included 23 mothers and 19 fathers (parents of 24 children), attending 1-2 standard medical visits within a 12-week period (treatment as usual).

Method. Parents from both groups were assessed twice using (1) the General Health Questionnaire (GHQ), (2) the Life Orientation Questionnaire (SOC-29), and (3) the Coping Inventory for Stressful Situations (CISS).

Results. (1) The experimental group showed a significant improvement in the severity of somatic symptoms and anxiety/insomnia in mothers and the general well-being of mothers and fathers. We observed the influence of workshops on manageability and reduction of the emotion-oriented coping in mothers; (2) the participation in the workshops was associated with a statistically significant effect (mostly moderate) in relation to general health of mothers, while TAU was mostly associated with a low or insignificant effect.
Conclusions. The assessed form of interventions improves the functioning of parents of children with ADHD

……..

Psychiatry and Clinical Psychopharmacology. 2019 Jun;29:220-22.

PROBABLE EMERGENCE OF SYMPTOMS OF TRICHOTILLOMANIA BY ATOMOXETINE: A CASE REPORT.

Ayaydin H.

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in childhood. Atomoxetine is the first nonpsychostimulant agent approved by the Food and Drug Administration for the treatment of ADHD. Trichotillomania (TTM) is an obsessive-compulsive and related disorder characterized by a long-term urge that results in the pulling out of one's hair from any part of his/her body. Studies have implicated dopaminergic and serotonergic dysfunction in the aetiology of TTM. We report a male patient with ADHD developing of symptoms of TTM following atomoxetine use. Atomoxetine indirectly affects dopamine levels in the mesolimbic dopamine system, similarly to methylphenidate/amphetamine, and can thus lead to hair pulling behaviour. Further studies concerning the potential adverse effects of atomoxetine, such as the development of TTM, are now needed

……..

Psychiatry and Clinical Psychopharmacology. 2019.

RETINAL NERVE FIBER LAYER, MACULAR THICKNESS AND ANTERIOR SEGMENT MEASUREMENTS IN ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.

Ayyildiz T, Ayyildiz D.

AIM: We aimed to explore whether there is difference in terms of Retinal Nerve Fiber Layer (RNFL) thickness, macula thickness and anterior segment structures of the eye between children and adolescents with ADHD and healthy controls.
METHOD: Children and adolescents aged 8-16 years who were admitted to the Child Psychiatry outpatient clinic of Ahi Evran University Hospital diagnosed with ADHD constituted the study group. Exclusion criteria included patients who had any systemic/ocular or psychiatric disorder other than ADHD and patients who had any psychopharmacological treatment. Participants in the control group were children and adolescents who applied to the outpatient clinic of Ophthalmology at the same hospital with no chronic medical or psychiatric disorder. Groups were compared in terms of central macular thickness, retinal nerve fibre layer thickness (RNFL), central corneal thickness, corneal diameter, mean corneal radius of curvature, anterior chamber depth, and axial length using Optical Coherence Tomography (OCT) and Optical Biometry.
RESULTS: Data obtained from the measurements of 60 eyes of 30 patients with ADHD and 60 eyes of 30 patients of the control group were evaluated. Groups were similar in terms of age and gender. Corneal thickness ($p = 0.001$) and axial length ($p = 0.04$) values were significantly higher in ADHD group while the mean corneal curvature radius ($p = 0.03$) was significantly lower in ADHD group than in controls. No significant difference was observed between groups in terms of RNFL thickness, macular thickness, the corneal diameter, and anterior chamber depth measurements.
CONCLUSION: In recent years, the use of OCT in neuropsychiatric diseases has increased the interest in identifying possible biomarkers and the elucidation of neurodegenerative and neurodevelopmental mechanisms that contribute to the nature of these diseases. Differences in the ophthalmic anatomical structures observed between healthy controls and cases with ADHD, which is a neurodevelopmental disorder, need to be supported by longitudinal studies with a larger sample and using OCT in connection with brain imaging

……..

Psychiatry and Clinical Psychopharmacology. 2019.

THE EFFECTS OF ATOMOXETINE ON WEIGHT, HEIGHT, AND BODY MASS INDEX IN TURKISH CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Turan S, Akay AP.

Background: We aimed to examine the long-term effects of atomoxetine on height, weight, and body mass index in Turkish children and adolescents with attention deficit hyperactivity disorder (ADHD).

Methods: Participants (6-18 years, 146 boys, 52 girls) with ADHD who used atomoxetine for at least 1 year were included in a retrospective study. Weight, height, and BMI z scores were converted to age- and gender-corrected z scores at baseline and last follow-up.

Results: Atomoxetine treatment was associated with a notional reduction in height and weight standard deviation scores (SDS). There were no differences in BMI-SDS before and after atomoxetine treatment. Results of multiple linear regression analysis assess the possible contribution of the different treatment-related factors, age starting treatment, and duration of treatment predicted final height. And also, only the duration of treatment predicted nal weight, not final height and BMI.

Conclusions: We conclude that atomoxetine shows a negative effect on height and weight in children. This study demonstrated that these findings obtained at the end of the study might be helpful in assessing the growth parameters that may facilitate the course of the ADHD

……..

Psychiatry Res. 2019;278:248-57.

EFFECTS OF INTEGRATED BRAIN, BODY, AND SOCIAL (IBBS) INTERVENTION ON ERP MEASURES OF ATTENTIONAL CONTROL IN CHILDREN WITH ADHD.

Smith SD, Crowley MJ, Ferrey A, et al.

A primary goal of this study was to examine the impact of an Integrated Brain, Body, and Social (IBBS) intervention (multi-faceted treatment consisting of computerized cognitive training, physical exercise, and behavior management) on ERPs of attentional control (P3 & N2) in children with ADHD. The secondary goal was to test the differences between children with and without ADHD on ERP and Go/No-Go behavioral measures. A total of twenty-nine participants (M age = 7.14 years; 52% male; 41.4% white) recruited from the IBBS efficacy study comparing IBBS to Treatment-As-Usual (TAU) completed a Go/No-Go task before and after treatment as brain activity was recorded using EEG. Thirty-four matched healthy controls (HC) completed the same EEG procedures at a single time point. Following treatment, the Go P3 latency was significantly earlier for the IBBS group relative to the TAU group. No treatment effects were found on any behavioral measures. Prior to treatment, there was a significant difference between the ADHD group and HC group for the N2 difference wave. Children with ADHD also showed slower reaction times on behavioral measures. Although this pilot study did not reveal robust treatment effects, it suggests that IBBS may prevent the worsening of attentional systems in the brain and larger studies are needed for replication purposes

……..

Psychiatry Res. 2019.

A SYSTEMATIC REVIEW OF QUANTITATIVE EEG AS A POSSIBLE BIOMARKER IN CHILD PSYCHIATRIC DISORDERS.

McVoy M, Lytle S, Fulchiero E, et al.

Quantitative EEG (qEEG) has emerged as a potential intermediate biomarker for diagnostic clarification in mental illness. This systematic review examines published studies that used qEEG in youth with psychiatric illness between 1996 and 2017. We conducted a comprehensive database search of CINAHL, PubMed, and Cochrane using the following keywords: quantitative EEG and depression (MDD), anxiety, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), eating disorder, conduct, substance use, schizophrenia, post-traumatic stress disorder, and panic disorder. Our search yielded 516 titles; 33 met final inclusion criteria, producing a total of 2268 youth aged 4ΓÇô18. qEEG was most frequently studied as a potential diagnostic tool in pediatric mental illness; few studies assessed treatment response. Studies show higher theta/beta ratio in ADHD vs healthy controls (HC). The most consistent finding in ASD was decreased coherence in ASD vs HC. Studies show MDD has lower temporal coherence and interhemispheric coherence

in sleep EEGs than HC. Further research is needed in the areas of mood, anxiety, ASD, and relationship to treatment. It remains unknown if abnormalities in qEEG are nonspecific markers of pediatric psychiatric illness or if they have the potential to differentiate types of psychopathology

……..

Psychiatry Res. 2019;278:289-93.

SEX DIFFERENCES IN NEUROPSYCHOLOGICAL FUNCTIONING AMONG CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Mundoz-Suazo MD, et al.

Cognitive impairments are often reported in research on children with attention-deficit/hyperactivity disorder (ADHD). However, studies analyzing sex differences in this context are still sparse. This study aimed to compare the neuropsychological performance of boys and girls with ADHD across several cognitive domains. Verbal comprehension, perceptual reasoning, working memory, processing speed, and general cognitive performance were assessed in 240 children aged 6ΓÇô17 years: 120 children (65 boys) with a clinical diagnosis of ADHD and 120 typically developing children (60 boys). Underperformance of children with ADHD compared to controls was observed in all the evaluated cognitive domains, except for verbal comprehension. Significantly lower scores in perceptual reasoning, with a medium effect size, were found in girls with ADHD relative to boys, although the sexes did not significantly differ in terms of the remaining variables. Children's ADHD subtypes did not correlate significantly with any performance measure, and no significant interaction effects between children's age and sex were noted in the results. The performance commonalities found between boys and girls with ADHD outweighed the differences, which highlights the importance of further research on cognitive dysfunction in girls with ADHD, regardless of sex differences in the prevalence of the disorder

……..

Res Dev Disabil. 2019;92.

DOPAMINE TRANSPORTER GENOTYPE MODULATES BRAIN ACTIVITY DURING A WORKING MEMORY TASK IN CHILDREN WITH ADHD.

Pineau G, Villemonteix T, Slama H, et al.

Dopamine active transporter gene (DAT1) is a candidate gene associated with attention-deficit/hyperactivity disorder (ADHD). The DAT1 variable number tandem repeat (VNTR)-3ΓÇÖ polymorphism is functional and 9R carriers have been shown to produce more DAT than 10R homozygotes. We used functional magnetic resonance imaging (fMRI) to investigate the effects of this polymorphism on the neural substrates of working memory (WM) in a small but selected population of children with ADHD, na+»ve of any psychotropic treatment and without comorbidity. MRI and genotype data were obtained for 36 children (mean age: 10,36 +/ΓêÆ 1,49 years) with combined-type ADHD (9R n = 15) and 25 typically developing children (TDC) (mean age: 9,55 +/ΓêÆ 1,25 years) (9R n = 12). WM performance was similar between conditions. We found a cross-over interaction effect between gene (9R vs. 10R) and diagnosis (TDC vs. ADHD) in the orbito-frontal gyrus, cerebellum and inferior temporal lobe. In these areas, WM-related activity was higher for 9R carriers in ADHD subjects and lower in TDC. In ADHD children only, 10R homozygotes exhibited higher WM-related activity than 9R carriers in a network encompassing the parietal and the temporal lobes, the ventral visual cortex, the orbito-frontal gyrus and the head of the caudate nucleus. There was no significant results in TDC group. Our preliminary findings suggest that DAT1 VNTR polymorphism can modulate WM-related brain activity ADHD children

……..

Sleep. 2019;42.

RESTLESS LEGS SYNDROME AND IRON DEFICIENCY IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lopez R, Franchi J-A, Chenini S, et al.

Study Objective: The association between restless legs syndrome (RLS), periodic leg movements during sleep (PLMS) and iron deficiency has been reported in children with attention-deficit/hyperactivity disorder (ADHD); however little is known in adults. The aim of this study was to assess frequencies of RLS, PLMS and other leg movements (LM) and iron deficiency and their relationships with ADHD phenotype in adults with ADHD.

Methods: Two hundred adults with ADHD (112 males, median age 31 years) were evaluated on lifetime ADHD symptoms and sleep characteristics. RLS was diagnosed according to standard criteria. Serum ferritin levels were measured, with iron deficiency defined as <50 ng/mL. A subgroup of 48 ADHD patients with RLS, 48 ADHD without RLS and 48 controls underwent a polysomnography to record sleep, LM, and PLMS.

Results: RLS was diagnosed in 33.0%, associated with earlier onset of ADHD, hyperactive presentation and more severe lifetime ADHD symptoms. Iron deficiency was found in 35.5% with higher frequency in patients with RLS. LM were more frequent in ADHD patients, with higher LM periodicity levels in those with comorbid RLS in comparison to controls. However, PLMS index did not differ between groups. Patients with ADHD and RLS had higher frequency of iron deficiency than other groups.

Conclusions: In a large sample of adults with ADHD, we individualized a subgroup characterized by earlier and severe ADHD symptoms, RLS, higher LM during sleep and iron deficiency. This endophenotype may reflect a different neurobiological mechanism that remains to be further studied

……..

Sleep Med. 2019;60:123-31.

SLEEP PHENOTYPES IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Miano S, Amato N, Foderaro G, et al.

Objective: A case-control study was performed to test the hypothesis that children with attention deficit hyperactivity disorder (ADHD) have chronic sleep deprivation and may be classified into specific sleep-related phenotypes.

Methods: Thirty outpatients with ADHD (nine females, mean age 10.1 -¦ 2.1 years) were recruited consecutively, and given a comprehensive sleep assessment, including blood exams, sleep questionnaires, laboratory video-polysomnographic recordings (v-PSG), multiple sleep latency tests, and one-week actigraphy. The PSG parameters were compared to those of 25 age-matched controls (12 females, mean age 10.34 -¦ 1.54 years) who underwent only the v-PSG.

Results: ADHD children were classified as follows: a narcolepsy-like phenotype was found in four; delayed sleep onset insomnia in five; obstructive sleep apnea (OSA) in 15; periodic limb movements in eight, and sleep epileptiform discharges in 10 children. All subjects had a total sleep time shorter than 9 h at actigraphy, ferritin levels lower than 60 mcg/L, and a history of sleep problems (mainly OSA and insomnia). Compared to controls, the ADHD group had a higher apnea-hypopnea index at PSG.

Conclusions: A full sleep assessment in children with ADHD confirmed the validity of the sleep phenotypes hypothesis, and revealed a much higher percentage of sleep problems than that found in the literature. Beyond the sleep phenotypes, all children reported a history of sleep problems and slept less than 9 h per night, indicating chronic sleep deprivation that should be evaluated as a possible unifying marker of ADHD

……..

Social Psychiatry and Psychiatric Epidemiology: The International Journal for Research in Social and Genetic Epidemiology and Mental Health Services. 2019 Jun;54:661-70.

FAMILY STRUCTURE, BIRTH ORDER, AND AGGRESSIVE BEHAVIORS AMONG SCHOOL-AGED BOYS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Hsu YC, Chen CT, Yang Hj, et al.

Purpose: To evaluate the associations between family structure, birth order, and aggressive behaviors among school-aged boys with attention deficit hyperactivity disorder (ADHD).

Methods: We conducted a matched case–control study. Data were retrieved from medical records at a psychiatry center in northern Taiwan. School-aged boys with ADHD who first visited the outpatient department at the psychiatric center between 2000 and 2011 were identified. The Child Behavior Checklist was used for aggressive behavior assessment. Boys with ADHD with T scores higher than 70 on the aggressive subscale were classified as cases and others with T scores lower than 70 were classified as controls at a 1:4 ratio. After controlling for other familial, personal, and parental factors, a multivariate conditional logistic regression was performed to evaluate the effects of family structure and birth order on aggressive behaviors of boys with ADHD.
Results: 277 cases and 1108 controls were included in the final analysis. Compared with living in a traditional family with both parents, living in a non-traditional family in which one or both parents were absent increased the risk of aggressive behaviors by 1.47-fold, with the highest risk for those in single parent families. Being the firstborn increased risk by 1.45-fold and the risk was higher when the firstborn had siblings.
Conclusions: Living in non-traditional families in which one or both parents were absent, and being the firstborn increased risk of aggression in school-aged boys with ADHD. Identification of this high-risk population and development of adequate preventive strategies are warranted

……..

Somnologie. 2019.

MELATONIN IN THE TREATMENT OF NEUROPSYCHIATRIC DISEASES IN CHILDREN AND ADOLESCENTS.

Fralich J, Wiater A, Lehmkuhl G.

Background: Attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and diverse rare neuropsychiatric disorders with psychomental retardation are often accompanied by comorbid problems concerning sleep onset and sleep maintenance. Measures of psychoeducation, sleep hygiene, and behavioral treatment remain the primary treatment of choice. However if these approaches are not effective, medical treatment with melatonin may be an additional treatment alternative.
Objective and methods: Based on Medline research, this article presents melatonin treatment results from metaanalyses, controlled treatment studies, and reviews.
Results: In particular, we discuss the indication and duration of treatment regarding chronic sleep problems in neuropsychiatric disorders as well as the fact that in many cases the medical treatment of the primary disorder may influence the patient's sleep. Additionally, possible interactions between melatonin and other medications may occur.
Conclusion: We conclude that melatonin is an effective and safe treatment option for sleep problems in neuropsychiatric diseases, if always implemented using multimodal approach and, if possible, in an interval-related manner

……..

Sports Health. 2019 Jul;11:332-42.

AGE OF FIRST EXPOSURE TO AMERICAN FOOTBALL AND BEHAVIORAL, COGNITIVE, PSYCHOLOGICAL, AND PHYSICAL OUTCOMES IN HIGH SCHOOL AND COLLEGIATE FOOTBALL PLAYERS.

Brett BL, Huber DL, Wild A, et al.

BACKGROUND: Although some studies have observed a relationship between age of first exposure (AFE) to American football and long-term outcomes, recent findings in collegiate athletes did not observe a relationship between AFE and more intermediate outcomes at early adulthood. This, however, requires independent replication. HYPOTHESIS: There will be no association between AFE to football and behavioral, cognitive, emotional/psychological, and physical functioning in high school and collegiate athletes. STUDY DESIGN: Cross-sectional study. LEVEL OF EVIDENCE: Level 3.
METHODS: Active high school and collegiate football players (N = 1802) underwent a comprehensive preseason evaluation on several clinical outcome measures. Demographic and health variables that significantly differed across AFE groups were identified as potential covariates. General linear models (GLMs) with AFE as the independent variable were performed for each clinical outcome variable. Similar

GLMs that included identified covariates, with AFE as the predictor, were subsequently performed for each clinical outcome variable.
RESULTS: After controlling for covariates of age, concussion history, race, and a diagnosis of ADHD, earlier AFE (<12 vs >/=12 years) did not significantly predict poorer performance on any clinical outcome measures (all P > 0.05). A single statistically significant association between AFE group and somatization score was recorded, with AFE <12 years exhibiting lower levels of somatization.
CONCLUSION: In a large cohort of active high school and collegiate football student-athletes, AFE before the age of 12 years was not associated with worse behavioral, cognitive, psychological, and physical (oculomotor functioning and postural stability) outcomes. CLINICAL RELEVANCE: The current findings suggest that timing of onset of football exposure does not result in poorer functioning in adolescence and young adults and may contribute to resilience through decreased levels of physically related psychological distress

……..

Transl Psychiatry. 2016;6.

TRAINING SENSORY SIGNAL-TO-NOISE RESOLUTION IN CHILDREN WITH ADHD IN A GLOBAL MENTAL HEALTH SETTING.

Mishra J, Sagar R, Joseph AA, et al.

Children with attention deficit/hyperactivity disorder (ADHD) have impaired focus on goal-relevant signals and fail to suppress goal-irrelevant distractions. To address both these issues, we developed a novel neuroplasticity-based training program that adaptively trains the resolution of challenging sensory signals and the suppression of progressively more challenging distractions. We evaluated this sensory signal-to-noise resolution training in a small sample, global mental health study in Indian children with ADHD. The children trained for 30 h over 6 months in a double-blind, randomized controlled trial. Training completers showed steady and significant improvements in ADHD-associated behaviors from baseline to post training relative to controls, and benefits sustained in a 6-month follow-up. Post-training cognitive assessments showed significant positive results for response inhibition and Stroop interference tests in training completers vs controls, while measures of sustained attention and short-term memory showed nonsignificant improvement trends. Further, training-driven improvements in distractor suppression correlated with the improved ADHD symptoms. This initial study suggests utility of signal-to-noise resolution training for children with ADHD; it emphasizes the need for further research on this intervention and substantially informs the design of a larger trial

……..

International Journal of
Environmental Research and Public Health

MDPI

Article

Parenting Stress and Broader Phenotype in Parents of Children with Attention Deficit Hyperactivity Disorder, Dyslexia or Typical Development

Paola Bonifacci [1,*], Laura Massi [2], Veronica Pignataro [1], Sara Zocco [1] and Simona Chiodo [2]

[1] Dipartimento di Psicologia, Università di Bologna, Viale Berti Pichat n.5, 40127 Bologna, Italy; veronica.pignataro@libero.it (V.P.); sara.zocco@gmail.com (S.Z.)
[2] UO NPIA, Servi territoriali, Ausl Bologna, Via Sant'Isaia 90, 40123 Bologna, Italy; laura.massi@ausl.bologna.it (L.M.); simona.chiodo@ausl.bologna.it (S.C.)
* Correspondence: paola.bonifacci@unibo.it; Tel.: +39-051-2091824; Fax: +39-051-243086

Received: 29 March 2019; Accepted: 24 May 2019; Published: 28 May 2019

Abstract: In the present study parenting stress and the broader phenotype are investigated in two highly common developmental disorders, namely Attention Deficit Hyperactivity Disorder (ADHD) and specific reading impairment (dyslexia). Within a total sample of 130 parents, 27 were parents of children with ADHD (P-ADHD), 38 were parents of children with a diagnosis of dyslexia (P-DYS) and the other 65 participants were parents of children with typical development (P-TD). A battery of cognitive tasks was administered which included verbal and non-verbal Intellectual Quotient (IQ), reading speed (passage and nonwords), verbal fluency and the Attention Network Task (ANT). Reading history, symptoms of ADHD in adults and parenting stress were measured through questionnaires. Group differences evidenced that the P-DYS group had lower scores in the reading tasks, in the verbal fluency task and in the reading history questionnaire. Conversely, the P-ADHD group had more transversal cognitive weaknesses (IQ, reading tasks, verbal fluency) and the highest scores in parenting stress and ADHD symptoms, together with poor reading history. The groups did not differ in the ANT task. Parenting stress was predicted, on the whole sample, by lower socioeconomic status (SES) and number of family members and higher ADHD symptoms. Implications for research and clinical settings are discussed.

Keywords: parenting stress; broader phenotype; endophenotypes; attention deficit hyperactivity disorder; dyslexia

1. Introduction

In the past few decades a great amount of research led to an outstanding knowledge about the genetic, biological and neural basis of developmental trajectories in both typical and atypical populations. After Morton and Frith's causal model [1], many studies investigated the etiology of developmental disorders on multiple levels of analysis (biological, cognitive and behavioral). Recent theoretical models, such as neuroconstructivism [2], reinforce the importance of considering how environmental variables, such as home literacy activities, parents' education and parents' cognitive skills, might interact with each of these levels. Robust evidence has shown that many neurodevelopmental disorders run in families and an increasing number of studies is addressing the issue of intergenerational transmission of risk and protective factors [3]. Parents' might share with their offspring some specific cognitive markers and this is referred to as the so-called broader phenotype [4].

The concept of broader phenotype derives from the definition of endophenotypes (or intermediate phenotypes) [5], described as heritable neurophysiological, biochemical, endocrinological,

neuroanatomical or neuropsychological constituents of disorders. One of the main characteristics of the endophenotypes is that they might be observable before the disease onset and, notably, in individuals with a heritable genetic risk for disease, such as unaffected family members (parents and siblings) [6]. The term broader phenotype refers specifically to the cognitive endophenotypes that can be observed in unaffected family members.

Thus, parents themselves might have similar cognitive weaknesses as their offspring, although at the behavioral and clinical level they might not meet criteria for diagnostic classification, or they did not undergo clinical evaluation in their life course. For example, parents of children with developmental dyslexia might themselves show weaknesses in phonological awareness skills, which is considered a clinical marker of reading impairment [4]. In the case of ADHD, if parents have low levels of response inhibition they might result to be impulsive in their interaction with the child and have difficulties in implementing daily routines. The concept of broader phenotype has received increasing attention in recent years because it directly poses an important question about the possible environment-child influence. That is, if parents themselves have some level of functional impairment in a set of specific cognitive functions, possibly the same that causes trouble in their offspring, how do they cope with their proper weaknesses? How do these weaknesses influence their parenting experience? In the present study, the broader phenotype of two highly common developmental disorders such as attention deficit hyperactivity disorder (ADHD) and specific reading impairment (dyslexia) is investigated both considering its usefulness in understanding the specificity of cognitive impairments within these families and evaluating how these cognitive weaknesses relate to parenting experience.

1.1. Dyslexia and ADHD: Two Common and Often Comorbid Neurodevelopmental Disorders

Dyslexia and ADHD are two of the most frequently occurring developmental patterns within the broader classification of neurodevelopmental disorders defined by DSM-5 [7]. Dyslexia is referred to as a specific learning disorder (SLD) that primarily affects the skills involved in accurate and fluent word reading and spelling. The latest definition given by DSM-5 [7] considers these disorders "specific" in that they are not primarily due to intellectual disability or global developmental delay, nor to neurological, motor or sensory disorders, or to a lack of opportunity of learning/inadequate instruction. Reading impairments may affect academic achievement or daily functioning if accommodations are not made. Consistent evidence has been collected that describes dyslexia as the behavioral outcome (poor reading fluency) of an underlying phonological deficit ([8]; for reviews), possibly associated with multiple risk factors [9]. In transparent orthographies, due to the high grapheme-phoneme consistency, reading impairment is better reflected by reading speed than by reading accuracy [10].

ADHD is a neurodevelopmental disorder whose main behavioral manifestations regard symptoms of inattention, impulsivity and hyperactivity, which occur in more than one social context (e.g., school, home) and significantly interfere with everyday life and social adaptability. These symptoms may resolve in adolescence or persist into adulthood, although the characteristics that mediate persistence or remission of ADHD during adulthood are still largely unexplored [11]. From a neurobiological perspective the putative endophenotypes considered to be core deficits of the disorder are referred to impairments in working memory, inhibition, cognitive control and time perception [12]. The Attention Network Task [13] is a two-choice reaction time (RT) task developed to independently and reliably test the efficiency of three attention networks, alerting, orienting and conflict resolution, which are theorized to be both anatomically and functionally segregated. The alerting network is thought to maintain the alerting state, the orienting network is hypothesized to allow the selection of sensory stimuli and the conflict network is designated to solve incongruent or competing stimuli. The strength of this task is specifically related to the data supporting high heritability for each attention network [14] and therefore has been suggested as a potential endophenotype of ADHD, with particular reference to the conflict network [15].

In sum, a neurobiological origin has been postulated both for ADHD and dyslexia, due to the interaction of genetic, epigenetic and environmental factors. Although different theoretical models

have been proposed for each of these neurodevelopmental disorders, it is recognized that their aetiology is best explained within a multiple deficit model in which genetic factors interact with other risk factors connected with the pre- or perinatal period [9,16]. Furthermore, it has been proposed, based on their high comorbidity, that the two disorders share common cognitive deficits due to common genetic influences that increase susceptibility to both disorders [17].

1.2. The Broader Phenotypes of ADHD and Dyslexia

Various studies have ascertained that both ADHD and dyslexia run in families, with an increased probability for parents who have family risk for the disorder to have a child with clinical symptoms for that disorder: up to 66% for reading impairment [18,19] and up to 57% for ADHD [20].

Based on the intergenerational multiple deficit model [3] both parents convey risk and protective factors through interlaced genetic and environmental pathways and these factors ultimately impact on behavioral disorders or traits through complex interactions at the neural, cognitive and relational levels.

Signs of intergenerational transmission of executive functions (EF) have been examined in a number of studies, although with mixed results. Cuevas et al. [21] found moderate correlations (0.41) between maternal and preschool-aged child EF-task performance and this correlation pattern remained stable after controlling for maternal socioeconomic status (SES) and children's verbal abilities. Goos et al. [22] found a significant correlation between children's and parents' response inhibition skills, that is the ability to inhibit a prepotent response, independently of ADHD symptom severity. Other studies, instead, have reported modest correlations between parents and children's EFs [23]. In a recent study by Thissen et al. [24] the authors found significant parent-child correlations in EF and ADHD symptoms, parental ADHD was not associated with offspring EF or vice versa, thus there were no cross-correlations between EFs skills and ADHD symptoms in parents and children. Family studies have found further evidence of signs of broader phenotypes in the unaffected siblings of children with ADHD, with impairments in tasks assessing inhibition, verbal working memory and delay aversion [25,26]. As suggested by Deater-Deckard [27], parents' own EFs skills might influence their caregiving behavior and, in turn, children's behaviors and functioning might affect parents' behavior. These reciprocal interactions should, therefore, be considered as candidate predictors of the quality of the parent-child relationship. However, following this undoubtedly valuable suggestion, family studies on ADHD under investigated other cognitive indexes of parents' functional profile, such as for example reading related skills, which are known to be, at least in children, highly related to ADHD symptomatology.

The analysis of parent-child correlations in reading skills has been the focus of many family risk studies in the area of reading impairments. Black et al. [28] reported that mother's, but not father's, history of reading difficulties was correlated with child's reading-related cognitive and behavioural scores. van Bergen et al. [29] showed that among children at family risk of dyslexia, parents of children who develop dyslexia underperformed in word reading fluency and letters and digits rapid automatized naming (RAN) compared to parents of children who did not develop dyslexia. Analogously, Torppa et al. [30] revealed that parents of children with reading impairments were poorer in reading and spelling accuracy, rapid word recognition, text reading fluency and vocabulary. Bonifacci et al. [31] found that parents of children with dyslexia differed from parents of children with typical development in all literacy measures (passage reading and accuracy, nonword reading, silent reading) and more frequently reported a history of poor reading. Recent evidence in the developmental pathway of children at family for dyslexia indicated that a family history of dyslexia is a predictor of literacy outcome from the preschool years. However, when children started formal schooling letter knowledge, phonological awareness, and RAN provided, beyond and above family risk, good sensitivity and specificity indexes of literacy achievement [16].

1.3. Parenting Stress in Parents of Children with ADHD or Dyslexia

Parenthood is an enriching experience, both from social and psychological perspectives, but it also constitutes a crucial transition due to the specific demands that an individual needs to manage in a sufficiently adequate manner. Parenting stress has been defined as *"the stress reaction to the demands of being a parent"* ([32], pp.314) and its determinants can be ascribed to parent characteristics, life stress and socio-demographic factors, and child characteristics [33]. A perceived discrepancy between parents' perception of his or her resources and the demands they are exposed to having a child might increase levels of parenting stress. There is evidence that parenting stress influences parenting practices and, as a consequence, child development ([32], for a review).

Being a parent of a child with neurodevelopmental disorders might challenge the perception to fulfill adequately these demands and therefore might increase the psychological cost of parenthood. This might be related to at least two main factors: (1) the child characteristics, which, due to the cognitive and behavioural impairments, might increase the demands and therefore the cost of parenthood; (2) parents' cognitive and psychological resources. Based on the literature previously discussed, parents of children with neurodevelopmental disorders might themselves have weaknesses at the cognitive and behavioural levels, often in the same areas of those manifested by their offspring. This, in turn, might amplify their perception of being inadequate in their parental role, particularly if their own weaknesses had never been appropriately recognized and treated in their life course. In the literature, higher levels of parenting stress have been documented in parents of children with a wide range of developmental disorders, included ADHD and dyslexia.

As far as ADHD was concerned, a meta-analysis reviewed research studies on parenting stress in families of children with ADHD (age 12 or younger) and showed that parents experienced much higher levels of parenting stress compared to parents of typically developing children [34]. Similar results have been found in parents of adolescents with ADHD [35].

With reference to SLD, there is still a paucity of research on parenting stress. Some studies were conducted on parents of children with mild or moderate intellectual dysfunctions and higher levels of parenting stress were found [36], together with higher levels of child monitoring [37], and worries about their children's future [38]) in mothers of children with learning disabilities. Considering more precisely parents of children with *dyslexia*, [39] observed that about 74% of parents reported that the child's disorder has had negative effects on family life and that mothers reported high anxiety and/or depression levels (see [40], for similar results on anxiety symptoms). Two recent studies specifically addressed the issue of parenting stress in parents of children with SLD. In the first study, [31] found that parents of children with dyslexia reported higher scores in the perception-child dysfunctional interaction scale and in the difficult child scale. The second study [41], involving children with SLD in comorbidity (at least two impairments, either in reading, writing, or calculation abilities) evidenced higher levels of parenting stress in all scales of the Parenting Stress Index [33]. In both of the latter studies, there were no differences between mothers and fathers.

To conclude, this introduction evidenced two main points. On the one hand, there is increasing evidence about the broader phenotype of developmental disorders, which suggests that parents of children with neurodevelopmental disorders might share cognitive and behavioural weaknesses with their offspring. On the other hand, a vast literature evidenced that parents of children with neurodevelopmental disorders such as ADHD and dyslexia, have higher levels of parenting stress compared to parents of children with typical development. However, scarce evidence has been collected on the interplay between parents' cognitive profiles and parenting stress in populations of children with ADHD and dyslexia.

1.4. The Present Study

The aims of the present study were threefold:

(1) To investigate group differences in cognitive and behavioral indexes of reading and attention impairments comparing three groups of parents: parents of children with ADHD (P-ADHD), parents of children with developmental dyslexia (P-DYS) and parents of children with typical development (P-TD). This first objective was intended to verify if the three groups of parents did indeed show endophenotypic patterns specific for their offspring developmental profile. Based on the literature review, P-DYS are expected to fail in reading related measures, whereas P-ADHD are expected to differ compared to the other groups in ANT task and in behavioural scales assessing ADHD symptoms in adulthood. Differences between mothers and fathers will be considered.

(2) To investigate group differences in parenting stress. Based on previous studies higher levels of parenting stress have been reported for parents of children with dyslexia and parents of children with ADHD compared to parents of typically developing children. We therefore expect replying these findings and evaluating, for the first time, differences in parenting stress between parents of children with dyslexia or ADHD.

(3) To analyse the relationships between cognitive indexes and parenting stress in the whole sample. Specifically, through a step-wise regression model the study aimed at evaluating which factors better predicted parental stress, an important index assessing parent-child interactions and known to correlate with parental styles. Cognitive measures are expected to significantly predict parenting stress, based on the assumption that parenting stress depends on parents' ability to cope cognitively with offspring's requests.

2. Methods

2.1. Participants

The study was conducted on a total sample of 130 parents (68 mothers and 62 fathers), with a mean age of 43.8 years (5.08 SD). Within the total sample, 38 were parents of children with a diagnosis of dyslexia (P-DYS) (mean age: 43.65 ± 5.08 years); 27 were parents of children with ADHD (P-ADHD) (mean age: 43.33 ± 5.7 years). The other 65 participants (mean age: 44.12 ± 4.98) were parents of children with typical development (P-TD). Parents of children with ADHD were recruited at the Maggiore Hospital, Department of Developmental Psychiatry and Psychology, in the city of Bologna. Children underwent a full clinical evaluation by a multidisciplinary team and, according to ICD-10 criteria, they received a diagnosis of ADHD (F 90.0), in the absence of comorbidity with dyslexia. The P-DYS group was recruited at LADA lab (Laboratory for the Assessment of Learning Disorders), Department of Psychology, University of Bologna. To be included in the study, they had to be parents of a child who received a diagnosis of specific reading disorder (ICD-10 code: F 81) in the last 2 years. None of the children with dyslexia had comorbidity with ADHD. The P-TD group was recruited through leisure centers and through word of mouth. None of the children of the control group had been previously referred for showing risk factors for dyslexia or ADHD. All parents fulfilled inclusion criteria as follows: being biological parents; free of psychiatric disorder; Italian monolinguals, family not in care of social services; intellectual functioning within the normal range (Total IQ > 70). Independently of their civil state (married or not), we asked both parents to take part in the study. Depending on their willingness to volunteer, for some children only one parent was included in the study. In the final sample there were 60 couples participating and 10 single parents (2 in the P-DYS group, 7 in the P-TD group and 1 in the ADHD group) ($\chi^2(2) = 1.78$, $p = 0.4$). Participants volunteered for the study and signed the informed consent and data treatment documents before starting. This study was carried out in accordance with the recommendations of American Psychological Association's Ethical Principles (1982), and the research ethics committee of the AUSL of Bologna approved the project (Prot. N.559/CE, Cod. CE: 12020).

2.2. Measures

2.2.1. Background Information

Both parents were asked to fill out a short questionnaire that included socio-demographic information, such as SES (calculated based on the Four Factor Index of Social Status, Hollingshead, 1975), civil state, and evaluation of previous scholastic achievement. Parents were also asked to evaluate their children scholastic achievement (reading, math, writing, science, grammar, history) and to indicate the number of family members.

2.2.2. Cognitive Measures

(1) Kaufman Brief Intelligence Test-2. ([42]; Italian version adapted and standardized by [43]). This test assesses intellectual functioning and comprises Vocabulary (verbal knowledge and riddles) and Matrices subtests. It gives standardized measures of Verbal (VIQ), Performance (PIQ) and Composite Full Scale IQ.

(2) Passage reading, taken from the "Reading tasks for the secondary schools" [44]. Participants were asked to read aloud a passage (729 words) and reading speed (syllables per second) and accuracy (number of errors) were recorded.

(3) Non-word reading task, taken from the "Battery for the assessment of developmental dyslexia and dysorthographia" [45]. Participants are required to read aloud a list of 48 nonwords and reading speed (syllables per second) was recorded.

(4) *Semantic fluency:* The participants were asked to produce as many words within the same semantic category (professions) in a test interval of 1 min.

(5) Attentional Network Task (ANT) [13]. This task is a combination of a cue reaction time task, and a flanker task exploring attentional abilities divided into three components: executive control (conflict resolution), alerting and orienting. It requires participants to indicate whether a central arrow is oriented to the right or left. The arrow is presented between flanker arrows pointing either in the same direction (→→→→→; congruent condition) or in different directions (→→←→→; incongruent condition) from the target. Responses are expected to be slower for incongruent than for congruent conditions, showing that more cognitive effort is needed to resolve the conflict. The alerting component is explored by showing that faster responses occur when a cue is presented before the target stimulus compared to when it is not. Finally, orienting is studied by showing that responses are faster when a cue indicates the position of a target stimulus compared when it does not. The presentation of the stimuli was as follows: (a) a fixation point (**+**) appeared on the center of the screen for 400 ms; (b) a cue (*) was presented for 100 ms; (c) a fixation period was provided for 400 ms after the cue; (d) the target arrow and the flankers were presented simultaneously until the participant's response or up to 1700 ms, (f) the target and flankers disappeared after response and the next trial began. Participants were instructed to focus on the fixation point and to respond by pressing a key on the computer keyboard, as quickly and accurately as possible, with their left hand when the arrow pointed to the left and with the right hand when it pointed to the right. A training phase consisting of 24 trials was administered.

2.3. Questionnaires

(1) Adult Reading History Questionnaire-Revised (ARHQ-R) [46]: The ARHQ-R is aimed at evaluating the presence of a significant history of reading difficulties. Parents are required to respond to twenty-three questions on a five-point Likert scale (from 0 to 4), with higher values corresponding to more problems with reading skills, less print exposure, or poorer attitude towards reading. The participant's score was calculated by dividing the total score by the maximum possible score (92). A score above 0.30 is indicative of a positive history of reading disorders.

(2) Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist. The Symptom Checklist is an instrument based on DSM-IV-TR criteria for ADHD, developed by World Health Organization (WHO). It includes 18 questions (e.g., How often do you have difficulty getting things in order when you have to do a task that requires organization?), based on a five points Likert-scale.

(3) Parenting Stress Index (PSI) [33]. The PSI is addressed to the evaluation of parenting and family characteristics with the aim of identifying indexes of parental behavior problems and child adjustment difficulties within the family system. In this work we used the Italian PSI Short Form (PSI/SF), it includes 36 items (e.g., My son often wakes up in a bad mood) and yields a Total Stress score from three scales: Parental Distress, Parent-Child Dysfunctional Interaction, and Difficult Child. It also provides a Defensive Response scale. Higher scores are representative of higher levels of parenting stress.

2.4. Data Analysis

In order to test group differences in background information, we performed a set of ANOVAs applying Bonferroni post-hoc tests. For categorical variables, we tested differences in groups' distribution through Chi-Square (χ) analysis. Then a set of ANOVAs and MANOVAs were run with Group (P-DYS, P-ADHD, P-TD) and Role (parents' gender: Mothers, Fathers) as independent factors and scores at cognitive tasks and questionnaires as dependent variables. Finally, in order to investigate which factors predicted Parenting Stress a regression model was run. In the first step SES, parents' age and number of family members were included, in the second step cognitive variables were included (Composite IQ, Verbal fluency, non word reading speed, attentional networks - conflict), and the third step included behavioral measures of reading history and ADHD symptoms in parents.

3. Results

3.1. Background Information

A summary of mean values related to background information is reported in Table 1.

Table 1. Means and standard deviation for demographic variables and parents evaluation of children scholastic achievement. for the three groups (P-ADHD, P-TD, P-DYS).

Measures	P-ADHD		P-TD		P-DYS		*p*-Values	Bonferroni Post-Hoc Comparisons
	Mean	SD	Mean	SD	Mean	SD		
Children age	9.3	1.5	9.8	1.8	10.3	1.7	0.06	NS
Parents age	43.3	5.7	44.1	5	43.7	4.9	0.7	NS
SES	35.24	11.04	43.82	9.32	36.68	12.42	<0.001	TD > DYS = ADHD
Reading *	2.05	0.38	2.26	0.44	1.45	0.6	<0.001	TD = ADHD > DISL
Writing *	1.81	0.68	2.25	0.43	1.61	0.64	<0.001	TD > DYS = ADHD
Grammar *	1.95	0.5	2.25	0.53	1.5	0.6	<0.001	TD = ADHD > DYS
History *	2.05	0.5	2.37	0.55	1.89	0.77	<0.001	TD > DYS
Mathematics *	1.9	0.77	2.28	0.55	1.58	0.76	<0.001	TD > DYS
Science *	2.1	0.54	2.29	0.52	1.84	0.69	<0.001	TD > DYS

* Parents' evaluation of children's skills. Calculated based on Hollinshead formula.

The three groups did not differ for children's age ($F(2,130) = 2.87$; $p = 0.06$, $\eta^2 = 0.04$), parents' age ($F(2,130) = 0.26$; $p = 0.7$, $\eta^2 = 0.0$) and civil state ($\chi^2(4) = 4.6$, $p = 0.33$); more than 85% of parents in each group were married or living together. There was instead a difference in mean SES ($F(2,122) = 8.08$; $p < 0.001$, $\eta^2 = 0.12$), with the P-TD group showing higher values compared to the other two groups ($p < 0.01$), which did not differ from each other. The P-TD group also reported to have reached brilliant scholastic results in a higher percentage of cases (58.5%) than the P-DYS (41.1%) and the P-ADHD group ($\chi^2(4) = 17.48$, $p < 0.01$). Families in the ADHD group reported to have a lower number of

children compared to families in the TD-group, who, in turn, had less children than families in the P-DYS group ($F(2,123) = 13.02$; $p < 0.001$, $\eta^2 = 0.17$).

Considering parents evaluation of their offspring scholastic achievement, the MANOVA showed a main effect of group ($F(12,232) = 5,74$; $p < 0.001$, $\eta^2 = 0.23$). It emerged that children in the P-DYS group were considered to have lower performance compared to the TD group in all disciplines considered. The ADHD group differed from the control group only in Writing skills ($p < 0.01$) and children with ADHD were reported having better scores in reading ($p < 0.001$) and grammar ($p < 0.05$) compared to the group of children with dyslexia.

3.2. Cognitive Measures

In Table 2 a summary of mean values for cognitive tasks is reported. The MANOVA with Group (P-DYS, P-ADHD, P-TD) and Role (parents' gender: Mothers, Fathers) as independent factors and VIQ and NVIQ as dependent variables, showed a main effect of group ($F(4,248) = 4.6$; $p = 0.001$, $\eta^2 = 0.07$). There was no effect for Role ($F(2,123) = 2.11$; $p = 0.12$, $\eta^2 = 0.03$), nor for the interaction Group*Role ($F(4,248)=2.03$; $p = 0.09$, $\eta^2 = 0.03$). Univariate analyses and Bonferroni post-hoc comparisons showed that the P-ADHD group had significantly lower scores compared to the P-TD group in both Verbal ($p = 0.001$) and Non Verbal IQ ($p = 0.001$).

Table 2. Means and standard deviations for cognitive tasks and questionnaires' scores for the three groups (P-ADHD, P-TD, P-DYS).

Measure	P-ADHD		P-TD		P-DYS		*p*-Values	Bonferroni Post-Hoc Comparisons
	Mean	SD	Mean	SD	Mean	SD		
Verbal IQ	100.10	7.50	108.40	9.60	105.20	10.30	<0.001	TD > ADHD DYS = ADHD; DYS = TD
Non Verbal IQ	96.80	17.00	108.90	13.80	104.70	11.80	<0.001	TD > ADHD; DYS = ADHD; DYS = TD
Semantic Fluency	14.70	3.40	19.20	4.60	16.20	4.50	<0.001	TD > ADHD = DYS
Passage reading speed (syll/sec)	5.38	1.21	6.10	1.04	4.91	0.98	<0.001	TD > ADHD = DYS
Non word reading speed (syll/sec)	2.65	0.76	3.03	0.71	2.41	0.69	<0.001	TD > DYS = ADHD
ARHQ Total	0.35	0.11	0.26	0.09	0.37	0.17	<0.001	TD > ADHD = DYS
ASRS Total	6.76	4.34	3.91	3.18	5.13	4.06	<0.01	ADHD > DYS = C
* PSI Defensive Scale	1.08	1.31	−0.08	0.95	−0.03	1.15	<0.001	ADHD > DYS = C
PSI Parent distress	0.96	1.34	−0.25	0.86	−0.15	1.11	<0.001	ADHD > DYS = C
PSI Difficult Child Interaction	1.49	1.77	0.12	0.88	0.62	1.30	<0.001	ADHD > DYS = C
PSI Difficult Child	1.74	1.58	0.21	0.96	0.57	1.06	<0.001	ADHD > DYS = C
PSI Total Score	1.76	1.42	0.02	0.83	0.39	1.22	<0.001	ADHD > DYS = C

* For Parenting Stress Index z scores are reported.

Considering Verbal Fluency, the ANOVA showed a main effect of Group ($F(2,129) = 12.04$; $p < 0.001$, $\eta^2 = 0.16$) and a marginal effect of Role ($F(1,129) = 3.9$; $p = 0.05$, $\eta^2 = 0.03$), but the interaction Group*Role was not significant ($F(2,129) = 0.4$; $p = 0.67$, $\eta^2 = 0.006$). Parents of children with TD outperformed compared to both P-ADHD ($p < 0.001$) and P-DYS ($p < 0.01$). Mothers tended to produce more words than fathers ($p = 0.5$).

As far as reading measures were concerned, the MANOVA on passage and nonword reading speed showed a main effect of Group ($F(4,466) = 7.06$; $p < 0.001$, $\eta^2 = 0.10$). Both univariate analyses were significant (Passage: $F(2,128) = 17.41$; $p < 0.001$, $\eta^2 = 0.2$; Nonwords: ($F(2,128) = 8.93$; $p < 0.001$, $\eta^2 = 0.13$) and Parents in the DYS group were slower compared to the P-TD group in both tasks ($p < 0.001$), whereas P-ADHD differed from the P-TD group only in passage reading speed ($p < 0.05$). Finally, to analyze results from the ANT task we performed two MANOVAs, one on accuracy and the other on RT parameters, see Figure 1.

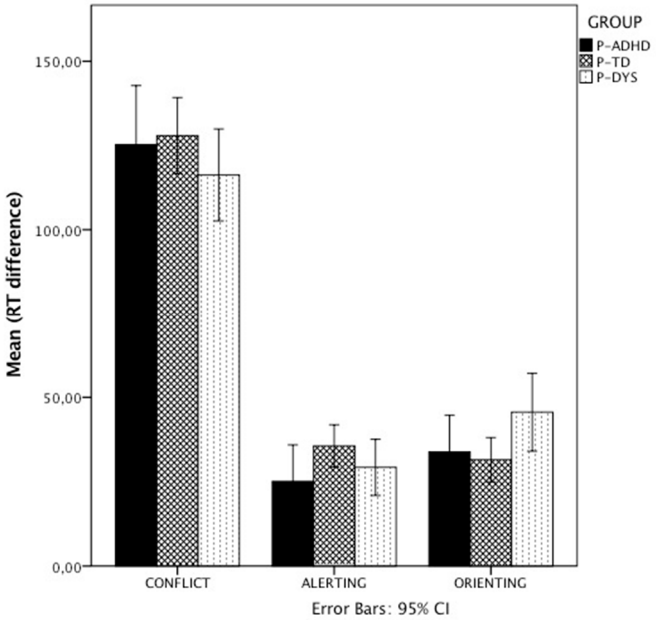

Figure 1. Magnitude (ms) of the three effects of the ANT task broken by group of participants. Error bars represent 95% CI.

In both analyses the main factor Group did not result to reach statistical significance (Accuracy: ($F(6,220) = 0.54$; $p = 0.78$, $\eta^2 = 0.01$; RT: ($F(6,220) = 1.82$; $p = 0.096$, $\eta^2 = 0.047$), nor it was for Role (Accuracy: ($F(3,109) = 1.11$; $p = 0.35$, $\eta^2 = 0.03$; RT: ($F(3,109) = 0.3$; $p = 0.8$, $\eta^2 = 0.01$) or for the interaction Group*Role (Accuracy: ($F(6,220) = 0.65$; $p = 0.68$, $\eta^2 = 0.017$; RT: ($F(6,220) = 0.3$; $p = 0.8$, $\eta^2 = 0.01$).

3.3. Questionnaires

In Table 2 a summary of mean values for questionnaires' scores is reported. Taking into account the Adult Reading History Questionnaire the ANOVA revealed a main effect of group ($F(2,123) = 11.2$; $p < 0.001$, $\eta^2 = 0.16$), with Bonferroni post-hocs showing that both P-DYS ($p < 0.001$) and P-ADHD ($p < 0.01$) reported more problems in reading history and attitude compared to the P-TD group. There was no effect of Role ($F(1,123) = 0.0$; $p = 0.9$, $\eta^2 = 0.0$), nor any significant interaction Group*Role ($F(2,123) = 1.57$; $p = 0.21$, $\eta^2 = 0.02$).

There was a main effect of Group ($F(2,123) = 5.19$; $p < 0.001$, $\eta^2 = 0.08$) also in the ASRS Questionnaire addressing ADHD symptoms in adulthood. Bonferroni post-hoc comparisons revealed the P-DYS group did not differ from either the P-TD ($p = 0.27$) group or the P-ADHD group ($p = 0.33$). Instead, the P-ADHD group showed higher scores ($p < 0.01$) compared to the P-TD group. There was no effect of Role ($F(1,123) = 0.52$; $p = 0.47$, $\eta^2 = 0.004$), nor of Group*Role interaction ($F(2,123) = 1.2$; $p = 0.3$, $\eta^2 = 0.02$).

Finally, considering the Parenting Stress Index, an ANOVA was run on the Total score and a main effect of Group arose ($F(1,123) = 20.23$; $p < 0.001$, $\eta^2 = 0.25$), but there was no effect of Role ($F(1,123) = 0.06$; $p = 0.8$, $\eta^2 = 0.001$), or of the interaction of Group*Role ($F(1,123) = 0.11$; $p = 0.89$, $\eta^2 = 0.002$). Bonferroni post-hoc comparisons showed that the P-ADHD group had higher scores

both compared to the P-TD ($p < 0.001$) and P-DYS ($p < 0.001$) groups, which did not differ each other ($p = 0.3$). The same pattern was observed when considering the single subscales (Defensive Scale, Parental Distress, Difficult Child, Difficult Child Interaction), where P-ADHD participants always obtained higher scores compared to the other two groups.

3.4. Regression Model

In order to investigate which factors predicted Parenting Stress a hierarchical regression model was run. Results are presented in Table 3. The results of the analysis showed that, at first step, SES and number of family members, but not parents' age, were significant predictors, explaining 13% of variance. At the second step, parents' cognitive skills did not add a significant contribution to the model (variance explained: 18%). At the final step, when parents' reading history and symptoms of adults' ADHD were added the model significantly increased in the portion of variance explained (27%) and in the final model it emerged that lower SES ($\beta = -0.24$, $p < 0.05$), minor number of family members ($\beta = -0.23$, $p < 0.05$) and higher ASRS score (symptoms of ADHD in parents) ($\beta = 0.299$, $p < 0.01$) were significant predictors of higher parenting stress.

Table 3. Hierarchical regression; dependent variable: Parenting Stress Total.

Step	Measure	B	SE B	β
1 ($R^2 = 0.137$)	SES	−0.6	0.176	−0.31 **
	Number family members	−4.679	1.677	−0.25 **
	Parents' age	0.008	0.395	0.002
2 ($\Delta R^2 = 0.047$. $p = 0.21$)	SES	−0.481	0.193	−0.251 *
	Number family members	−4.818	1.777	−0.264 **
	Parents' age	−0.027	0.398	−0.006
	Non-word reading speed	−3.493	2.958	−0.116
	Verbal fluency	−0.67	0.432	−0.157
	ANT-Conflict (RTs)	0.024	0.046	0.046
	Composite IQ	0.001	0.189	0.001
3 ($\Delta R^2 = 0.084$. $p < 0.01$) ($R^2 = 0.268$)	SES	−0.453	0.197	−0.236 *
	Number family members	−4.23	1.709	−0.231 *
	Parents' age	−0.072	0.382	−0.017
	Non-word reading speed	−3.968	2.949	−0.132
	Verbal fluency	−0.581	0.415	−0.137
	ANT-Conflict (RTs)	0.019	0.045	0.037
	Composite IQ	0.076	0.182	0.042
	ARHD (reading history)	0.083	17.701	0
	ASRS (ADHD symptoms)	1.771	0.534	0.299 **

* $p < 0.05$; ** $p < 0.01$.

4. Discussion

The present study investigated the cognitive and behavioral profiles of parents of children with neurodevelopmental disorders, specifically ADHD and dyslexia, and with typical development. The aims were threefold. First, we wanted to evaluate the broader phenotype of ADHD and dyslexia by assessing putative endophenotypes of these disorders within family members (parents). Secondly, we wanted to test differences in levels of parenting stress amongst the three groups. Finally, the study aimed to test which cognitive and behavioural indexes better predicted parenting stress. Considering the first aim, group differences on demographic, cognitive and behavioural variables depicted a complex picture of overlapping and distinct features amongst the three groups considered. Both P-ADHD and P-DYS parents had lower SES compared to parents of typically developing children, but the three groups did not differ in civil state, parents' and children's age. The difference in SES between P-ADHD and P-TD groups is quite consistent with data reported in the literature (e.g., [35]),

and in our sample, it was consistent for both mothers and fathers. Data on SES in the P-DYS group are in line with van Bergen and colleagues [29,47], who found differences between at-risk and control families in the educational level.

Moving to the cognitive profile, it emerged that the P-ADHD differed from the P-TD group in both verbal and non verbal IQ whereas the P-DYS did not differ from the other two groups. Furthermore, both the P-DYS and P-ADHD group significantly underperformed compared to the P-TD group in verbal fluency and passage reading speed, whereas in nonword reading speed it was the P-DYS group that underperformed compared to the P-TD group. There were no differences between the three groups in the ANT task, either considering accuracy or speed parameters.

When considering the questionnaires assessing behavioural symptoms of ADHD and troubles in reading history, it emerged that both P-DYS and P-ADHD groups reported a significant poor reading history compared to P-TD group. Instead, in the ASRS questionnaire, only the P-ADHD group showed consistent signs of ADHD symptoms.

Finally, when analyzing parenting stress, the P-ADHD group resulted to report the highest level in all dimensions considered: parental distress, defensive response, difficult child, difficult child-interaction. In contrast, the P-DYS group did not differ from the P-TD group, although mean values tended to be slightly higher in DC and DCI scales

Taken as a whole, these results evidence some aspects of specificity with regards to the two distinct profiles analyzed, i.e., ADHD and dyslexia. In particular, the group of parents of children with dyslexia show a profile quite similar to what is reported in the literature for children with dyslexia: they show a fully adequate intellectual functioning, similar to that of parents of children with typical development. Nevertheless, they present specific weaknesses in reading speed, notably they underperform compared to the other two groups in reading nonwords, which is a task assessing the phonological basis of decoding skills. These weaknesses are also associated with poorer reading history, remarkably with mean scores in the clinical range. They do not differ from the other groups in behavioral symptoms of ADHD, suggesting that for these parents ADHD symptomatology is not crucially associated to their profile and its occurrence might be explained as an epiphenomenon of their cognitive profile [48]. This is in line with their adequate performances in the ANT task assessing executive functions and attentional networks. Interestingly, in this study, and differently from other evidence in the literature, they did not result to have a higher level of parenting stress. These relatively modest discrepancies in parenting stress might be due to the differential composition of the control group, because, actually, the mean values of the P-DYS group are in the same range of those observed in previous studies [31,41]. As outlined by [32] parenting stress is a dimensional variable that occurs on a continuum, on which probably parents of children with dyslexia are not positioned at the upper extreme, but rather in a medium to high range, depending on a number of different variables which would deserve further attention in future investigations.

The profile of parents of children with ADHD is instead much less clear-cut. They seem to have more transversal cognitive weaknesses involving intellectual functioning, word reading speed and verbal fluency. However, they do not show specific impairments in attention networks, and do not differ from P-TD group on a phonological based measure such as non-word reading. At the behavioural levels, they report both reading history troubles and adult ADHD symptoms, the latter being significantly higher compared to those of parents of typically developing children. They also reported the highest level of parenting stress compared to the other groups. The higher incidence of ADHD symptomatology in parents of children with ADHD confirms previous data [49] and reinforces the idea that ADHD runs in families, although, according to [24], non-EF factors might play a crucial role in the intergenerational model of ADHD aetiology, challenging the concept of EF as core endophenotypes of ADHD.

The present study also considered the parental role (fathers vs mothers) and it was found that, except for a tendency for mothers to have better verbal fluency skills compared to parents, no other significant differences emerged in demographic, cognitive and behavioral indexes considered, and none

of the group*role interactions resulted to be significant. This trend might be considered as indirect support of the non-random mating hypothesis [3,48], with both parents within each group showing very similar characteristics.

Finally, considering the predictors of parenting stress at the cognitive and behavioural level it emerged that behavioral (ADHD symptoms in parents) and demographic (SES, number of family members) significantly predicted parenting stress, within a model that explained around 27% of variance. Thus, parents with higher levels of ADHD symptoms, lower SES and smaller family sizes are more susceptible to higher levels of parenting stress. Instead, markers of parents' cognitive profile did not seem to be crucially associated to how parents cope with the demands of their role. This aspect would deserve further investigation in future studies, since, to our knowledge, this is an under-investigated area.

This study has a number of limitations that might limit the generalizability of results. First of all, the sample size, which, particularly for the ADHD group, is relatively modest. Furthermore, the selection of markers of the broader phenotypes for the two clinical groups considered might have included other measures such as paradigms of delay aversion and time perception, which have been advocated for being important endophenotypic measures of ADHD. Referred to the broader phenotype of dyslexia further studies might include more specific measures of phonological awareness that are considered as putative markers of the broader phenotype of dyslexia [4,31]. Finally, it would be of interest to include in future studies samples of children with comorbid ADHD and dyslexia. Notwithstanding, this is, to our knowledge, the first study linking measures of cognitive functioning to parenting stress in a cross-group comparison involving parents of children with two different clinical profile and parents of children with typical development and the results reported shed important insight for future research in this new research area.

5. Conclusions

Considering the main aims of the study the paper offered a rich pattern of findings. As far as parent's group differences in cognitive profile were concerned the study highlighted that parents of children with ADHD had transversal cognitive weaknesses (IQ, reading tasks, verbal fluency), whereas the P-DYS group showed more specific falls in the reading related tasks. Turning to the second aim, it emerged that the P-ADHD had the highest levels of parenting stress and ADHD symptoms. Finally, the main predictors of parenting stress resulted to be a lower SES together with a minor number of family members and higher levels of ADHD symptoms in parents.

Lastly, some clinical implications might be proposed. First of all, the fact that parents of children with dyslexia or ADHD might themselves show some cognitive weaknesses that are similar to those of their offspring needs to be taken seriously into account when clinicians suggest intervention programs and, especially, when they recommend parental best practices for dealing with children impairments. Actually, many parents might encounter significant difficulties in fulfilling these requirements because they have problems similar to those of their children and might not be endowed with the necessary cognitive and psychological resources to accomplish clinician requirements. On the other hand, to see the glass half full, clinicians might valorize parents' experience trying to understand how they have afforded difficulties in their life course, what themselves would have or have found helpful, and treasure their knowledge of their children habits and demands. Within a systemic perspective, it would be important to accurately consider strengths and weaknesses within the family system, avoiding transmitting feeling of guil in parents who actually already perceive themselves as non-sufficiently adequate in managing parenthood demands.

Author Contributions: Conceptualization, P.B. and S.C.; methodology, P.B., V.P. and S.Z.; formal analysis, P.B.; investigation, S.Z., V.P. and L.M.; data curation, S.Z., V.P. and P.B.; writing—original draft preparation, P.B.; writing—review and editing, P.B.; supervision, P.B. and S.C; project administration, S.C. and L.M."

Funding: This research received no external funding.

Acknowledgments: The authors thank all the families for their participation.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Morton, J.; Frith, U. Causal modelling: A structural approach to developmental psychopathology. *Manual Develop. Psychopathol.* **1995**, *1*, 357–390.
2. Westermann, G.; Mareschal, D.; Johnson, M.; Sirois, S.; Spratling, M.; Thomas, M. Neuroconstructivism. *Dev. Sci.* **2007**, *10*, 75–83. [CrossRef]
3. van Bergen, E.; van der Leij, A.; de Jong, P.F. The intergenerational multiple deficit model and the case of dyslexia. *Front. Hum. Neurosci.* **2014**, *8*, 1–13. [CrossRef] [PubMed]
4. Snowling, M.J. Specific disorders and broader phenotypes: The case of dyslexia. *Q. J. Exp. Psychol.* **2008**, *61*, 142–156. [CrossRef] [PubMed]
5. Gottesman, I.I.; Gould, T.D. The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am. J. Psychiatr.* **2003**, *160*, 636–645. [CrossRef]
6. Caspi, A.; Moffitt, T.E. Gene–environment interactions in psychiatry: Joining forces with neuroscience. *Nat. Rev. Neurosci.* **2006**, *7*, 583–590. [CrossRef]
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American Psychiatric Pub: Washington, DC, USA, 2013.
8. Vellutino, F.R.; Fletcher, J.M.; Snowling, M.J.; Scanlon, D.M. Specific reading disability (dyslexia): What have we learned in the past four decades? *J. Child. Psychol. Psychiatry* **2004**, *45*, 2–40. [CrossRef]
9. Pennington, B.F. From single to multiple deficit models of developmental disorders. *Cognition* **2006**, *101*, 385–413. [CrossRef]
10. Tressoldi, P.E.; Stella, G.; Faggella, M. The development of reading speed in Italians with dyslexia a longitudinal study. *J. Learn. Disabil.* **2001**, *34*, 414–417. [CrossRef]
11. Karam, R.; Breda, V.; Picon, F.; Rovaris, D.; Victor, M.; Salgado, C.; Vitola, E.; Silva, K.L.; Guimarães-da-Silva, P.O.; Mota, N.R.; et al. Persistence and remission of ADHD during adulthood: A 7-year clinical follow-up study. *Psychol. Med.* **2015**, *45*, 2045–2056. [CrossRef] [PubMed]
12. Castellanos, X.; Tannock, R. Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nat. Rev. Neurosci.* **2002**, *3*, 617–628. [CrossRef]
13. Fan, J.; McCandliss, B.D.; Sommer, T.; Raz, A.; Posner, M.I. Testing the efficiency and independence of attentional networks. *J. Cogn. Neurosci.* **2002**, *14*, 340–347. [CrossRef]
14. Fan, J.; Wu, Y.; Fossella, J.A.; Posner, M.I. Assessing the heritability of attentional networks. *BMC Neurosci.* **2001**, *2*, 1. [CrossRef]
15. Johnson, K.A.; Robertson, I.H.; Barry, E.; Mulligan, A.; Dáibhis, A.; Daly, M.; Watchorn, A.; Gill, M.; Bellgrove, M.A. Impaired conflict resolution and alerting in children with ADHD: Evidence from the Attention Network Task (ANT). *J. Child Psychol. Psychiatry* **2008**, *49*, 1339–1347. [CrossRef]
16. Thompson, P.; Hulme, C.; Nash, H.; Gooch, D.; Hayiou-Thomas, E.; Snowling, M. Developmental dyslexia: Predicting individual risk. *J. Child Psychol. Psychiatry* **2015**, *56*, 976–987. [CrossRef] [PubMed]
17. Willcutt, E.; Betjemann, R.; McGrath, L.; Chhabildas, N.; Olson, R.; DeFries, J.; Pennington, B. Etiology and neuropsychology of comorbidity between RD and ADHD: The case for multiple-deficit models. *Cortex* **2010**, *46*, 1345–1361. [CrossRef]
18. Pennington, B.F.; Lefly, D.L. Early reading development in children at family risk for dyslexia. *Child Dev.* **2001**, *72*, 816–833. [CrossRef]
19. Snowling, M.J.; Gallagher, A.M.; Frith, U. Family risk of dyslexia is continuous: Individual differences in the precursors of reading skill. *Child Dev.* **2003**, *74*, 358–373. [CrossRef]
20. Biederman, J.; Faraone, S.V.; Mick, E.; Spencer, T.; Wilens, T.; Keily, K.; Guite, J.; Ablon, J.S.; Reed, E.; Warburton, R. High risk for attention deficit hyperactivity disorder among children of parents with childhood onset of the disorder: A pilot study. *Am. J. Psychiatry* **1995**, *152*, 431–435.
21. Cuevas, K.; Deater-Deckard, K.; Kim-Spoon, J.; Wang, Z.; Morasch, K.C.; Bell, M.A. A longitudinal intergenerational analysis of executive functions during early childhood. *Br. J. Dev. Psychol.* **2014**, *32*, 50–64. [CrossRef] [PubMed]

22. Goos, L.M.; Crosbie, J.; Payne, S.; Schachar, R. Validation and extension of the endophenotype model in ADHD patterns of inheritance in a family study of inhibitory control. *Am. J. Psychiatry* **2009**, *166*, 711–717. [CrossRef] [PubMed]
23. Nigg, J.T.; Blaskey, L.G.; Stawicki, J.A.; Sachek, J. Evaluating the endophenotype model of ADHD neuropsychological deficit: Results for parents and siblings of children with ADHD combined and inattentive subtypes. *J. Abnorm. Psychol.* **2004**, *11*, 614–625. [CrossRef]
24. Thissen, A.; Rommelse, N.; Hoekstra, P.; Hartman, C.; Heslenfeld, D.; Luman, M.; Lieshout, M.; Franke, B.; Oosterlaan, J.; Buitelaar, J.K. Attention deficit hyperactivity disorder (ADHD) and executive functioning in affected and unaffected adolescents and their parents: Challenging the endophenotype construct. *Psychol. Med.* **2013**, *44*, 881–892. [CrossRef]
25. Rommelse, N.; Arias-Vásquez, A.; Altink, M.; Buschgens, C.; Fliers, E.; Asherson, P.; Faraone, S.; Buitelaar, J.K.; Sergeant, J.A.; Oosterlaan, J.; et al. Neuropsychological Endophenotype Approach to Genome-wide Linkage Analysis Identifies Susceptibility Loci for ADHD on 2q21.1 and 13q12.11. *Am. J. Hum. Genet.* **2008**, *83*, 99–105. [CrossRef]
26. Bitsakou, P.; Psychogiou, L.; Thompson, M.; Sonuga-Barke, E.J. Delay aversion in attention deficit/hyperactivity disorder: An empirical investigation of the broader phenotype. *Neuropsychologia* **2009**, *47*, 446–456. [CrossRef] [PubMed]
27. Deater-Deckard, K. Family matters: Intergenerational and interpersonal processes of executive function and attentive behavior. *Curr. Dir. Psychol. Sci.* **2014**, *23*, 230–236. [CrossRef]
28. Black, J.M.; Tanaka, H.; Stanley, L.; Nagamine, M.; Zakerani, N.; Thurston, A.; Kesler, S.; Hulme, C.; Lyytinen, H.; Glover, G.H.; et al. Maternal history of reading difficulty is associated with reduced language-related gray matter in beginning readers. *NeuroImage* **2012**, *59*, 3021–3032. [CrossRef] [PubMed]
29. van Bergen, E.; de Jong, P.F.; Plakas, A.; Maassen, B.; van der Leij, A. Child and parental literacy levels within families with a history of dyslexia. *J. Child. Psychol. Psychiatry* **2012**, *53*, 28–36. [CrossRef]
30. Torppa, M.; Eklund, K.; van Bergen, E.; Lyytinen, H. Parental literacy predicts children's literacy: A longitudinal family-risk study. *Dyslexia* **2011**, *17*, 339–355. [CrossRef]
31. Bonifacci, P.; Montuschi, M.; Lami, L.; Snowling, M.J. Parents of children with dyslexia: Cognitive, emotional and behavioural profile. *Dyslexia* **2014**, *20*, 175–190. [CrossRef]
32. Deater-Deckard, K. Parenting stress and child adjustment: Some old hypotheses and new questions. *Clin. Psychol. Sci. Pract.* **1998**, *5*, 314–332. [CrossRef]
33. Abidin, R.R. *Parenting Stress Index: Professional Manual*, 3rd ed.; Psychological Assessment Resources: Odessa, FL, USA, 1995.
34. Theule, J.; Wiener, J.; Jenkins, J.; Tannock, R. Parenting stress in families of children with ADHD: A meta-analysis. *J. Emot. Behav. Disord.* **2013**, *21*, 3–17. [CrossRef]
35. Wiener, J.; Biondic, D.; Grimbos, T.; Herbert, M. Parenting Stress of Parents of Adolescents with Attention-Deficit Hyperactivity Disorder. *J. Abnorm. Child Psychiatry* **2015**, *44*, 561–574. [CrossRef]
36. Fuller, G.B.; Rankin, R.E. Differences in the levels of parental stress among mothers of learning disabled, emotionally impaired and regular school children. *Percept Motor Skill* **1994**, *78*, 583–592. [CrossRef]
37. Margalit, M.; Heiman, T. Family climate and anxiety in families with learning disabled boys. *J. Am. Acad. Child. Psychiatry* **1986**, *25*, 841–846. [CrossRef]
38. Waggoner, K.; Wilgosh, L. Concerns of families of children with learning disabilities. *J. Learn. Disabil.* **1990**, *23*, 97–113. [CrossRef] [PubMed]
39. Snowling, M.J.; Muter, V.; Carroll, J. Children at family risk of dyslexia: A follow-up in early adolescence. *J. Child. Psychol. Psychiatry* **2007**, *48*, 609–618. [CrossRef] [PubMed]
40. Karande, S.; Kumbhare, N.; Kulkarni, M.; Shah, N. Anxiety levels in mothers of children with specific learning disability. *J. Postgrad. Med.* **2009**, *55*, 165–170. [CrossRef] [PubMed]
41. Bonifacci, P.; Storti, M.; Tobia, V.; Suardi, A. Specific learning disorders: A look inside children's and parents' psychological well-being and relationships. *J. Learn. Disabil.* **2016**, *49*, 532–545. [CrossRef]
42. Kaufman, A.S.; Kaufman, N.L. *Kaufman Brief Intelligence Test*, 2nd ed.; Pearson: Bloomington, MN, USA, 2004.
43. Bonifacci, P.; Nori, R. *Kaufman Brief Intelligence Test*, 2nd ed; Italian Standardization; Giunti OS: Firenze, Italy, 2016.
44. Cornoldi, C.; Colpo, G. *Nuove Prove di Lettura MT per la Scuola Media Inferiore*; Giunti OS: Firenze, Italy, 1995.

45. Sartori, G.; Job, R.; Tressoldi, P.E. DDE-2. In *Batteria per La Valutazione Della Dislessia E Della Disortografia Evolutiva*; Giunti OS: Firenze, Italy, 2007.
46. Lefly, D.L.; Pennington, B. Reliability and validity of the Adult Reading History Questionnaire. *J. Learn. Disabil.* **2000**, *33*, 286–296. [CrossRef] [PubMed]
47. van Bergen, E.; de Jong, P.F.; Regtvoort, A.; Oort, F.; van Otterloo, S.; van der Leij, A. Dutch children at family risk of dyslexia: Precursors, reading development, and parental effects. *Dyslexia* **2011**, *17*, 2–18. [CrossRef] [PubMed]
48. Faraone, S.V.; Biederman, J.; Lehman, B.K.; Keenan, K.; Norman, D.; Seidman, L.J.; Kolodny, R.; Kraus, I.; Perrin, J.; Chen, W.J. Evidence for the independent familial transmission of attention deficit hyperactivity disorder and learning disabilities: Results from a family genetic study. *Am. J. Psychiat.* **1993**, *150*, 891–895. [PubMed]
49. Schlarb, A.; Starck, M.; Grünwald, J. Occurrence of ADHD in parents of ADHD children in a clinical sample. *Neuropsychiatr. Dis. Treat.* **2016**, *12*, 581–588. [CrossRef] [PubMed]

INTERNATIONAL JOURNAL OF PSYCHIATRY IN CLINICAL PRACTICE
https://doi.org/10.1080/13651501.2019.1628277

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Comorbidity between ADHD and anxiety disorders across the lifespan

Elisa D'Agati, Paolo Curatolo and Luigi Mazzone

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

ABSTRACT

Objectives: Attention deficit/hyperactivity disorder (ADHD) and anxiety disorders are among the most common psychiatric disorders with a 25% comorbidity rate with each other. In this study, we overview the comorbidity between ADHD and anxiety disorders in a longitudinal perspective across the lifespan and we discuss possible therapeutic strategies.

Methods: A literature search was performed using PubMed to identify clinical studies assessing comorbidity between ADHD and anxiety disorders from childhood to adulthood.

Results: Anxiety disorders may substantially change the presentation, the prognosis, and the treatment of ADHD itself. In childhood, the presence of generalised anxiety disorder, could prevent the typical inhibitory dysfunction present in ADHD, in adolescence may increase the deficit of working memory, and in adulthood may enhance the presence of sleep problems. Individuals with comorbid ADHD and anxiety disorders would benefit from adjunctive psychosocial or adjunctive pharmacotherapy interventions to cognitive behavioural treatment.

Conclusions: The management of individuals with comorbid ADHD and anxiety disorders could be challenging for clinicians, and assessing the developmental course is crucial in order to shed light on individualised treatment.

KEYPOINTS

- The comorbidity between ADHD and anxiety disorders changes the clinical presentation, the prognosis and treatment of patients with ADHD across lifespan.
- ADHD and anxiety disorders shared common neurobiological dysfunctions but have also different neurobiological abnormalities suggesting that they are different diagnoses.
- These patients are less likely to benefit from cognitive behavioural treatment strategies alone and often need adjunctive pharmacological treatments.
- Studies that evaluated the response to MPH reported conflicting results. These patients could respond less well and get more unpleasant arousal side-effects, but these findings need to be confirmed.
- For his unique mechanism of action, low dose aripiprazole treatment in adolescents and adults with this comorbid condition could be an intriguing avenue of exploration.

ARTICLE HISTORY
Received 17 June 2018
Revised 26 April 2019
Accepted 27 May 2019

KEYWORDS
ADHD; anxiety disorders; pharmacological treatment

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder with onset in early childhood and documented brain abnormalities with prominent associated symptoms that affect several aspects of daily functioning during lifespan (Curatolo, Paloscia, D'Agati, Moavero, & Pasini, 2009). Willcutt (2012) in his meta-analysis stated that whether ADHD symptoms are defined by parents and teachers' rating scales, the prevalence of ADHD is 5.9–7.1% in children and adolescents, while in young adults is of 5% by self-report measures of symptoms (Willcutt, 2012). ADHD is characterised by the presence of several psychiatric comorbidities, such as conduct disorder, autism spectrum disorder (ASD), mood disorders and anxiety disorders, which remain the most prevalent disturbances across the lifespan (Souza, Pinheiro, & Mattos, 2005). A 10-year prospective study of young individuals with ADHD found that the lifetime prevalence for all categories of psychopathology were significantly greater in young adults with ADHD compared with controls (Biederman et al., 2008). This included markedly elevated rates of antisocial, addictive, mood as well as anxiety disorders (Biederman et al., 2008). ADHD is often the first disorder to develop, and children with severe ADHD symptoms are at greater risk of developing other psychiatric comorbidities (Connor et al., 2003). Children with comorbid ADHD and anxiety disorders tend to have severe anxiety symptoms, early age of onset of anxiety and frequent additional psychiatric comorbidities (Katzman, Bilkey, Chokka, Fallu, & Klassen, 2017). Comorbidity between ADHD and anxiety is also common in patients with ASD (Postorino et al., 2017; Rosen, Mazefsky, Vasa, & Lerner, 2018), and both in idiopathic and syndromic forms such as fragile X syndrome, tuberous sclerosis complex (Curatolo, Moavero, & de Vries, 2015), and neurofibromatosis type I (Vogel, Gutmann, & Morris, 2017).

The comorbidity between ADHD and anxiety disorders may substantially change the presentation, the prognosis and treatment of ADHD itself (Schatz & Rostain, 2006). Therefore, choosing the best therapeutic option in patients with this comorbid disorder is crucial and could be a challenge for clinicians. Some interesting literature studies have attempted to describe the

CONTACT Elisa D'Agati elisadagati@gmail.com Department of Systems Medicine, Unit of Child Neurology and Psychiatry, 'Tor Vergata' University of Rome, Viale Oxford 81, Rome 00100, Italy

clinical phenotype of patients with such comorbidity and have provided treatment strategies, predominantly in adults (Katzman, Bilkey, Chokka, Fallu, & Klassen, 2017; Reimherr, Marchant, Gift, & Steans, 2017).

In this overview, we aim to:

- Discuss the most relevant findings on clinical features of individuals with comorbid ADHD and anxiety disorders from childhood to adulthood;
- Provide a longitudinal view of the clinical course of this comorbidity in order to help clinicians to collect useful information while taking medical history:
- Describe therapeutic strategies for the treatment of individuals with comorbid ADHD and anxiety disorders across lifespan.

Prevalence of comorbid ADHD and anxiety disorders across the lifespan

Souza et al. (2005) reported a high prevalence of anxiety disorders (23.05%) in a clinical sample of children and adolescent with ADHD according to DSM-IV-TR. The generalised anxiety disorder (GAD) had a prevalence of 12.8%, social phobia of 3.84% and separation anxiety disorder of 3.8% (Souza et al., 2005). The reported prevalence of comorbid anxiety disorders among adults with ADHD was 47–53% in another study (Kessler et al., 2005), but it can vary considerably depending upon whether the research used a prospective or retrospective design (Marks, Newcorn, & Halperin, 2006).

Clinical features of comorbid ADHD and anxiety disorders across the lifespan

Are anxiety symptoms a phenotypic manifestation of ADHD or a comorbid disorder? What is the role of environmental factors for this comorbid condition?

Anxiety seems to be more common in patients with ADHD, though it is not yet clear whether it is the ADHD *per se* that generates the risk or the coexisting presence of anxiety disorders. The presence of ADHD in young people increased the risk for lower academic performance and poorer social, emotional and adaptive functioning that could contribute to the onset of anxiety symptoms (Biederman et al., 2008). The problems associated with ADHD appear in different ways at different ages (Taylor & Sonuga-Barke, 2008), and a lower self-esteem profile is more common in children and adolescents with ADHD than in healthy controls (Mazzone et al., 2013). The experience of ADHD can affect the whole family and often the community. Impaired family relationships have been reported in families of children with ADHD (August, Braswell, & Thuras, 1998). Follow-up studies indicate that mothers of children with ADHD have more difficulty in child behaviour management, and display higher rates of conflict behaviours that can lead to the development of anxiety symptoms in young patients with ADHD (Psychogiou, Daley, Thompson, & Sonuga-Barke, 2007). Maternal anxiety before and during pregnancy has been associated with the risk of ADHD in children (Vizzini et al., 2018). Coexistence of anxiety and emotional problems in the family may drive the association between maternal expressed emotion (negativity, resentment and emotional over-involvement) and ADHD (Psychogiou et al., 2007).

Clinicians should investigate if the presence of anxiety disorders is a consequence of ADHD symptoms, and the role of the environmental factors in the symptomology of these patients. When ADHD and anxiety disorders are present in a comorbid condition, the clinical features of patients are different across lifespan:

Childhood

Bowen, Chavira, Bailey, Stein, and Stein (2008) studied the clinical characteristics of children with ADHD and comorbid anxiety disorders. The authors found that 50% of children with ADHD also had an anxiety disorder (Bowen et al., 2008). Children with this comorbidity, had more anxiety and depressive symptoms, more attention problems and were less socially competent than children with only-anxiety or only-ADHD (Bowen et al., 2008). Interestingly, in this study, parents reported that the age of onset of hyperactivity symptoms in children with ADHD and anxiety disorder was 5.2 years compared with 2.2 years of children with ADHD-only. These findings suggested that the presence of this comorbid condition could alter the typical presentation of ADHD symptoms (Bowen et al., 2008).

Several studies suggested a specific relationship between anxiety and ADHD-inattentive type (Biederman et al., 2006). By contrast, other studies found no relationship between anxiety and ADHD type in children (Ghanizadeh, 2008). The presence of GAD in children with ADHD could also prevent the inhibitory dysfunction typically present in ADHD (Menghini et al., 2018). Only children with ADHD and GAD showed no deficit in inhibitory control such as rule maintenance, stimulus detection, action selection and action execution (Menghini et al., 2018). These results demonstrate that the presence of GAD may partially inhibit the impulsivity and response inhibition deficits typically present in children with ADHD (Carlson & Mann, 2002).

Social phobia is an anxiety disorder that is characterised by excessive fear and/or avoidance of social situations and is a frequently comorbid condition in primary school-age children with ADHD, leading to significant impairment in school, family and social functioning (Lee et al., 2015; Solanto, Pope-Boyd, Tryon, & Stepak, 2009). In children with ADHD, the presence of social phobia and emotional problems results in more missed school days (Golubchik, Sever, & Weizman, 2014). ADHD symptoms and poorer social competence determined a negative association with cognitive outcomes (Ramos et al., 2013).

Adolescence

The prevalence of anxiety disorders in patients with ADHD increases after puberty, primarily owing to increased rates in females (Newcorn, 2009). In these patients, the comorbid anxiety disorders may increase their deficit of working memory (Tannock, Ickowicz, & Schachar, 1995). Youth patients with comorbid ADHD and anxiety disorders experience increased social and academic impairment. Using event-related potentials, Klymkiw et al. (2017) found that patients with this comorbidity exhibited larger N2 amplitudes to no-go stimuli with variable attention allocation to nontarget stimuli, and concluded that the addition of anxiety to ADHD appears to alter early attentional processing in these patients (Klymkiw et al., 2017). The prevalence of comorbid psychiatric disorders in adolescents with ADHD was not related with gender or different subtypes of ADHD (Ghanizadeh, 2009), and the presence of anxiety during childhood or adolescence did not predict the persistence of ADHD into adulthood (Kessler et al., 2005).

Adulthood

Adults with ADHD had a poorer quality of life with a greater level of functional impairment, and they were prone to unstable relationships, and frequently presented depression and anxiety symptoms (Kessler et al., 2006). In addition, adults with ADHD reported more sleep disturbances such as severe excessive sleepiness or decreased sleep (Chao et al., 2008). All these symptoms, if untreated and under-recognised, could increase the risk of a comorbid anxiety disorder related to ADHD symptomatology. ADHD symptoms, in adult patients with anxiety, increased the presence of sleep problems such as delayed sleep phase syndrome, and reduced sleep duration to less than 6 h per night (Bron et al., 2016). ADHD is frequently unrecognised among adult psychiatric patients. Pehlivanidis, Papanikolaou, Spyropoulou, and Papadimitriou (2014) demonstrated that adult patients with depressive or anxiety disorder who are reporting more severe symptomatology should be carefully screened for possible comorbid adult ADHD (Pehlivanidis et al., 2014). Furthermore, adults with ADHD and high levels of anxiety symptoms, presented emotional dysregulation and were more commonly included in the DSM-IV combined type (Reimherr, Marchant, Gift, & Steans, 2017). Impairment from ADHD increases with age, and as ADHD symptoms change over time, the comorbidities may also change and reflect patients' developmental shifts. Patients with childhood ADHD whit comorbid GAD had a higher than expected risk of suicidality with an observed odds ratio of 10.94 compared with an expected odds ratio of 4.86, consistent with a synergistic interaction effect (Yoshimasu et al., 2017) (Figure 1).

Neurobiology of ADHD and anxiety disorders

The neurobiological substrates that mediate ADHD symptoms, share commonalities with those involved in comorbid disorders (Faraone, 2018). The vulnerability to ADHD is mediated by several genes of slight effect and is associated with the high phenotypic heterogeneity seen in ADHD. These findings lead Braaten et al. (2003) to present different hypotheses: the first suggests that ADHD and anxiety disorders are different expressions of the same genetic risk factor, the second suggests that patients with comorbid ADHD and anxiety disorders compose a distinct ADHD subtype, and the third theorises that ADHD and anxiety symptoms have independent transmission. The study of Segenreich, Fortes, Coutinho, Pastura, and Mattos (2009) corroborates the last hypothesis as suggested also by Braaten et al. (2003). Genetic studies have also identified shared genetic risk factors between ADHD and associated comorbid disorders (Carey et al., 2015; Faraone, 2018). The pathophysiology of this complex comorbid condition is not well described in the literature. The evidence suggests that ADHD and anxiety disorders are separate conditions linked by complex dopaminergic gating disturbances at the level of the ventral striatum and nucleus accumbens, influenced by the hippocampus and amygdala (Levy, 2004). Dopamine and serotonin transporters (DAT and 5-HTT) were investigated in PET studies of patients with GAD, where the DAT availability in the striatum was significantly lower, while the 5-HTT availability did not differ between patients and healthy subjects (Lee et al., 2015). The lower availability of DAT in the striatum was documented in patients with ADHD (Curatolo et al., 2009).

Patients with ADHD and patients GAD that represents the most common anxiety disorder in comorbidity with ADHD (Souza et al., 2005) share some neurodevelopmental abnormalities in the brain. MRI studies demonstrated an increased grey matter volume in the amygdala, in the dorsomedial prefrontal cortex (PFC), and grey matter volume changes on the right cerebellar hemisphere in patients with GAD (Hilbert, Evens, Maslowski, Wittchen, & Lueken, 2015). Another study showed a grey matter increase in superior temporal gyrus and a decrease in medial and superior frontal gyri in adolescents with GAD (Strawn et al., 2013). Increased grey matter volume in the right inferior frontal gyrus, and in right PFC was documented in patients with ADHD aged 9–16 years (Garrett et al., 2008; Semrud-Clikeman, Pliszka, Bledsoe, & Lancaster, 2014). A systematic review of fMRI studies in patients with GAD, reported that neuroimaging studies differed largely in methodology, making it difficult to identify common findings (Mochcovitch, da Rocha Freire, Garcia, & Nardi, 2014).

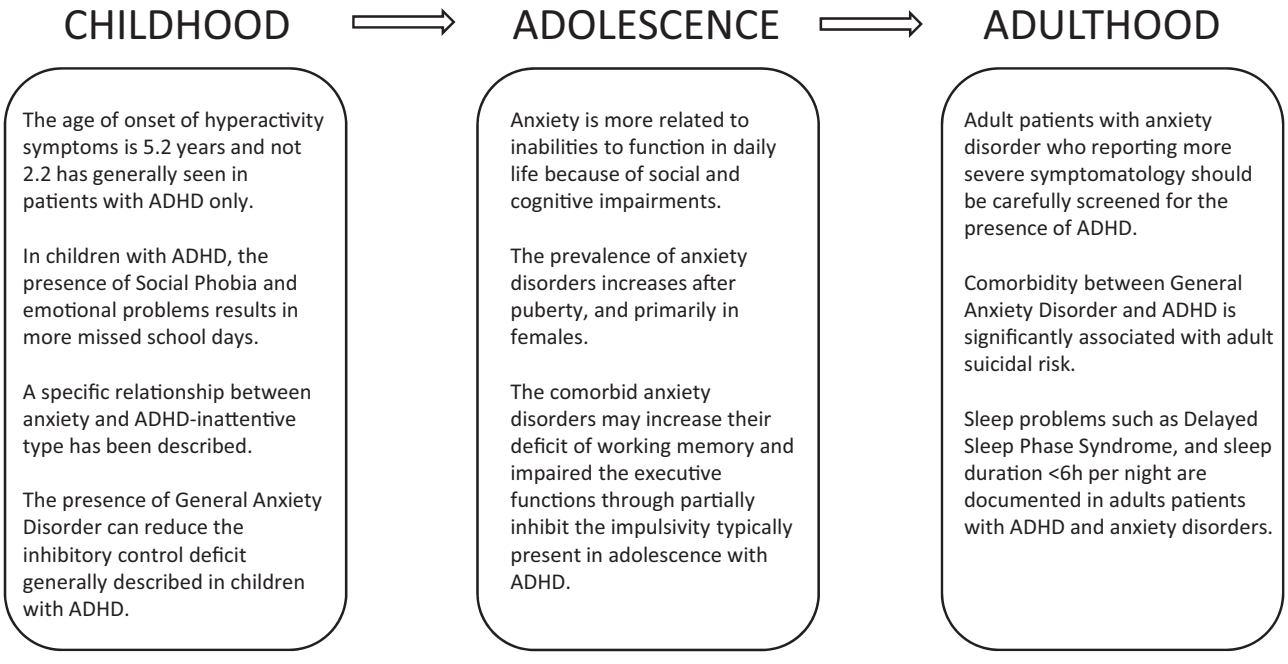

Figure 1. The clinical manifestation of anxiety symptoms in patients with ADHD during the lifespan.

Treatment options in patients with ADHD and anxiety disorders

Anxiety disorders can be secondary to ADHD or can develop independently and assessing the developmental course of these conditions is important because the sequencing of disorders may affect the sequencing of treatment (Newcorn, 2009) that is always a challenge for clinicians. In everyday clinical practice, if a child has an anxiety disorder that followed the onset of ADHD, the treatment of ADHD may be the priority to determine whether improvement in ADHD would also lead to an improvement in anxiety. It is reasonable to treat the ADHD first with cognitive behavioural treatment (CBT) and/or medication, and then reassess the anxiety symptoms. Furthermore, CBT treatment positively affected academic, social function and ADHD symptoms (Jensen et al., 2001), youth patients with comorbid anxiety disorders are less likely to benefit from CBT strategies alone and need adjunctive psychosocial or pharmacotherapy interventions (Halldorsdottir et al., 2015).

Methylphenidate (MPH) treatment

Studies that evaluated the response to MPH in children with ADHD and comorbid anxiety disorders reported conflicting results (Masi et al., 2012; Ter-Stepanian, Grizenko, Zappitelli, & Joober, 2010). Tannock et al. (1995) in a series of children with ADHD and ADHD + anxiety disorders evaluated the effect of MPH treatment during a working memory task. The results showed that MPH treatment improved working memory in children with ADHD only, but not in patients with comorbid condition (Tannock, Ickowicz, & Schachar, 1995). The presence of anxiety disorders has been identified as a potential moderator of short-term treatment response in children with ADHD, and has been reported to be a side effect of MPH treatment (Coughlin et al., 2015). Some studies have found that children with comorbid ADHD and anxiety respond less well to stimulant medication and get more unpleasant arousal side-effects, but these findings need to be confirmed and may be more relevant to girls than boys (Gadow, Nolan, Sverd, Sprafkin, & Schwartz, 2002; Newcorn et al., 2001). A reduced response to MPH observed in anxious boys with ADHD hyperactive/impulsive and combined type suggested that at least some of the symptomatology in these children could be attributed to anxiety rather than ADHD (Moshe, Karni, & Tirosh, 2012).

ADHD symptoms and impaired executive functions typically present in children with ADHD may lead to insecure or anxious attachment with the development of social phobia (Finzi-Dottan, Manor, & Tyano, 2006). MPH-related improvement in social cognition and emotion recognition may contribute to the reduction of social anxiety symptoms and social phobia (Golubchik et al., 2014). Psychostimulants are believed to decrease state anxiety in adults with ADHD (Bloch et al., 2013), but evidence suggests that stimulant treatment is less effective than nonstimulants in adults patients with comorbid ADHD and anxiety (Newcorn, 2009).

Atomoxetine (ATX)

Monotherapy with ATX, a selective norepinephrine uptake inhibitor, effectively improves the symptoms of both ADHD and comorbid general anxiety disorder in children (Geller et al., 2007). In adults with ADHD and anxiety disorders, ATX can reduce anxiety as well as ADHD symptoms (Okada, 2015). Large-scale, double-blind studies are needed to substantiate these findings.

Serotonin selective reuptake inhibitor (SSRI)

Although serotonin selective reuptake inhibitor (SSRI) is considered the first-line treatment in children with anxiety disorders, they have less or no efficacy on ADHD symptoms (Waxmonsky, 2003). The presence of ADHD symptoms may reduce the responsiveness of the anxiety symptoms to antidepressant medications (Geller et al., 2003). There are reports of worsening hyperactivity symptoms using SSRI in children with ADHD and anxiety disorders, and there is evidence that these patients require treatment with an SSRI and a stimulant medication (Waxmonsky, 2003).

Aripiprazole

Aripiprazole is a second-generation antipsychotic with a unique mechanism of action (dopamine D2 partial agonism, serotonin 5-HT1A partial agonism and 5-HT2A antagonism) that make it an effective anxiolytic agent (Stern, Petti, Bopp, & Tobia, 2009). Aripiprazole has been described as a dopamine system stabiliser (Tadori Forbes, McQuade, & Kikuchi, 2008). The 5-HT1A receptor stimulation is thought to be one of the mediators of antianxiety effects, leading to changes in the serotonin and dopamine neurotransmitter systems in the prefrontal cortex and other brain regions associated with anxiety (Pae, Serretti, Patkar, & Masand, 2008) and ADHD. Pharmacological agents with agonistic affinities at the 5-HT1A receptor are described to be effective anxiolytic drugs (Stern et al., 2009). Aripiprazole has been suggested in the treatment of patients with ADHD and ASD (Lamberti et al., 2016), as well as in combination with MPH in children and adolescence with ADHD and disruptive mood dysregulation disorder (Pan, Fu, & Yeh, 2018). It has been found to be effective as monotherapy and adjunct therapy for the treatment of post-traumatic stress disorder (Britnell, Jackson, Brown, & Capehart, 2017), obsessive-compulsive disorder (Albert et al., 2016), and anxiety disorders (Albert et al., 2016; Katzman, 2011). In our clinical practice, low dose aripiprazole treatment is effective as first-line option in adolescents and young adults with ADHD and severe anxiety symptoms and as a second choice treatment in the same patients after a first-line therapy with MPH, in those who experience a decreased response to MPH and more side effects, such as severe anxiety. Large-scale randomised, controlled trials are needed to clarify its efficacy in these patients, as well as to determine optimal dosing.

Discussion

When a patient presents with symptoms shared between ADHD and anxiety disorders, the clinician should consider one of the following possibilities:

1. The patient presenting with ADHD and anxiety symptoms has only an anxiety disorder and may have been misdiagnosed as having also ADHD.
2. The patient presenting with ADHD and anxiety symptoms has only ADHD but may have been misdiagnosed as having also an anxiety disorder.
3. The patient has both ADHD and anxiety disorder.

The presence of a comorbid condition may substantially change the presentation, the prognosis, and the treatment of patients across lifespan.

ADHD patients with comorbid anxiety disorders are less likely to benefit from CBT and need adjunctive pharmacotherapy. Literature studies that evaluated the response to MPH treatment in these patients, reported mixed results. Previous studies suggested that children with ADHD and anxiety disorders might exhibit a decreased response to MPH and experience more side

effects than children with ADHD only. Given that anxiety disorders are a common comorbidity in patients with ADHD, and that psychostimulants are the most-effective short-term treatment in patients ADHD, clinicians should carefully examine the presence of anxiety as a side-effect of psychostimulant.

For its unique mechanism of action, aripiprazole treatment in adolescents and adults with this comorbid condition could be an intriguing avenue of exploration particularly given the need for therapeutic alternatives. Large-scale, double-blind studies are needed to substantiate this finding, and studies comparing MPH + CBT or MPH + selective serotonin reuptake inhibitors, and ATX + CBT are required to reveal the best therapeutic option for these patients.

Acknowledgements

The author would like to thank Dr. Franco De Crescenzo for his assistance in the revision of this manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

Albert, U., Carmassi, C., Cosci, F., De Cori, D., Di Nicola, M., Ferrari, S., … Fiorillo, A. (2016). Role and clinical implications of atypical antipsychotics in anxiety disorders, obsessive-compulsive disorder, trauma-related, and somatic symptom disorders: A systematized review. *International Clinical Psychopharmacology*, *31*, 249–258. doi:10.1097/YIC.0000000000000127

August, G. J., Braswell, L., & Thuras, P. (1998). Diagnostic stability of ADHD in a community sample of school-aged children screened for disruptive behavior. *Journal of Abnormal Child Psychology*, *26*, 345–356. doi:10.1023/A:1021999722211

Biederman, J., Monuteaux, M. C., Spencer, T., Wilens, T. E., Macpherson, H. A., & Faraone, S. V. (2008). Stimulant therapy and risk for subsequent substance use disorders in male adults with ADHD: A naturalistic controlled 10-year follow-up study. *American Journal of Psychiatry*, *165*, 597–603. doi:10.1176/appi.ajp.2007.07091486

Biederman, J., Petty, C., Fried, R., Fontanella, J., Doyle, A. E., Seidman, L. J., & Faraone, S. V. (2006). Impact of psychometrically defined deficits of executive functioning in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *163*, 1730–1738. doi:10.1176/ajp.2006.163.10.1730

Bowen, R., Chavira, D. A., Bailey, K., Stein, M. T., & Stein, M. B. (2008). Nature of anxiety comorbid with attention deficit hyperactivity disorder in children from a pediatric primary care setting. *Psychiatry Research*, *157*, 201–209. doi:10.1016/j.psychres.2004.12.015

Bloch, Y., Aviram, S., Segev, A., Nitzan, U., Levkovitz, Y., Braw, Y., & Mimouni Bloch, A. (2017). Methylphenidate Reduces State Anxiety During a Continuous Performance Test That Distinguishes Adult ADHD Patients From Controls. *J Atten Disord*, *21*, 46–51. doi:10.1177/1087054712474949

Braaten, E. B., Beiderman, J., Monuteaux, M. C., Mick, E., Calhoun, E., Cattan, G., & Faraone, S. V. (2003). Revisiting the association between attention-deficit/hyperactivity disorder and anxiety disorders: A familial risk analysis. *Biological Psychiatry*, *53*, 93–99. doi:10.1016/S0006-3223(02)01434-8

Britnell, S. R., Jackson, A. D., Brown, J. N., & Capehart, B. P. (2017). Aripiprazole for post-traumatic stress disorder: A systematic review. *Clinical Neuropharmacology*, *40*, 273–278. doi:10.1097/WNF.0000000000000251

Bron, T. I., Bijlenga, D., Kooij, J. J., Vogel, S. W., Wynchank, D., Beekman, A. T., & Penninx, B. W. (2016). Attention-deficit hyperactivity disorder symptoms add risk to circadian rhythm sleep problems in depression and anxiety. *Journal of Affective Disorders*, *2016*, 74–81. doi:10.1016/j.jad.2016.04.022

Carey, C. E., Agrawal, A., Bucholz, K. K., Hartz, S. M., Lynskey, M. T., Nelson, E. C., … Bogdan, R. (2015). Associations between polygenic risk for psychiatric disorders and substance involvement. *Frontiers in Genetics*, *15*, 7–149. doi:10.3389/fgene.2016.00149

Carlson, C. L., & Mann, M. (2002). Sluggish cognitive tempo predicts a different pattern of impairment in the attention deficit hyperactivity disorder, predominantly inattentive type. *Journal of Clinical Child and Adolescent Psychology*, *31*, 123–129. doi:10.1207/153744202753441738

Chao, C. Y., Gau, S. S., Mao, W. C., Shyu, J. F., Chen, Y. C., & Yeh, C. B. (2008). Relationship of attention-deficit-hyperactivity disorder symptoms, depressive/anxiety symptoms, and life quality in young men. *Psychiatry and Clinical Neurosciences*, *2*, 421–426. doi:10.1111/j.1440-1819.2008.01830.x

Connor, D. F., Edwards, G., Fletcher, K., Baird, J., Barkley, R. A., & Steingard, R. J. (2003). Correlates of comorbid psychopathology in children with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, *42*, 193–200. doi:10.1097/00004583-200302000-00013

Coughlin, C. G., Cohen, S. C., Mulqueen, J. M., Ferracioli-Oda, E., Stuckelman, Z. D., & Bloch, M. H. (2015). Meta-analysis: Reduced risk of anxiety with psychostimulant treatment in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, *25*, 611–617. doi:10.1089/cap.2015.0075

Curatolo, P., Moavero, R., & de Vries, P. J. (2015). Neurological and neuropsychiatric aspects of tuberous sclerosis complex. *Lancet Neurology*, *14*, 733–745. doi:10.1016/S1474-4422(15)00069-1

Curatolo, P., Paloscia, C., D'Agati, E., Moavero, R., & Pasini, A. (2009). The neurobiology of attention deficit/hyperactivity disorder. *European Journal of Paediatric Neurology*, *13*, 299–304. doi:10.1016/j.ejpn.2008.06.003

Faraone, S. V. (2018). The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neuroscience & Biobehavioral Reviews*, *87*, 255–270. doi:10.1016/j.neubiorev.2018.02.001

Finzi-Dottan, R., Manor, I., & Tyano, S. (2006). ADHD, temperament, and parental style as predictors of the child's attachment patterns. *Child Psychiatry and Human Development*, *37*, 103–114. doi:10.1007/s10578-006-0024-7

Gadow, K. D., Nolan, E. E., Sverd, J., Sprafkin, J., & Schwartz, J. (2002). Anxiety and depression symptoms and response to methylphenidate in children with attention-deficit hyperactivity disorder and tic disorder. *Journal of Clinical Psychopharmacology*, *22*, 267–274. doi:10.1097/00004714-200206000-00007

Garrett, A., Penniman, L., Epstein, J. N., Casey, B. J., Hinshaw, S. P., Glover, G., … Reiss, A. L. (2008). Neuroanatomical abnormalities in adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 1321–1328. doi:10.1097/CHI.0b013e318185d285

Geller, D. A., Coffey, B., Faraone, S., Hagermoser, L., Zaman, N. K., Farrell, C. L., … Biederman, J. (2003). Does comorbid attention-deficit/hyperactivity disorder impact the clinical expression of

pediatric obsessive compulsive disorder? *CNS Spectrums*, *8*, 259–264. doi:10.1017/S1092852900018472

Geller, D., Donnelly, C., Lopez, F., Rubin, R., Newcorn, J., Sutton, V., … Sumner, C. (2007). Atomoxetine treatment for pediatric patients with attention-deficit/hyperactivity disorder with comorbid anxiety disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*, 1119–1127. doi:10.1097/chi.0b013e3180ca8385

Ghanizadeh, A. (2008). Psychiatric comorbidity differences in clinic—referred children and adolescents with ADHD according to the subtypes and gender. *Journal of Child Neurology*, *24*, 679–684. doi:10.1177/0883073808331086

Ghanizadeh, A. (2009). Psychiatric comorbidity differences in clinic-referred children and adolescents with ADHD according to the subtypes and gender. *Journal of Child Neurology*, *24*, 679–684. doi:10.1177/0883073808331086

Golubchik, P., Sever, J., & Weizman, A. (2014). Methylphenidate treatment in children with attention deficit hyperactivity disorder and comorbid social phobia. *International Clinical Psychopharmacology*, *29*, 212–215. doi:10.1097/YIC.0000000000000029

Halldorsdottir, T., Ollendick, T. H., Ginsburg, G., Sherrill, J., Kendall, P. C., Walkup, J., … Piacentini, J. (2015). Treatment outcomes in anxious youth with and without comorbid ADHD in the CAMS. *Journal of Clinical Child & Adolescent Psychology*, *44*, 985–991. doi:10.1080/15374416.2014.952008

Hilbert, K., Evens, R., Maslowski, N. I., Wittchen, H. U., & Lueken, U. (2015). Neurostructural correlates of two subtypes of specific phobia: A voxel-based morphometry study. *Psychiatry Research*, *231*, 168–175. doi:10.1016/j.pscychresns.2014.12.003

Jensen, P. S., Hinshaw, S. P., Kraemer, H. C., Lenora, N., Newcorn, J. H., Abikoff, H. B., … Vitiello, B. (2001). ADHD comorbidity findings from the MTA study: Comparing comorbid subgroups. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*, 147–158. doi:10.1097/00004583-200102000-00009

Katzman, M. A. (2011). Aripiprazole: A clinical review of its use for the treatment of anxiety disorders and anxiety as a comorbidity in mental illness. *Journal of Affective Disorders*, *128*, S11–S20. doi:10.1016/S0165-0327(11)70004-0

Katzman, M. A., Bilkey, T. S., Chokka, P. R., Fallu, A., & Klassen, L. J. (2017). Adult ADHD and comorbid disorders: Clinical implications of a dimensional approach. *BMC Psychiatry*, *22*, 302. doi:10.1186/s12888-017-1463-3

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., … Zaslavsky, A. M. (2006). The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. *American Journal of Psychiatry*, *163*, 716–723. doi:10.1176/appi.ajp.163.4.716

Kessler, R. C., Adler, L. A., Barkley, R., Biederman, J., Conners, C. K., Faraone, S. V., … Zaslavsky, A. M. (2005). Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: Results from the national comorbidity survey replication. *Biological Psychiatry*, *57*, 1442–1451. doi:10.1016/j.biopsych.2005.04.001

Klymkiw, D. F., Milligan, K., Lackner, C., Phillips, M., Schmidt, L. A., & Segalowitz, S. J. (2017). Does anxiety enhance or hinder attentional and impulse control in youth with ADHD? An ERP analysis. *Journal of Attention Disorders*, *1*, doi:10.1177/1087054717707297

Lamberti, M., Siracusano, R., Italiano, D., Alosi, N., Cucinotta, F., Di Rosa, G., … Gagliano, A. (2016). Head-to-head comparison of aripiprazole and risperidone in the treatment of ADHD symptoms in children with autistic spectrum disorder and ADHD: A pilot, open-label, randomized controlled study. *Pediatric Drugs*, *18*, 319–329. doi:10.1007/s40272-016-0183-3

Lee, L.-T., Tsai, H. C., Chi, M. H., Chang, W. H., Chen, K. C., Lee, I. H., … Yang, Y. K. (2015). Lower availability of striatal dopamine transporter in generalized anxiety disorder: A preliminary two-ligand SPECT study. *International Clinical Psychopharmacology*, *30*, 175–178. doi:10.1097/YIC.0000000000000067

Levy, F. (2004). Synaptic gating and ADHD: A biological theory of comorbidity of ADHD and anxiety. *Neuropsychopharmacology*, *28*, 1–8. doi: 10.1038/sj.npp.1300469

Marks, D. J., Newcorn, J. H., & Halperin, J. M. (2006). Comorbidity in adults with attention-deficit/hyperactivity disorder. *Annals of the New York Academy of Sciences*, *931*, 216–238. doi:10.1111/j.1749-6632.2001.tb05781.x

Masi, G., Pfanner, C., Mucci, M., Berloffa, S., Magazù, A., Parolin, G., & Perugi, G. (2012). Pediatric social anxiety disorder: Predictors of response to pharmacological treatment. *Journal of Child & Adolescent Psychopharmacology*, *22*, 410–414. doi:10.1089/cap.2012.0007

Mazzone, L., Postorino, V., Reale, L., Guarnera, M., Mannino, V., Armando, M., … Vicari, S. (2013). Self-esteem evaluation in children and adolescents suffering from ADHD. *Clinical Practice and Epidemiology in Mental Health: CP & Emh*, *9*, 96–102. doi:10.2174/1745017901309010096

Menghini, D., Armando, M., Calcagni, M., Napolitano, C., Pasqualetti, P., Sergeant, J. A., … Vicari, S. (2018). The influence of generalized anxiety disorder on executive functions in children with ADHD. *European Archives of Psychiatry and Clinical Neuroscience*, *268*, 349–357. doi:10.1007/s00406-017-0831-9

Mochcovitch, M. D., da Rocha Freire, R. C., Garcia, R. F., & Nardi, A. E. (2014). A systematic review of fMRI studies in generalized anxiety disorder: Evaluating its neural and cognitive basis. *Journal of Affective Disorders*, *167*, 336–342. doi:10.1016/j.jad.2014.06.041

Moshe, K., Karni, A., & Tirosh, E. (2012). Anxiety and methylphenidate in attention deficit hyperactivity disorder: A double-blind placebo-drug trial. *ADHD Attention Deficit and Hyperactivity Disorders*, *4*, 153–158. doi:10.1007/s12402-012-0078-2

Newcorn, J. H. (2009). Managing ADHD and comorbidities in adults. *The Journal of Clinical Psychiatry*, *70*, e40.

Newcorn, J. H., Halperin, J. M., Jensen, P. S., Abikoff, H. B., Arnold, L. E., Cantwell, D. P., … Vitiello, B. (2001). Symptom profiles in children with ADHD: Effects of comorbidity and gender. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*, 137–146. doi:10.1097/00004583-200102000-00008

Okada, T. (2015). Diagnosis and treatment of adult ADHD comorbid with mood or anxiety disorders. *Seishin Shinkeigaku Zasshi = Psychiatria et Neurologia Japonica*, *117*, 768–774.

Pae, C. U., Serretti, A., Patkar, A. A., & Masand, P. S. (2008). Aripiprazole in the treatment of depressive and anxiety disorders: A review of current evidence. *CNS Drugs*, *22*, 367–388. doi:10.2165/00023210-200822050-00002

Pan, P. Y., Fu, A. T., & Yeh, C. B. (2018). Aripiprazole/methylphenidate combination in children and adolescents with disruptive mood dysregulation disorder and attention-deficit/hyperactivity disorder: An open-label study. *Journal of Child & Adolescent Psychopharmacology*, *28*, 682–689. doi:10.1089/cap.2018.0068

Pehlivanidis, A., Papanikolaou, K., Spyropoulou, A. C., & Papadimitriou, G. N. (2014). Comorbid attention-deficit/hyperactivity disorder in adult psychiatric outpatients with *depressive* or anxiety disorders. *International Journal of Psychiatry in*

Clinical Practice, *18*, 265–271. doi:10.3109/13651501.2014.941878

Postorino, V., Kerns, C. M., Vivanti, G., Bradshaw, J., Siracusano, M., & Mazzone, L. (2017). Anxiety disorders and obsessive-compulsive disorder in individuals with autism spectrum disorder. *Current Psychiatry Reports*, *19*, 92. doi:10.1007/s11920-017-0846-y

Psychogiou, L., Daley, D. M., Thompson, M. J., & Sonuga-Barke, E. J. (2007). Mothers' expressed emotion toward their school-aged sons. Associations with child and maternal symptoms of psychopathology. *European Child & Adolescent Psychiatry*, *16*, 458–464. doi:10.1007/s00787-007-0619-y

Ramos, R., Freire, C., Julvez, J., Fernández, M. F., García-Esteban, R., Torrent, M., … Olea, N. (2013). Association of ADHD symptoms and social competence with cognitive status in preschoolers. *European Child & Adolescent Psychiatry*, *22*, 153–164. doi:10.1007/s00787-012-0334-1

Reimherr, F. W., Marchant, B. K., Gift, T. E., & Steans, T. A. (2017). ADHD and anxiety: Clinical significance and treatment implications. *Current Psychiatry Reports*, *20*, 109. doi:10.1007/s11920-017-0859-6

Rosen, T. E., Mazefsky, C. A., Vasa, R. A., & Lerner, M. D. (2018). Co-occurring psychiatric conditions in autism spectrum disorder. *Int Rev Psychiatry*, *30*, 40–61. doi:10.1080/09540261.2018.1450229

Schatz, D. B., & Rostain, A. L. (2006). ADHD with comorbid anxiety: A review of the current literature. *Journal of Attention Disorders*, *10*, 141–149. doi:10.1177/1087054706286698

Segenreich, D., Fortes, D., Coutinho, G., Pastura, G., & Mattos, P. (2009). Anxiety and depression in parents of a Brazilian non-clinical sample of attention-deficit/hyperactivity disorder (ADHD) students. *Brazilian Journal of Medical and Biological Research*, *42*, 465–469. doi:10.1590/S0100-879X2009000500011

Semrud-Clikeman, M., Pliszka, S. R., Bledsoe, J., & Lancaster, J. (2014). Volumetric MRI differences in treatment naïve and chronically treated adolescents with ADHD-combined type. *Journal of Attention Disorders*, *18*, 511–520. doi:10.1177/1087054712443158

Solanto, M. V., Pope-Boyd, S. A., Tryon, W. W., & Stepak, B. (2009). Social functioning in predominantly inattentive and combined subtypes of children with ADHD. *Journal of Attention Disorders*, *13*, 27–35. doi:10.1177/1087054708320403

Souza, I., Pinheiro, M. A., & Mattos, P. (2005). Anxiety disorders in an attention-deficit/hyperactivity disorder clinical sample. *Arquivos de Neuro-Psiquiatria*, *63*, 407–409. doi:10.1590/S0004-282X2005000300008

Stern, R. G., Petti, T. A., Bopp, K., & Tobia, A. (2009). Aripiprazole for the treatment of schizophrenia with co-occurring social anxiety: An open-label cross-taper study. *Journal of Clinical Psychopharmacology*, *29*, 206–209. doi:10.1097/JCP.0b013e3181a48e12

Strawn, J. R., Wehry, A. M., Chu, W.-J., Adler, C. M., Eliassen, J. C., Cerullo, M. A., … DelBello, M. P. (2013). Neuroanatomic abnormalities in adolescents with generalized anxiety disorder: A voxel-based morphometry study. *Depression and Anxiety*, *30*, 842–848. doi:10.1002/da.22089

Tadori, Y., Forbes, R. A., McQuade, R. D., & Kikuchi, T. (2008). Characterization of aripiprazole partial agonist activity at human dopamine D3 receptors. *European Journal of Pharmacology*, *597*, 27–33. doi:10.1016/j.ejphar.2008.09.008

Tannock, R., Ickowicz, A., & Schachar, R. (1995). Differential effects of methylphenidate on working memory in ADHD children with and without comorbid anxiety. *Journal of the American Academy of Child and Adolescent Psychiatry*, *34*, 886–896. doi:10.1097/00004583-199507000-00012

Taylor, E., & Sonuga-Barke, E. (2008). Disorders of attention and activity. In M. Rutter, E. Taylor, J. S. Stevenson (Eds.), *Rutter's child and adolescent psychiatry* (5th ed). London: Blackwell. 521–542.

Ter-Stepanian, M., Grizenko, N., Zappitelli, M., & Joober, R. (2010). Clinical response to methylphenidate in children diagnosed with attention-deficit hyperactivity disorder and comorbid psychiatric disorders. *The Canadian Journal of Psychiatry*, *55*, 305–312. doi:10.1177/070674371005500506

Vizzini, L., Popovic, M., Zugna, D., Vitiello, B., Trevisan, M., Pizzi, C., … Richiardi, L. (2018). Maternal anxiety, depression and sleep disorders before and during pregnancy, and preschool ADHD symptoms in the NINFEA birth cohort study. *Epidemiology and Psychiatric Sciences*, *18*, 1–11. doi:10.1017/S2045796018000185

Vogel, A. C., Gutmann, D. H., & Morris, S. M. (2017). Neurodevelopmental disorders in children with neurofibromatosis type 1. *Developmental Medicine & Child Neurology*, *59*, 1112–1116. doi:10.1111/dmcn.13526

Waxmonsky, J. (2003). Assessment and treatment of attention deficit hyperactivity disorder in children with comorbid psychiatric illness. *Current Opinion in Pediatrics*, *15*, 476–482. doi:10.1097/00008480-200310000-00006

Willcutt, E. G. (2012). The prevalence of DSM-IV attention-deficit/hyperactivity disorder: A meta-analytic review. *Neurotherapeutics*, *9*, 490–499. doi:10.1007/s13311-012-0135-8

Yoshimasu, K., Barbaresi, W., Colligan, R. C., Voigt, R. G., Killian, J. M., Weaver, A. L., & Katusic, S. K. (2017). Psychiatric comorbidities modify the association between childhood ADHD and risk for suicidality: A population-based longitudinal study. *Journal of Attentions Disorders*, *23*, 777–786. doi:10.1177/1087054717718264

Adverse Drug Reactions Related to Mood and Emotion in Pediatric Patients Treated for Attention Deficit/Hyperactivity Disorder

A Comparative Analysis of the US Food and Drug Administration Adverse Event Reporting System Database

Marco Pozzi, PhD, Carla Carnovale, PharmD,† Faizan Mazhar, BiolD,† Gabriëlla G.A.M. Peeters, MD,† Marta Gentili, PharmD,† Maria Nobile, PhD,* Sonia Radice, PharmD,† and Emilio Clementi, PhD*†*

Abstract:

Background: Attention deficit/hyperactivity disorder (ADHD) can be comorbid with frequent anxiety and mood disorders, as well as emotional symptoms (anxiety, irritability, mood lability). These may also be triggered by drugs and appear as adverse drug reactions (ADRs).

Methods: We mined data from the US Food and Drug Administration Adverse Event Reporting System pharmacovigilance database, focused on methylphenidate, atomoxetine, amphetamine, lisdexamfetamine, and their derivatives. We collected reports of ADRs connected with mood or emotional symptoms in pediatric patients, excluding drug abuse/accidents. Reporting odds ratios (RORs) were calculated and compared between drug classes and children/adolescents.

Results: We collected 6176 ADRs of interest of which 59% occurred in children. Atomoxetine accounted for 50.7% of reports, methylphenidate for 32.5%, lisdexamfetamine for 14.2%, and amphetamine for 2.6%. Irritability, anxiety, obsessive thoughts, depressed mood, and euphoria scored significant RORs for all drugs, overall with an increasing risk from methylphenidate to atomoxetine, lisdexamfetamine, and amphetamine. Apathy regarded mostly atomoxetine, and crying regarded all drugs except methylphenidate. Several age-based differences were found. Notably, affect lability hit only adolescents. All drugs scored significant self-injury RORs, except lisdexamfetamine in adolescents, with an increasing risk from methylphenidate to lisdexamfetamine, atomoxetine, and amphetamine. For suicidality, all drugs had significant RORs in children, and methylphenidate was better than atomoxetine and lisdexamfetamine. In adolescents, only methylphenidate and atomoxetine scored significant RORs.

Conclusions: We conclude that real-world data from the US Food and Drug Administration Adverse Event Reporting System are consistent with previous evidence from meta-analyses. They support a hierarchy of drug safety for several ADRs (except self-injury/suicidality) with methylphenidate as safest, followed by atomoxetine, lisdexamfetamine, and amphetamine last. Self-injury and suicidality RORs were overall higher in children.

Key Words: ADHD, mood, emotion, adverse drug reactions, data mining

(*J Clin Psychopharmacol* 2019;39: 386–392)

From the *Scientific Institute IRCCS Eugenio Medea, Italy; and †Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences L. Sacco, "Luigi Sacco" University Hospital, Università di Milano, Milan, Italy.

Received November 12, 2018; accepted after revision April 23, 2019.

Reprints: Emilio Clementi, PhD, Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, University of Milano, Via GB Grassi 74, 20157 Milan, Italy (e-mail: emilio.clementi@unimi.it).

Marco Pozzi and Carla Carnovale contributed equally to the manuscript.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000001058

Attention deficit/hyperactivity disorder (ADHD) is often associated with comorbid mental disorders[1–4] and with the presence of disturbed emotional regulation.[5] Child and adolescent patients who experience disturbed emotion have a severe reduction in their quality of life; moreover, drug therapies may aggravate them, as shown by recent meta-analyses on adverse events linked with mood and emotions from clinical trial reports. They have shown that anxiety was reduced by stimulants,[6] whereas irritability was reduced in association with methylphenidate treatments but it was increased with amphetamine.[7,8] A recent meta-analysis, on a broad range of adverse events, found methylphenidate to be associated with reduced anxiety and euphoria symptoms; however, it led to increased apathy symptoms and reduced disposition to talk.[8] Treatment with amphetamine derivatives was associated with increased emotional lability.[8] A network meta-analysis evidenced an increased risk of irritability connected with the use of lisdexamfetamine.[9] Atomoxetine has been associated with a nonsignificant increase of suicidality.[10] However, meta-analyses are not yet conclusive, as they are based on adverse events reports from a limited set of clinical trials. This prevents to conduct a comparison for all outcomes of interest, between all drug classes, and is a major limitation of current meta-analyses. In addition, meta-analyses have a high level of evidence quality but may not be optimal to elucidate the mood/emotional impacts of pharmacological therapies. This depends on the fact that clinical trials tend to exclude from enrolment patients with comorbidities that put them at risk or disadvantaged socioeconomic conditions,[11,12] and this is a second major limitation of current data drawn from meta-analyses. Real-life based studies can thus provide valuable information, to complete the evidence from clinical trials and meta-analyses.[13] For example, a recent study on the health care claims showed an absence of causal links between suicidality and actual methylphenidate use. It instead found a link between suicidality and the clinical severity required for methylphenidate prescription.[14] Another useful data source comes from data mining of freely available pharmacovigilance databases: the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) has been successfully used in several studies of this type.[15] A recent analysis of the FAERS has shown how amphetamine use was associated with a 10% reporting rate of adverse drug reactions (ADRs) regarding the affective domain.[16] Pharmacovigilance databases can be more effectively and accurately mined through analyses of reporting disproportionality, that is, by identifying pairs of *ADR-drug* that are reported significantly more than *other ADR-drug* or *ADR-other drug* combinations. Here we used this approach to analyze information in the FAERS, to assess mood and emotional symptoms emerging in connection with drugs used for ADHD pharmacotherapies. In particular, we aimed to find

evidence on adverse events that are not often reported in clinical trials or that may be differently reported in the clinical practice, owing to the influence of comorbid conditions that may constitute exclusion criteria in clinical trials.

METHODS

Data Source

Adverse drug reaction reports from the FAERS database were used for this study. The FAERS database is a passive surveillance system that relies on voluntary reporting of postmarketing suspected ADRs to FDA by health care professionals, consumers, or lawyers, as well as on mandatory reporting by pharmaceutical manufacturers. The FAERS includes spontaneous reports from US sources; serious and unlabeled spontaneous reports from non-US sources; and serious, unlabeled, and attributable postmarketing clinical trial reports from all sources. It contains more than 9 million suspected ADR reports, including all reports from 1969 to the present time. The database is designed in accordance with the international safety reporting guidance issued by the International Conference on Harmonization and updated quarterly. Adverse drug reactions are recorded using the Medical Dictionary for Regulatory Affairs Preferred Terms (PTerms), the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The major limitation of the FAERS (as for all pharmacovigilance databases) is the lack of detailed medical information regarding diagnoses and comorbidities, because the focus is only on the ADRs.

The publicly available STATA (Stata Corp, College Station, TX) compatible files of the FAERS database were downloaded, corresponding to the time frame from the first quarter of year 2004 until the second quarter of year 2017 (https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm082193.htm). Data files of each quarter were combined into a relational database. Key identification fields were validated, and case reports that were missing or contained malformed key identification fields were discarded.

Data Extraction and Processing

Data extraction was focused on individual reports indicating at least a drug of interest (amphetamine, atomoxetine, lisdexamfetamine, methylphenidate) as suspect for an ADR of interest. The extraction included both generic and brand drug names. By this process, we excluded reports that indicated the drugs of interest as *concomitant* or *interacting*. Because FAERS data occasionally contain misspelling and miswords, pattern-matching algorithms were used to capture common drug name misspellings and concatenations. An open source program for cleaning and transforming disordered data, OpenRefine (http://openrefine.org/), was used to standardize drug name variants in the database so that they were consistent with international nonproprietary nomenclature defined by the World Health Organization Anatomical Therapeutic Chemical classification. The ADRs of interest were identified by several steps. All ADRs reported in the FAERS for the suspect drugs were retrieved and sorted by the System-Organ-Class classification. Adverse drug reactions under the System-Organ-Class classification *psychiatric disorders* and *general disorders and administration site conditions* were further examined, to create meaningful groups of PTerms. The grouping process was deemed necessary owing to the heterogeneity in the reported PTerms, as the analysis of single PTerms, for instance, *depression*, *major depression*, and *depressed mood*, would have produced unworkable results. Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/JCP/A577) reports the ADR groups we designed and the PTerms included in each group, in accordance with previous literature.[8,17] Before data mining, duplicate case reports were removed following FDA recommendations, that is, by using the earliest Individual Case Safety Report (ICSR) for the same patient identification number in the same calendar year. Data were processed further to ensure a clinically relevant analysis: all ICSRs indicating drug abuse or misuse were excluded; all ICSRs reporting a patient age less than 6 years (lower prescription age limit) or above 17 years (pediatric focus only), or not reporting patient age, were excluded. The data set was then subdivided in 2 subsets: ICSRs reporting ages 6 to 12 years were included in the children's data set; ICSRs reporting ages 13 to 17 years were included in the adolescents' data set.

Disproportionality Analysis

To identify drug/ADR pairs that were reported more frequently than expected, we used a disproportionality analysis. Reporting odds ratios (RORs) were used as measures of disproportionality, based on a 2×2 contingency table as shown in Supplementary Table 2 (Supplemental Digital Content 2, http://links.lww.com/JCP/A578). To have a statistically significant signal of disproportional reporting, the lower boundary of the 95% 2-sided confidence interval (LB) of a ROR must exceeded 1.[14] Of note, this method is used to filter out observations made only on sporadic events: an insufficient events sample size produces a nonsignificant ROR LB. To compare RORs statistically, beta estimates (ln of the ROR) and the standard error of the ln ROR were computed. Statistical analysis for the difference between RORs was done with a 2-tailed, unpaired Z test. P values corresponding to the comparison were calculated, and a P value of less than 0.05 was considered statistically significant. All statistical analyses were performed by STATA version 14.2.

RESULTS

The ADR groups *staring*, *nail-picking*, and *mutism* were excluded from the analysis because they did not meet the minimum number of reports required (all RORs were not significant). We collected 6176 ADRs of interest, 59% of which regarded children (6–12 years) and 41% regarded adolescents (13–17 years). The drug category most concerned by reports was atomoxetine (50.7%), followed by methylphenidate (32.5%) and then by lisdexamfetamine (14.2%) and amphetamine (2.6%). We report hereafter the results categorized by ADR group (see also Tables 1 and 2).

Irritability

Irritability (Fig. 1A) was reported with significant RORs for all drugs of interest, with an increase from methylphenidate to atomoxetine, lisdexamfetamine, and amphetamine, both in children and adolescents. Significant differences showed lower RORs for methylphenidate versus lisdexamfetamine and higher RORs for amphetamine versus any other drug category. When considering the effect of age on drug RORs, irritability was reported similarly in children and adolescents for methylphenidate and amphetamine, whereas for atomoxetine and lisdexamfetamine RORs were significantly higher in adolescents than in children.

Anxiety

Significant RORs were reported for all drugs also considering anxiety (Fig. 1B), with an age-based difference. In children,

TABLE 1. Reporting Odds Ratio Estimates for the Children Age Category (6–12 Years)

	Methylphenidate			Atomoxetine			Lisdexamphetamine			Amphetamine		
ADR group	**ROR**	**LB**	***P* < 0.05 vs**	**ROR**	**LB**	***P* < 0.05 vs**	**ROR**	**LB**	***P* < 0.05 vs**	**ROR**	**LB**	***P* < 0.05 vs**
Irritability	2.03	1.66	LD, AM	2.27	1.90	AM*	3.09	2.32	MP, AM*	9.58	5.14	All
Anxiety	1.75	1.48	AM*	1.39	1.17	AM	1.40	1.01	AM*	4.42	2.20	All
Obsessive thoughts	3.25	2.30	LD, AT	1.62	1.08	All*	7.24	4.81	MP, AT	9.00	2.81	AT
Apathy	**0.99**	**0.84**	AT	2.51	2.24	MP, LD*	**0.68**	**0.48**	AT*	**1.59**	**0.69**	None
Crying	**0.81**	**0.62**	All	3.21	2.76	MP	3.06	2.33	MP*	3.14	1.26	MP
Depressed mood	1.58	1.32	All	1.92	1.64	MP, AM	2.22	1.68	MP, AM	6.03	3.17	All
Affect lability	**0.01**	**0.01**	LD, AT*	**0.01**	**0.01**	All*	**0.03**	**0.03**	All*	**0.08**	**0.05**	LD, AT*
Euphoria	3.34	2.54	LD	2.59	1.97	AM, LD	9.12	6.72	MP, AT*	7.66	2.78	AT
Self-injury	2.07	1.56	AM, AT	3.73	2.99	MP, AM*	2.77	1.81	AM*	9.21	3.97	All*
Suicidality	2.12	1.80	LD, AT*	2.70	2.35	MP*	3.16	2.49	MP*	2.82	1.22	None*

To be indicative of a significant reporting disproportion, both the ROR and LB must be above 1.00. Bold characters display RORs not indicative of a reporting risk; normal character displays RORs indicative of a reporting risk. For each drug category, the results of statistical tests indicate the other drug categories against which a 2-tailed *Z* test scored a *P* value lower than 0.05.

*Age-based differences: comparisons of the same AE/drug class with adolescents (results in Table 2) in which a 2-tailed *Z* test scored a *P* value lower than 0.05.

MP indicates methylphenidate; AT, atomoxetine; LD, lisdexamphetamine; AM, amphetamine.

amphetamine had RORs higher than other drugs. In adolescents, methylphenidate and atomoxetine had RORs lower than lisdexamfetamine and amphetamine. Considering the effect of age on RORs, methylphenidate was worse in children and lisdexamfetamine in adolescents.

Obsessive Thoughts

Obsessive thoughts (Fig. 1C) were also reported with significant RORs for all drugs of interest. In children, atomoxetine was significantly the best of all analyzed drugs, followed by methylphenidate that was better than lisdexamfetamine and by amphetamine (no significant difference). In adolescents, methylphenidate was significantly better than lisdexamfetamine and amphetamine, whereas atomoxetine was intermediate. When considering the effect of age on drug RORs, atomoxetine was worse in adolescents.

Apathy

Regarding apathy, a significant ROR was reported in children only for atomoxetine, which was statistically worse than methylphenidate and lisdexamfetamine (Fig. 1D). In adolescents, only atomoxetine and lisdexamfetamine showed significant RORs, statistically worse than that of methylphenidate. The effect of age on drug RORs was neat for lisdexamfetamine, holding a significant ROR only in adolescents. Atomoxetine was worse in children.

Crying

Crying was reported with significant RORs for all drugs of interest except methylphenidate (Fig. 1E), which consequently resulted to have significantly lower RORs than any other drug. In children, other drugs displayed similar RORs. In adolescents, the ROR of amphetamine was higher than that of lisdexamfetamine.

TABLE 2. Reporting Odds Ratio Estimates for the Adolescent Age Category (13–17 Years)

	Methylphenidate			Atomoxetine			Lisdexamphetamine			Amphetamine		
ADR group	**ROR**	**LB**	***P* < 0.05 vs**	**ROR**	**LB**	***P* < 0.05 vs**	**ROR**	**LB**	***P* < 0.05 vs**	**ROR**	**LB**	***P* < 0.05 vs**
Irritability	2.10	1.59	All	3.52	2.82	All*	5.43	3.86	All*	12.89	6.91	All
Anxiety	1.32	1.08	AM, LD*	1.39	1.15	AM, LD	2.58	1.93	MP, AT*	2.99	1.48	MP, AT
Obsessive thoughts	2.46	1.57	LD, AM	2.87	1.91	None*	5.16	2.87	MP	8.64	2.70	MP
Apathy	**1.16**	**0.96**	LD, AT	2.20	1.90	MP*	1.74	1.28	MP*	**1.54**	**0.67**	None
Crying	**0.60**	**0.33**	All	3.21	2.43	MP	2.28	1.25	MP, AM*	7.35	2.95	MP, LD
Depressed mood	1.85	1.56	LD	1.75	1.48	AM, LD	2.67	2.02	MP, AT	3.52	1.85	AT
Affect lability	1.37	1.11	AM, AT*	2.00	1.68	MP, AM*	1.74	1.22	AM*	8.57	5.07	All*
Euphoria	3.12	2.30	LD	2.27	1.62	LD	6.36	4.24	MP, AT*	6.38	2.32	None
Self-injury	1.70	1.28	AM, AT	2.56	2.02	MP, LD*	**1.31**	**0.72**	AM, AT*	5.17	2.24	MP, LD*
Suicidality	1.43	1.25	AM*	1.72	1.52	LD, AM*	**1.22**	**0.92**	AT*	**0.85**	**0.37**	MP, AT*

To be indicative of a significant reporting disproportion, both the ROR and LB must be above 1.00. Bold characters display RORs not indicative of a reporting risk; normal character displays RORs indicative of a reporting risk. For each drug category, the results of statistical tests indicate the other drug categories against which a 2-tailed *Z* test scored a *P* value lower than 0.05.

*Age-based differences: comparisons of the same AE/drug class with children (results in Table 1) in which a 2-tailed *Z* test scored a *P* value lower than 0.05.

MP indicates methylphenidate; AT, atomoxetine; LD, lisdexamphetamine; AM, amphetamine.

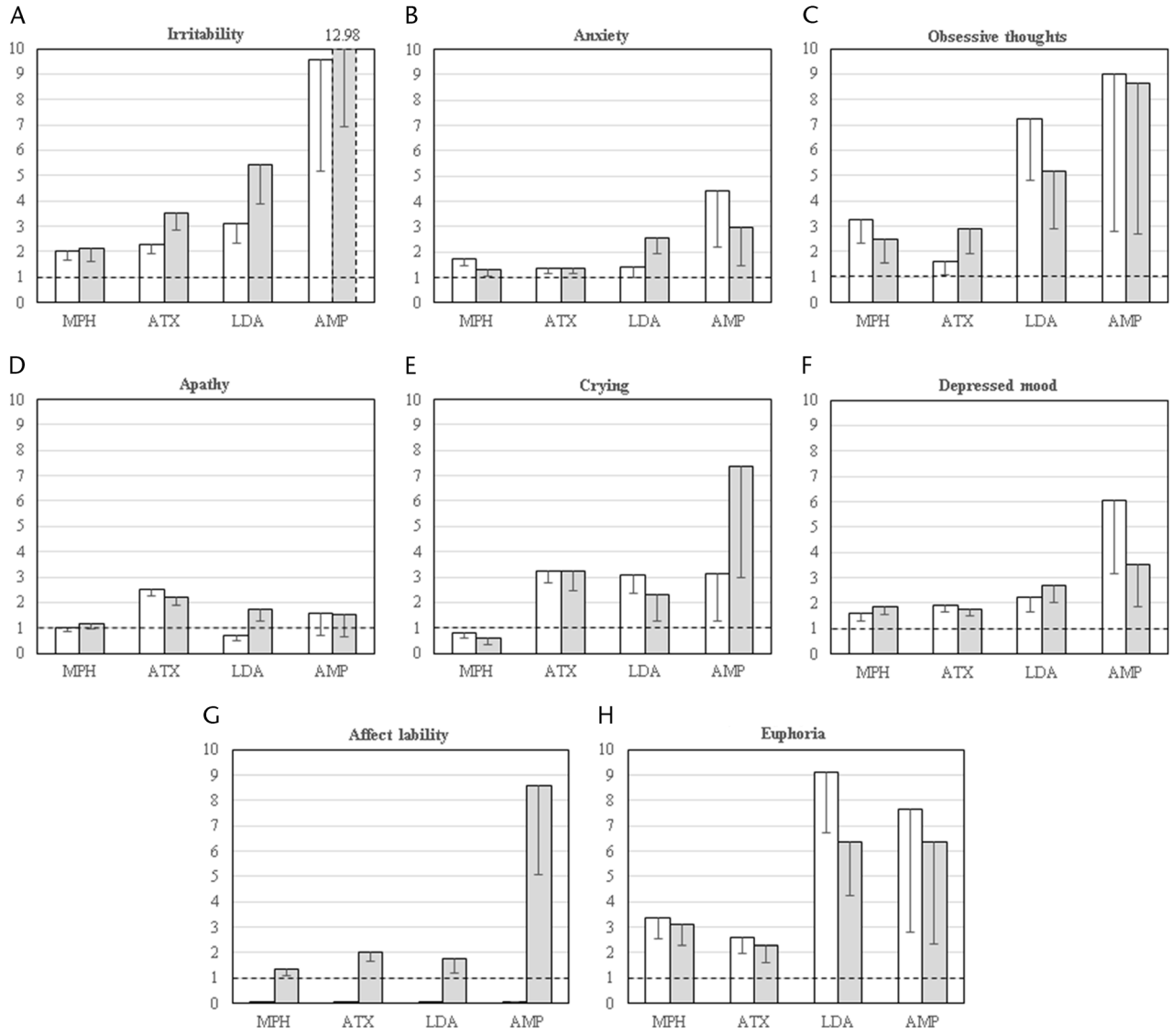

FIGURE 1. Reporting odds ratios for the first eight ADR groups, across different drug groups. Vertical axis shows the number corresponding to each ROR; error bars indicate lower boundaries of the 95% confidence intervals. Dotted lines indicate ROR equal to 1, which is the significance threshold; therefore, bars that surpass the dotted line represent significant RORs. White bars represent the RORs regarding children, and gray bars represent the RORs regarding adolescents. MPH indicates methylphenidate; ATX, atomoxetine; LDX, lisdexamfetamine; AMP, amphetamine.

Considering the effect of age on drug RORs, LDX was worse in children. Methylphenidate was also worse in children, albeit still having a nonsignificant ROR.

Depressed Mood

Depressed mood was reported with significant RORs for all drugs of interest, with different patterns (Fig. 1F). Considering RORs in children, methylphenidate was at the significantly best end and amphetamine at the significantly worst, whereas atomoxetine and lisdexamfetamine were in the middle. In adolescents, a different picture was seen, with an ascending ROR order: atomoxetine (best) similar to methylphenidate and then amphetamine similar to lisdexamfetamine (worst). Significant differences emerged between atomoxetine and amphetamine/lisdexamfetamine, and lisdexamfetamine and atomoxetine/methylphenidate. No difference emerged between children and adolescents.

Affect Lability

Significant RORs for affect lability were only reported in adolescent patients (Fig. 1G). The RORs of atomoxetine were worse than those of methylphenidate and lisdexamfetamine, and those of amphetamine were worse than all others.

Euphoria

Euphoria was reported with significant RORs for all drugs of interest, increasing from atomoxetine to methylphenidate, amphetamine, and lisdexamfetamine (Fig. 1H). Statistical differences were found in children between atomoxetine, better than amphetamine

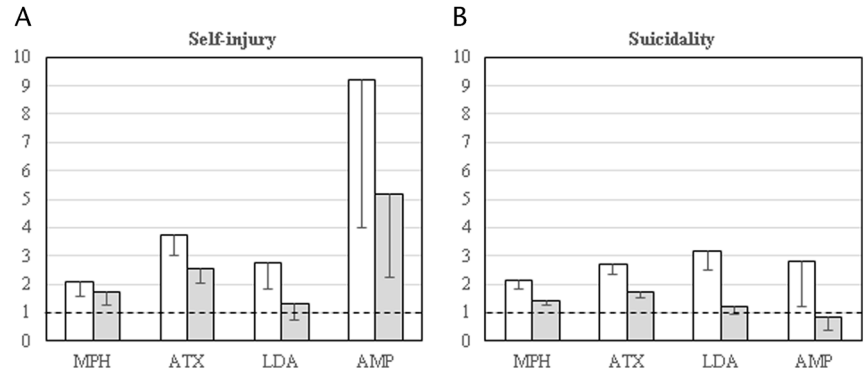

FIGURE 2. Reporting odds ratios for the ADR groups self-injury and suicidality, across different drug groups. Vertical axis shows the number corresponding to each ROR; error bars indicate lower boundaries of the 95% confidence intervals. Dotted lines indicate ROR equal to 1, which is the significance threshold; therefore, bars that surpass the dotted line represent significant RORs. White bars represent the RORs regarding children, and gray bars represent the RORs regarding adolescents. MPH indicates methylphenidate; ATX, atomoxetine; LDX, lisdexamfetamine; AMP, amphetamine.

and lisdexamfetamine, and methylphenidate, better than lisdexamfetamine only. In adolescents, the difference between atomoxetine and methylphenidate was not conserved: atomoxetine and methylphenidate were safer than lisdexamfetamine. Regarding the effect of age on drug RORs, lisdexamfetamine was worse in children.

Self-Injury

All drugs of interest were reported with significant RORs for self-injury, except for lisdexamfetamine in adolescents (Fig. 2A). In children, they increased from methylphenidate, to lisdexamfetamine, atomoxetine, amphetamine, with significant differences between methylphenidate and atomoxetine, amphetamine, and between lisdexamfetamine and amphetamine. In adolescents, both methylphenidate and lisdexamfetamine were better than both atomoxetine and amphetamine. Considering the effect of age, self-injury RORs were higher in children for all drug categories except methylphenidate.

Suicidality

All drugs of interest were reported with significant RORs for suicidality in children; only methylphenidate and atomoxetine had significant RORs in adolescents (Fig. 2B). In children, methylphenidate was better than atomoxetine and lisdexamfetamine, whereas amphetamine did not differ significantly owing to high variability. In adolescents, lisdexamfetamine and amphetamine did not score significant RORs, being respectively better than atomoxetine and atomoxetine/methylphenidate. Regarding the effect of age on drug RORs, suicidality was higher in children for all drug categories.

DISCUSSION

We observed that, in most cases, all of the drugs used to treat ADHD that we have investigated increased the reporting rate of ADRs connected with mood and emotion disturbances, producing significant RORs. This result may derive from the widespread presence of comorbidities involving mood and emotion disorders in patients with ADHD.[1–4] Consequently, negative findings acquire prominence and shall be discussed first. It is important to note that there were almost no reports of affect lability in children, whereas it is affected in adolescents. This is consistent with the observations of a beneficial effect of methylphenidate treatment on the affect lability of children[18] and the relevance of affect lability in patients who retained ADHD into the young adulthood.[19] Results regarding the higher reporting disproportion of emotional lability with amphetamine were also found to be consistent with a recent meta-analysis.[8] Other negative findings regarded apathy, which was disproportionately reported only for atomoxetine in children and adolescents, and for lisdexamfetamine in adolescents. This result was not consistent with the increased risks of apathy with methylphenidate, recently shown by a meta-analysis,[8] although the present level of evidence from FAERS is not strong enough to confront with a meta-analytic result. Among ADR groups that were most disproportionately reported, results on irritability deserve special mention, as they may relate closely with therapeutic efficacy. It is important to note that FAERS data suggest methylphenidate having the smallest ROR for irritability, a finding consistent with its protective effect against irritability, as reported in meta-analyses.[7,8] The same FAERS data also suggest a detrimental effect of amphetamine, which was also shown in a meta-analysis.[8] A clinically useful inference from these pharmacovigilance data is that they support current treatment guidelines,[20] which consider methylphenidate as a first-line medication and atomoxetine as a second-line medication, whereas amphetamines, which scored higher RORs for irritability, are not indicated for ADHD in several countries, for safety reasons. Similarly, also anxiety showed the lowest reporting proportion with methylphenidate, as observed in meta-analyses[6,8] and with atomoxetine, whereas amphetamine data showed an increased reporting proportion, in accordance with another previous meta-analysis,[21] further supporting the hypothesis of a safety hierarchy consistent with international prescription guidelines. We also found disproportionate reporting rates similar across drug groups for depressed mood and crying. Regarding obsessive thoughts and euphoria, both amphetamine and lisdexamfetamine were in general more disproportionately reported, as compared with low reporting proportions for methylphenidate and atomoxetine, once again suggesting that these may be safer than amphetamine derivatives. No previous observations are available in the literature on such aspects, although hypothetically a dopaminergic boost may sustain both obsessive/repetitive[22] and euphoric/delusive thoughts. The 2 ADR categories of self-injury and suicidality deserve a separate evaluation in view of their clinical relevance. Self-injury showed the most disproportionate reporting with atomoxetine and amphetamine, whereas suicidality was most disproportionately reported with atomoxetine. This result seems to be consistent with the presence of a black box warning for atomoxetine and with a warning for amphetamine, both of them regarding self-injury and suicidality. Self-injury and suicidality were in general reported more disproportionately among children than adolescents. This finding is

again consistent with the previous observation that self-injury and suicidality in adolescents are becoming increasingly associated with the need of pharmacotherapy (resulting from the morbidity status and/or patient-specific characteristics), rather than with pharmacological effects.[8,11] Our present results support the notion that children, differently from adolescents, are influenced by pharmacological actions, as all drugs used to treat ADHD that we examined appeared to increase the RORs of self-injury and suicidality in children.

Limitations

This work was carried out based on data from the FAERS database: there is no guarantee against selective reporting and/or underreporting. However, because the database is independent, no specific bias regarding the aims of this study can be hypothesized.[13,15] Another issue was a lack of power to calculate the RORs of infrequent ADRs, which indeed happened for the ADR groups *staring*, *nail-picking,* and *mutism*. The use of a vast database such as the FAERS (the data set we used for this work counted more than 5 million unique reports) was intended to minimize such issues but did not serve the purpose for all ADRs. In addition, reports on amphetamine were infrequent as compared with the others, an issue that resulted in a loss of statistical significance in most comparisons made against amphetamine. It must be remembered, however, that when RORs are significant, they are indeed valid despite the seemingly high or low number of reports. Comparisons between drug classes, even with a sizable difference in the number of reports, are technically valid. From a clinical point of view, it can be difficult to generalize observations made from less than 200 reports, such as in the case of amphetamine, but pharmacovigilance databases cannot provide alternative solutions. When appraising the increased risks connected with almost all drug and ADR pairs, it must also be considered that spontaneous postmarketing ADR reports are not subject to a strict analysis of causal attribution, which is instead the case with individual case safety reports from clinical trials. Therefore, the ADRs we analyzed in this work might also be comorbid features of ADHD that were not properly diagnosed. This confounding factor cannot be formally assessed in the present work, as the FAERS database does not include data on codiagnoses. However, the calculation of RORs also takes into account the number of reports of ADRs of interest caused by drugs not of interest, which should minimize the effects of uncertain causal attribution.

Clinical Relevance

We report for the first time that real-world data from the FAERS pharmacovigilance database are consistent with previous evidence from meta-analyses on mood and emotional disturbances attributed to pharmacotherapies for ADHD. Our findings thus support a hierarchy of drug safety regarding several outcomes (except self-injury/suicidality) that puts methylphenidate in the safest position, followed by atomoxetine, lisdexamfetamine, and lastly amphetamine. With respect to ADRs regarding self-injury and suicidality, we confirm what is already known on the risks connected with the use of atomoxetine and amphetamine. Further systematic assessments of mood and emotional disturbances/symptoms are needed, possibly in the context of large-scale observational studies of neuropsychiatric rehabilitation settings, which can reflect the actual conditions of use of drugs prescribed for ADHD.

AUTHOR DISCLOSURE INFORMATION

All authors declare that they have no conflicts of interest regarding the subject of this work. This work was supported by the Regional Centre of Pharmacovigilance of Lombardy (to E.C.), the Italian Medicines Agency—Agenzia Italiana del Farmaco (to E.C.), and the Italian Ministry of Health (Ricerca Corrente 2018, to M.P. and M.N.) which are gratefully acknowledged. The funding public institutions had no role in any part of the work.

REFERENCES

1. Anderson JC, Williams S, McGee R, et al. DSM-III disorders in preadolescent children. Prevalence in a large sample from the general population. *Arch Gen Psychiatry*. 1987;44:69–76.
2. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163:716–723.
3. Kunwar A, Dewan M, Faraone SV. Treating common psychiatric disorders associated with attention-deficit/hyperactivity disorder. *Expert Opin Pharmacother*. 2007;8:555–562.
4. Tzang RF, Chang YC. Behavior problems and subtypes of attention-deficit hyperactivity disorder with comorbidities. *Kaohsiung J Med Sci*. 2009;25:530–536.
5. Shaw P, Stringaris A, Nigg J, et al. Emotion dysregulation in attention deficit hyperactivity disorder. *Am J Psychiatry*. 2014;171:276–293.
6. Coughlin CG, Cohen SC, Mulqueen JM, et al. Meta-analysis: reduced risk of anxiety with psychostimulant treatment in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2015;25:611–617.
7. Stuckelman ZD, Mulqueen JM, Ferracioli-Oda E, et al. Risk of irritability with psychostimulant treatment in children with ADHD: a meta-analysis. *J Clin Psychiatry*. 2017;78:e648–e655.
8. Pozzi M, Carnovale C, Peeters GGAM, et al. Adverse drug events related to mood and emotion in paediatric patients treated for ADHD: a meta-analysis. *J Affect Disord*. 2018;238:161–178.
9. Padilha SCOS, Virtuoso S, Tonin FS, et al. Efficacy and safety of drugs for attention deficit hyperactivity disorder in children and adolescents: a network meta-analysis. *Eur Child Adolesc Psychiatry*. 2018;27:1335–1345.
10. Bangs ME, Wietecha LA, Wang S, et al. Meta-analysis of suicide-related behavior or ideation in child, adolescent, and adult patients treated with atomoxetine. *J Child Adolesc Psychopharmacol*. 2014;24:426–434.
11. Pozzi M, Radice S, Clementi E, et al. Antidepressants and, suicide and self-injury: causal or casual association? *Int J Psychiatry Clin Pract*. 2016;20:47–51.
12. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;297:1683–1696.
13. Gentili M, Pozzi M, Peeters G, et al. Review of the methods to obtain paediatric drug safety information: spontaneous reporting and healthcare databases, active surveillance programmes, systematic reviews and meta-analyses. *Curr Clin Pharmacol*. 2018;13:28–39.
14. Man KKC, Coghill D, Chan EW, et al. Association of risk of suicide attempts with methylphenidate treatment. *JAMA Psychiat*. 2017;74:1048–1055.
15. Sakaeda T, Tamon A, Kadoyama K, et al. Data mining of the public version of the FDA Adverse Event Reporting System. *Int J Med Sci*. 2013;10:796–803.
16. Marimuthu SP, Iyer G, Segal JB, et al. Patient-relevant outcomes associated with generic tamsulosin, levothyroxine and amphetamine in the FDA Adverse Event Reporting System: a pilot study. *J Comp Eff Res*. 2017;6:437–447.
17. Lee J, Grizenko N, Bhat V, et al. Relation between therapeutic response and side effects induced by methylphenidate as observed by parents and teachers of children with ADHD. *BMC Psychiatry*. 2011;11:70.
18. Winters DE, Fukui S, Leibenluft E, et al. Improvements in irritability with open-label methylphenidate treatment in youth with comorbid attention

deficit/hyperactivity disorder and disruptive mood dysregulation disorder. *J Child Adolesc Psychopharmacol*. 2018;28:298–305.

19. Hirsch O, Chavanon M, Riechmann E, et al. Emotional dysregulation is a primary symptom in adult attention-deficit/hyperactivity disorder (ADHD). *J Affect Disord*. 2018;232:41–47.
20. Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128:1007–1022.
21. Punja S, Shamseer L, Hartling L, et al. Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev*. 2016;CD009996.
22. Borcherding BG, Keysor CS, Rapoport JL, et al. Motor/vocal tics and compulsive behaviors on stimulant drugs: is there a common vulnerability? *Psychiatry Res*. 1990;33:83–94.

Neuropsychiatric Disease and Treatment

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Effects of melatonin in children with attention-deficit/hyperactivity disorder with sleep disorders after methylphenidate treatment

This article was published in the following Dove Medical Press journal:
Neuropsychiatric Disease and Treatment

Gabriele Masi[1]
Pamela Fantozzi[1]
Arianna Villafranca[1]
Annalisa Tacchi[1]
Federica Ricci[1]
Laura Ruglioni[1]
Emanuela Inguaggiato[1]
Chiara Pfanner[1]
Samuele Cortese[2]

[1]IRCCS Stella Maris, Scientific Institute of Child Neurology and Psychiatry, Calambrone, Pisa, Italy; [2]Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK

Purpose: Methylphenidate (MPH), the first-line medication in children with attention-deficit/hyperactivity disorder (ADHD), is associated with increased risk of sleep disorders. Melatonin has both hypnotic and chronobiotic properties that influence circadian rhythm sleep disorders. This study explores the effectiveness of melatonin in children with ADHD who developed sleep problems after starting MPH.

Patients and methods: This study, based on a clinical database, included 74 children (69 males, mean age 11.6±2.2 years) naturalistically treated with MPH (mean dosage 33.5±13.5 mg/d). The severity of sleep disorder (sleep onset delay) was recorded at baseline and after a follow-up of at least 4 weeks using a seven-point Likert scale according to the Clinical Global Impression Severity score. Effectiveness of melatonin on sleep (mean dosage 1.85±0.84 mg/d) after 4 weeks was assessed using a seven-point Likert scale according to the Clinical Global Impression Improvement (CGI-I) score, and patients who scored 1 (very much improved) or 2 (much improved) were considered responders.

Results: Clinical severity of sleep disorders was 3.41±0.70 at the baseline and 2.13±1.05 after the follow-up ($P<0.001$). According to the CGI-I score, 45 patients (60.8%) responded to the treatment with melatonin. Gender and age (children younger and older than 12 years) did not affect the response to melatonin on sleep. Patients with or without comorbidities did not differ according to sleep response. Specific comorbidities with disruptive behavior disorders (oppositional defiant disorder or conduct disorder), affective (mood and anxiety) disorders and learning disabilities did not affect the efficacy of melatonin on sleep. Treatment was well tolerated, and no side effects related to melatonin were reported.

Conclusion: In children with ADHD with sleep problems after receiving MPH treatment, melatonin may be an effective and safe treatment, irrespective of gender, age and comorbidities.

Keywords: attention–deficit/hyperactivity disorder, sleep disorders, children, melatonin, methylphenidate

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder.[1] According to the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (*DSM-5*),[2] ADHD is characterized by a persistent and impairing pattern of inattention and/or hyperactivity/impulsivity. A large body of evidence shows that ADHD is often comorbid with other psychiatric conditions, such as oppositional defiant disorder/conduct disorder, specific learning disorders, mood and anxiety disorders.[3]

Correspondence: Gabriele Masi
IRCCS Stella Maris, Scientific Institute of Child Neurology and Psychiatry, Viale del Tirreno 331A, 56025 Calambrone, Pisa, Italy
Tel +39 05 088 6111
Fax +39 05 088 6301
Email gabriele.masi@fsm.unipi.it

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/NDT.S193891

Available treatments for ADHD include pharmacological and non-pharmacological strategies (including parent training programs and cognitive training). Pharmacological treatments are an important element of the multimodal therapeutic strategy for ADHD and are recommended as the first choice option in several guidelines/practice parameters, at least for severe cases,[4–6] or as a treatment strategy for patients who have not responded to non-pharmacological interventions.[5,6] Commonly used medications for ADHD include psychostimulants, namely methylphenidate (MPH), amphetamines and non-psychostimulant drugs (eg, atomoxetine or guanfacine).

One of the most common adverse effects during treatment with MPH is disruption of sleep patterns, including bedtime resistance, sleep-onset difficulties, night awakenings, difficulties with morning awakening, with secondary daytime sleepiness, "difficulty falling asleep" being the most frequently reported sleep disorder.[7] Although this effect is often transitory (limited to the first weeks of treatment) in a number of children treated with MPH, in others it is persistent, which leads to stop a treatment that is otherwise effective for ADHD core symptoms.[7]

Melatonin is an endogenously produced indoleamine secreted by the pineal gland usually during darkness; its secretion is suppressed by light. Melatonin plays a key role in regulating the circadian rhythm[8] and has many other biological functions, including chronobiotic and antioxidant properties, anti-inflammatory effects and free radical scavenging.[9,10] Additionally, melatonin regulates the vigilance states depending on the activated melatonin receptors (MT1, MT2 or both), whereby MT2 and MT1 receptors are mainly involved in NREM and REM sleep, respectively.[11]

Several studies have demonstrated that melatonin has both hypnotic and chronobiotic properties[12] that influence circadian rhythmicity and affect circadian rhythm sleep disorders.[13] Because of these properties, melatonin can improve sleep-wake rhythm disturbances and decrease sleep latency in children with sleep disorders.[14] Indeed, it is one of the most commonly used drugs for sleep problems in infants, children and adolescents, in particular those with neurodevelopmental disorders.[15]

Proof of the efficacy of melatonin in sleep latency and sleep duration in ADHD children has been supported by observational studies.[16] Mohammadi et al[17] explored the efficacy of melatonin in children with ADHD receiving MPH in a placebo-controlled study. This study reported a positive effect of melatonin (3–6 mg/d) on sleep latency and overall sleep disturbances, without effects on ADHD measures.

This study aimed at assessing the effectiveness of melatonin in children and adolescents with ADHD who developed a sleep problem after receiving MPH treatment (at the target clinical dose). Gender, age (pre- and post-pubertal children) and comorbidities were explored as possible elements associated with lesser effectiveness on melatonin.

Methods

Participants and procedures

This naturalistic study is based on a clinical database of 74 consecutive patients with ADHD, treated with a monotherapy of MPH (10 immediate release and 64 sustained release) (mean dosage 33.5±13.5 mg/d), who presented sleep problems (difficulty in falling asleep at bedtime, with a significant sleep onset delay), after starting stimulant treatment. Although sleep habits or difficulties were not specifically explored before starting MPH, clinically relevant sleep problems were not reported by parents in the pre-treatment clinical assessment and in the medical reports. This sample was derived from a larger cohort of about 600 consecutive youths screened and treated for ADHD in our unit for pharmacological treatments in ADHD. The diagnosis of ADHD was made at the end of the diagnostic procedure, which included a structured clinical interview according to *DSM-4* criteria, the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al[18]) as well as the Conners' Parent (27 items rated by the parents) and Teacher Rating Scales-Revised: Short Form (28 items rated by the teachers).[19] (Italian versions of the K-SADS-PL,[20] CPRS-R:S and CTRS-R:S[21] are available.)

All the patients were naturalistically treated with add-on melatonin as a sleep inductor. The melatonin was used as usual in our clinical practice; information about the efficacy and tolerability of the medication was included in the medical reports; and this study is based on these reports. According to the Italian Regulatory Agency for Medications indications, the suggested dose of melatonin for sleep disorders in youth is one milligram at bedtime, and the preparations available in Italy are marketed accordingly. For this reason, starting dose was one milligram after dinner (around 8–9 pm, about 1–2 hours before bedtime), with possible increases of 0.5 mg every week, up to 5 mg/d, according to clinical needs (mean dosage 1.85±0.84 mg/d). The duration of the treatment was at least 4 weeks, with a maximum duration of 12 months, based on clinical outcomes. Twelve patients (16.2%) received a co-treatment with a behavioral psychotherapy aimed to improve cognitive, behavioral and emotional self-regulation.

The severity of the sleep disorder was recorded at baseline by a seven-point Likert scale according to the Clinical Global Impression Severity (CGI-S) score, based on

parents' reports.[20] The patients were followed up according to a scheduled program for patients with ADHD receiving medications, with monthly visits, and the first assessment of sleep problems was 1 month after starting melatonin. Efficacy of melatonin on sleep was assessed using a seven-point Likert scale according to the Global Impression Improvement (CGI-I) score[22] (patients with a score 1 – very much improved, or 2 – much improved, were considered responders), based on parents' reports.

All patients and their families participated voluntarily in the study after written informed consent was obtained for assessment and treatment procedures. The institutional review board of the Scientific Institute Stella Maris (Pisa) approved the study in accordance with the Declaration of Helsinki.

Statistical analyses

Subjects were compared using chi-square analysis on categorical variables and paired *t*-test on continuous variables, setting significance at 0.05 level, two tailed.

Results

Clinical severity at the baseline according to CGI-S was 3.41±0.70, after the follow-up 2.13±1.05 (paired *t*-test 12.2 (74), $P<0.001$). Clinical improvement according to CGI-I was 2.35±1.01. According to a CGI-I 1 (very much improved) or 2 (much improved), 45 patients (60.8%) were considered responders.

Sixty-nine males and five females were compared according to response to melatonin, and all the five females (100%) (dose 1.8±0.8 mg/d) and 40 out of 69 males (58.0%) (dose 1.9±0.8 mg/d) were responders (χ^2=1.9 (1), *P*=ns).

When age of the patients was considered, pre-pubertal children younger than 12 years were 42, of whom 27 (64.3%) responded to melatonin (1.6±0.7 mg/d), whereas adolescents older than 12 were 32, of whom 18 (57.2%) were responders to melatonin (2.1±1 mg/d) (χ^2=0.2 (1), *P*=ns).

When comorbidities were considered, patients without comorbidities were 16, of whom 12 (75%) responded to melatonin (dose 1.7±0.8 mg/d), whereas patients with any comorbidity were 58, of whom 33 (56.9%) were responders (dose 1.9±0.9 mg/d) (χ^2=1.0 (1), *P*=ns).

When specific comorbidities were considered, 34 patients presented an ODD/CD comorbidity, of whom 20 (58.8%) were responders to melatonin (1.9±0.8 mg/d), and 40 patients did not present such comorbidity, of whom 25 (62.5%) being responders to melatonin (1.8±0.9 mg/d) (χ^2=0.007 (1), *P*=ns).

Nineteen patients presented an affective (mood and/or anxiety) comorbidity, of whom 12 (63.2%) responded to melatonin (dose 1.9±1.1 mg/d), and 55 did not present such comorbidity, of whom 33 (60%) were responders to melatonin (dose 1.8±0.7 mg/d) (χ^2=0.001 (1), *P*=ns).

Finally, 19 patients presented a comorbid learning disability, of whom 9 (47.4%) were responders to melatonin (dose 1.7±0.7 mg/d), whereas 55 did not present learning disabilities, of whom 36 (65.5%) were non-responders (dose 1.9±0.9 mg/d) (χ^2=1.3 (1), *P*=ns).

Discussion

Although MPH is the gold standard among the treatments for ADHD symptom, one of the most common AEs during treatment with MPH is disruption of sleep patterns, sometimes persistent and impairing. Melatonin can improve sleep–wake rhythm disturbances and decrease sleep latency in children with sleep disorders.

In this study, we aimed to explore the efficacy of melatonin in ADHD patients treated with MPH who developed sleep problems after starting MPH treatment to control ADHD symptoms. According to our findings, melatonin was effective in improving sleep problems in 60.8% of the patients. The efficacy was similar in males and females and in children when compared to adolescents. Furthermore, the comorbidities, frequently occurring in youth with ADHD, did not affect the efficacy of melatonin. Finally, melatonin was well tolerated, and no side effects were reported during the follow-up.

This naturalistic study has several important limitations. The most important is that we used CGI-I as an outcome measure, not a specific measure of sleep disorder severity and improvement. The lack of other methods, such as previously validated questionnaires, sleep diary and actigraphy, limits the reliability of the results. However, the methodology of reassessment of the patients, using clinical global impression in the scheduled visits (usually every month), is consistent with the naturalistic design of the study and with the routinary clinical care in the real life. Another limitation is the lack of specific information about the sleep habits before starting MPH. However, clinically significant sleep problems were not reported by parents in the first clinical reports, but only after starting stimulant treatment.

However, CGI-I is the criterion according to which usually clinicians decide treatment strategies, ie, to continue or change a pharmacotherapy. Another limitation is that, based on Italian Regulatory Agency for Medications indications, the suggested dose of melatonin for sleep disorders in youth is one milligram at bedtime, and the preparations available in Italy are marketed accordingly. The use of relatively low doses of medications in our patients may have reduced the efficacy of the treatment. However, an observational,

naturalistic study suggested that in children with different neurodevelopmental disorders about two-third of the patients responded to relatively medium doses (2.5–6 mg/d), whereas doses above 6 mg added further benefit only in a small percentage of children.[23]

A strength of this study is that it is based on a consecutive, unselected sample of children naturalistically treated, with few exclusion criteria (except for intellectual disability, autism spectrum disorders and schizophrenia). Most comorbid conditions, which are the rule in clinical settings but are often excluded in controlled trials, were included in the study, increasing the applicability of the study to clinical practice.

Although sleep disturbances associated with ADHD have been neglected in the past, there is now an increasing interest on this topic,[24] since: 1) sleep disturbances may be a source of distress for the child and the family; 2) sleep problems may worsen ADHD symptoms as well as associated emotional disorders; 3) quantitative or qualitative alterations of sleep may cause problems with mood, attention and behavior, and 4) sleep disturbances may mimic ADHD symptoms in children misdiagnosed with ADHD. For these reasons, sleep disorders may represent a target of intervention in all the children with ADHD, both receiving or not receiving stimulant treatments.

Acknowledgment

This research was supported by a donation from Humana Italia SpA to the IRCCS Stella Maris.

Disclosure

GM was in an advisory board for Angelini, has received research grants from Lundbeck, FB Health, and Humana Italia, and has been a speaker for FB Health and Otsuka. SC declares reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH), a non-profit organization, in relation to lectures delivered for ACAMH, and from the Healthcare Convention for Educational Activity on ADHD. The authors report no other conflicts of interest in this work.

References

1. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol*. 2014;43(2):434–442.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
3. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet*. 2005;366(9481):237–248.
4. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894–921.
5. National Institute for Health and Care Excellence [webpage on the Internet]. Attention deficit hyperactivity disorder CG72; 2008. Available from: http://www.nice.org.uk/CG72. Accessed March 1, 2018.
6. Taylor E, Dopfner M, Sergeant J, et al. European clinical guidelines for hyperkinetic disorder ? first upgrade. *Eur Child Adolesc Psychiatry*. 2004;13(S1):17–30.
7. Cortese S, Holtmann M, Banaschewski T, et al. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry*. 2013;54(3):227–246.
8. Gordon N. The therapeutics of melatonin: a paediatric perspective. *Brain Dev*. 2000;22(4):213–217.
9. Mauriz JL, Collado PS, Veneroso C, Reiter RJ, González-Gallego J. A review of the molecular aspects of melatonin's anti-inflammatory actions: recent insights and new perspectives. *J Pineal Res*. 2013;54(1):1–14.
10. Porfirio MC, Gomes de Almeida JP, Stornelli M, Giovinazzo S, Purper-Ouakil D, Masi G. Can melatonin prevent or improve metabolic side effects during antipsychotic treatments? *Neuropsychiatr Dis Treat*. 2017;13:2167–2174.
11. Comai S, Ochoa-Sanchez R, Gobbi G. Sleep-wake characterization of double MT_1/MT_2 receptor knockout mice and comparison with MT_1 and MT_2 receptor knockout mice. *Behav Brain Res*. 2013;243:231–238.
12. Wirz-Justice A, Armstrong SM. Melatonin: nature's soporific? *J Sleep Res*. 1996;5(2):137–141.
13. van Geijlswijk IM, Korzilius HP, Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. *Sleep*. 2010;33(12):1605–1614.
14. Appleton RE, Gringras P. Melatonin: helping to mend impaired sleep. *Arch Dis Child*. 2013;98(3):216–217.
15. Hartz I, Furu K, Bratlid T, Handal M, Skurtveit S. Hypnotic drug use among 0–17 year olds during 2004–2011: a nationwide prescription database study. *Scand J Public Health*. 2012;40(8):704–711.
16. Anand S, Tong H, Besag FMC, Chan EW, Cortese S, Wong ICK. Safety, tolerability and efficacy of drugs for treating behavioural insomnia in children with attention-deficit/hyperactivity disorder: a systematic review with methodological quality assessment. *Pediatr Drugs*. 2017;19(3):235–250.
17. Mohammadi MR, Mostafavi SA, Keshavarz SA, et al. Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: a randomized double blind clinical trial. *Iran J Psychiatry*. 2012;7(2):87–92.
18. Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age Children-Present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980–988.
19. Conners CK. *Conners' Rating Scales: Revised Technical Manual*. Multi-Health Systems Inc ed. NY: North Tonawanda; 1997.
20. Kaufman J, Birmaher B, Rao U, Ryan N. *Test K-SADS-PL – Intervista diagnostica per la valutazione dei disturbi psicopatologici in bambini e adolescenti*. Trento: Erikson; 2004.
21. Nobile M, Alberti B, Zuddas A. *Conners' Rating Scales-Revised-Italian Version*. Giunti OS. ed; 2007.
22. Guy W. *ECDEU Assessment Manual for Psychopharmacology, revised*. Rockville, MD: US Department of Health, Education and Welfare; 1976.
23. Ayyash HF, Preece P, Morton R, Cortese S. Melatonin for sleep disturbance in children with neurodevelopmental disorders: prospective observational naturalistic study. *Exp Rev Neurother*. 2015;15(6):711–717.
24. Kirov R, Brand S. Sleep problems and their effect in ADHD. *Expert Rev Neurother*. 2014;14(3):287–299.

EDITORIALE

Recenti episodi di dimenticanza e abbandono

Maurizio Bonati
Dipartimento di Sanità Pubblica
Istituto di Ricerche Farmacologiche
Mario Negri IRCCS, Milano
maurizio.bonati@marionegri.it

Rémi, bambino francese di otto anni, è il protagonista di *Senza famiglia* pubblicato nel 1878 e scritto da Hector Malot[1]. Un classico della narrativa per ragazzi che ha rappresentato uno dei libri di iniziazione alla lettura per passate generazioni delle classi medio-popolari. Numerosi sono stati gli adattamenti cinematografici e televisivi. L'abbandono dei bambini per vergogna o povertà ha tristemente accompagnato la storia dell'uomo e affascinato la fantasia popolare oltre ad essere un produttivo filone di studi e ricerche[2,3]. In Italia sono circa 15.000 i bambini e i ragazzi in affidamento familiare affinché possano crescere in un ambiente che soddisfi le loro esigenze educative e affettive, in cui esprimersi liberamente e affermare le proprie capacità[4]. La sconcertante inchiesta "angeli e demoni" condotta dai Carabinieri di Reggio Emilia, a partire da un'inchiesta giornalistica, su una rete di malaffare e di complicità per sottrarre bambini alle loro famiglie è espressione di abbandono e dimenticanza quando le buone intenzioni si limitano a rimandare (normando, legiferando, delegando) ad un istituto di diritto quale quello dell'affido istituito nel 1983, senza valutarne l'efficacia e l'efficienza in modo continuo e sistematico. Già nel 1992 con *Ladro di bambini* diretto da Gianni Amelio, veniva posto all'attenzione pubblica il problema delle possibili distorsioni tra buone intenzioni (sentimenti), realtà sociale e strumenti istituzionali. La distribuzione di diritti e doveri, opportunità e obblighi, libertà e limiti risulta quindi iniqua e disuguale se le regole possono essere discrezionali perché non partecipate[5]. E tutto questo non dovrebbe essere compito (solo) dell'amministrazione della giustizia, ma essere uno degli obiettivi/mandati di una Agenzia nazionale, indipendente e trasparente, a tutela dei diritti dell'infanzia e dell'adolescenza. Un Osservatorio permanente sul nascere e crescere in Italia che monitorizzi lo "star bene" dei bambini e dei ragazzi italiani (e delle loro famiglie) individuando i determinanti, documentando le criticità, indicando ai decisori i possibili interventi migliorativi.

Circa 15.000 bambini e ragazzi sono in affidamento familiare in Italia.

Nel mondo sono 180 milioni i bambini senza famiglia, la maggior parte dei quali in Africa. Una popolazione di minori soli e dimenticati dall'agenda politica e dalla cooperazione internazionale, come è avvenuto nella prima Conferenza Pubblica sulla Cooperazione allo Sviluppo[6]. È abbandonata e ignorata l'infanzia dei minori stranieri non accompagnati e separati (MNSA): poco meno di 13.000 quelli presenti e censiti nel 2018 in Italia e 5000 quelli irreperibili[4]. Sono stati 16.750 gli sbarchi in Italia nel 2018, 3536 (21%) i MNSA: questi i dati certi. Certi anche i molti "scomparsi in mare" di cui non si ha dimensione dei numeri: vittime ignote che meriterebbero un "altare", simbolo internazionale di diritti negati. L'indecorosa pagina di inciviltà scritta con il caso Sea-Watch 3 ha ulteriormente testimoniato come i "migranti" rappresentino un "carico" indifferenziato e i

180 milioni i bambini senza famiglia nel mondo: una popolazione dimenticata dall'agenda politica.

MNSA presenti a bordo un "carico" ignorato, sebbene l'articolo 3 della legge 47/2017 stabilisca che: "In nessun caso può disporsi il respingimento alla frontiera di minori stranieri non accompagnati". Migranti, profughi, rifugiati, naufraghi, situazioni e condizioni differenti, termini spesso usati come sinonimi che solo per i minori possono esserlo, perché c'è una Convenzione ONU sui diritti dell'infanzia e dell'adolescenza, approvata il 20 novembre 1989 e a tutt'oggi ratificata da 196 Paesi, che li riconosce comunque come titolari di diritti civili, sociali, politici, culturali ed economici ovunque nel mondo. Questo dicono le "carte"; la realtà è ben diversa. I drammi nel Mediterraneo, al largo di Lampedusa o sulla spiaggia di Bodrum, o quelli al confine tra USA e Messico, nel Rio Grande, e in molte altre realtà nel mondo sono l'esito di abbandoni e dimenticanze, di inadempienza a regole sottoscritte, di impunità. Le foto choc di Ayal (3 anni) respinto dalle acque dell'Egeo e di Angie Valeria (2 anni) nell'acqua melmosa del Rio Grande documentano i quotidiani "abbandoni" e i disturbi della memoria di diritti negati nel colpevole e ipocrita ritiro nella "famiglia del mulino bianco".

La Convenzione ONU riconosce i minorenni come titolari di diritti civili, sociali, politici, culturali ed economici.

Un immaginario della famiglia italiana lontano dalla realtà descritta dall'Istat con il report sulla povertà di giugno[7]. Nel 2018, la povertà assoluta in Italia colpisce 1.260.000 minori (12,6% rispetto all'8,4% degli individui a livello nazionale). Le famiglie con minori in povertà assoluta (con una spesa mensile pari o inferiore al valore soglia che per una famiglia di 2 adulti e un minorenne è di 1400-1000 €) sono 725mila e sono più povere di quelle povere senza minori. Le famiglie composte da soli stranieri con minorenni sono più povere di quelle povere di soli italiani. L'incidenza dei minori in povertà assoluta va dal 10,1% nel Centro fino al 15,7% nel Mezzogiorno dove risulta sostanzialmente stabile rispetto al 2017. Analoga situazione per la povertà relativa nelle cui condizioni sono stimate circa 3 milioni di famiglie (11,8%), per un totale di 9 milioni di individui (15,0%).

In Italia 1,2 milioni di minorenni vivono in condizioni di povertà assoluta.

Si è tenuta a Roma, il 13 e 14 giugno 2019, la conferenza nazionale per la salute mentale "Diritti, libertà e servizi" a conclusione di un percorso lungo un anno, articolato in 31 incontri realizzati su tutto il territorio nazionale e sostenuta da un cartello di 113 organizzazioni. Anche in questo caso/percorso si sono dimenticati dei minori. Il disagio psichico in età evolutiva in Italia interessa circa 1,3 milioni di bambini/ragazzi (e le loro famiglie) che vivono in modo aggravato la fatica di crescere, senza i supporti e le cure necessarie. Solo un terzo accede ai servizi pubblici di neuropsichiatria dopo una lunga attesa (mesi, ma anche anni). Gli operatori reclamano risorse e attenzione, anche se dopo anni di abbandono e disattenzione istituzionali ad un aumento di risorse non necessariamente consegue un miglioramento delle cure e della qualità degli interventi nonostante la soddisfazione degli operatori e degli utenti. La domanda di servizi per la salute mentale in età evolutiva è cronicamente orfana di risposte e di investimenti necessari per garantire diagnosi e cure appropriate. Le soluzioni messe in campo sono dichiarazioni con auspici di diritti non garantiti. È quanto successo anche con il Decreto del Presidente del Consiglio dei Ministri del 12 gennaio 2017 con la definizione e aggiornamento dei livelli essenziali di assistenza (LEA). L'articolo 25 (Assistenza sociosanitaria ai minori con disturbi in ambito neuropsichiatrico e del neurosviluppo) recita "Nell'ambito dell'assistenza distrettuale, domiciliare e territoriale ad accesso diretto, il Servizio sanitario nazionale garantisce ai minori con disturbi in ambito neuropsichiatrico e del neurosviluppo la

In Italia 1,3 milioni di minorenni (e le relative famiglie) vivono nello spettro del disagio psichico.

presa in carico multidisciplinare e lo svolgimento di un programma terapeutico individualizzato differenziato per intensità, complessità e durata, che include le prestazioni, anche domiciliari, mediche specialistiche, diagnostiche e terapeutiche, psicologiche e psicoterapeutiche, e riabilitative, mediante l'impiego di metodi e strumenti basati sulle più avanzate evidenze scientifiche…" e l'articolo 60 (Persone con disturbi dello spettro autistico) aggiunge "Ai sensi della legge 18 agosto 2015, n. 134, il Servizio sanitario nazionale garantisce alle persone con disturbi dello spettro autistico, le prestazioni della diagnosi precoce, della cura e del trattamento individualizzato, mediante l'impiego di metodi e strumenti basati sulle più avanzate evidenze scientifiche". Tutti contenti, famiglie e operatori, ma a distanza di tempo? La realtà è ben diversa da quanto auspicato e legiferato. Sebbene i LEA siano le prestazioni e i servizi che il Servizio sanitario nazionale è tenuto a fornire a tutti i cittadini, gratuitamente o dietro pagamento di una quota di partecipazione (ticket), con le risorse pubbliche raccolte attraverso la fiscalità generale (tasse)[8], le disuguaglianze territoriali nella prestazione delle cure sono croniche, come le incapacità di rientro dei deficit sanitari regionali. Diritti ancora disattesi in una realtà in cui i minorenni restano "minori" in tutti i sensi. Ridisegnare il sistema di cure senza ipocrisie, in una popolazione con sempre maggiore disagio psichico, è un bisogno essenziale che necessita però di altri sguardi.

Ridisegnare il sistema di cure senza ipocrisie è un bisogno essenziale.

Se *I bambini ci guardano*, diretto da Vittorio de Sica nel 1943, rappresenta l'anticipazione del neorealismo italiano cinematografico, la storia del piccolo Pricò è un'esortazione ancora inevasa affinché gli adulti guardino con gli occhi dei bambini (dalla parte dei bambini, all'altezza dei bambini) nel percorso di accoglienza e accompagnamento reciproco della vita. **R&P**

BIBLIOGRAFIA

1. Malot H. Senza famiglia. Firenze: Salani Editore, 1927.

2. Da Molin G. Per una storia dell'infanzia abbandonata in età moderna: i messaggi dell'abbandono. Itinerari di ricerca storica, XXX - 2016, numero 2: 79-94.

3. Lomastro F, Reggiani F. Per la storia dell'infanzia abbandonata in Europa. Tra est e ovest: ricerche e confronti. Roma: Viella Libreria Editrice, 2013.

4. Gruppo di lavoro CRC. I diritti dell'infanzia e dell'adolescenza in Italia. I dati regione per regione. Rapporto 2018. http://gruppocrc.net/wp-content/uploads/2019/04/rapporto-CRC-2018-ok_-aprile-2019-002.pdf (ultimo accesso, 2 luglio 2019).

5. Colombo G. Sulle regole. Milano: Feltrinelli, 2008.

7. 18 giugno 2018. Le statistiche dell'Istat sulla povertà. https://www.istat.it/it/files//2019/06/La-povertà-in-Italia-2018.pdf

6. Ministro degli Affari Esteri. Conferenza Pubblica sulla Cooperazione allo Sviluppo. 24 e 25 gennaio 2018 a Roma. www.aibi.it/ita/conferenza-pubblica-sulla-cooperazione -allo-sviluppo-linfanzia-abbandonata-nel-mondo-la-grande-assente-dellappuntamento/ (ultimo accesso 2 luglio 2019).

8. Servizio sanitario nazionale: i LEA. www.salute.gov.it/portale/lea/homeLea.jsp (ultimo accesso 2 luglio 2019).

https://www.gazzettaufficiale.it/eli/id/2019/07/15/19A04671/SG

GAZZETTA UFFICIALE

AGENZIA ITALIANA DEL FARMACO

DETERMINA 1 luglio 2019

Aggiornamento dell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale, ai sensi della legge 23 dicembre 1996, n. 648, relativo ai medicinali con uso consolidato per il trattamento di patologie del sistema nervoso ed apparato muscolo-scheletrico (Allegato P8). (Determina n. 75065/2019). (19A04671) (GU Serie Generale n.164 del 15-07-2019)

IL DIRIGENTE
dell'area pre-autorizzazione

Visti gli articoli 8 e 9 del decreto legislativo 30 luglio 1999, n. 300;

Visto l'art. 48 del decreto-legge 30 settembre 2003, n. 269, convertito, con modificazioni, dalla legge 24 novembre 2003, n. 326, che istituisce l'Agenzia italiana del farmaco (AIFA);

Visto il decreto del Ministro della salute, di concerto con il Ministro della funzione pubblica ed il Ministro dell'economia e delle finanze, 20 settembre 2004, n. 245, e successive modificazioni ed integrazioni, recante norme sull'organizzazione ed il funzionamento AIFA;

Visto il regolamento di organizzazione, del funzionamento e dell'ordinamento del personale dell'AIFA, adottato dal consiglio di amministrazione con deliberazione 8 aprile 2016, n. 12;

Visto il decreto del Ministro della salute del 27 settembre 2018, registrato ai sensi dell'art. 5, comma 2 del decreto legislativo 30 giugno 2011, n. 123, dall'ufficio centrale del bilancio presso il Ministero della salute in data 4 ottobre 2018, al n. 1011, con cui il dott. Luca Li Bassi e' stato nominato direttore generale dell'AIFA ed il relativo contratto individuale di lavoro con decorrenza 17 ottobre 2018, data di effettiva assunzione delle funzioni;

Vista la determina direttoriale n. 1792 del 13 novembre 2018, con cui la dott.ssa Sandra Petraglia, dirigente dell'area pre-autorizzazione, e' stata delegata dal direttore generale all'adozione dei provvedimenti di autorizzazione della spesa di farmaci orfani per malattie rare e di farmaci che rappresentano una speranza di cura, in attesa della commercializzazione, per particolari e gravi patologie, nei limiti della disponibilita' del «Fondo del 5%», di cui all'art. 48, commi 18 e 19, lettera a) del decreto-legge n. 269/2003, convertito, con modificazioni, dalla legge n. 326/2003 e dei provvedimenti per l'aggiornamento dell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale, ai sensi della legge n. 648/1996;

Visto il decreto del Ministro della salute 28 settembre 2004 che ha

costituito la Commissione consultiva tecnico-scientifica (CTS) dell'AIFA;

Visto il decreto-legge 21 ottobre 1996, n. 536, convertito, con modificazioni, dalla legge 23 dicembre 1996, n. 648, relativo alle misure per il contenimento della spesa farmaceutica e la determinazione del tetto di spesa per l'anno 1996 ed, in particolare, l'art. 1, comma 4, che dispone l'erogazione a totale carico del Servizio sanitario nazionale per i medicinali innovativi la cui commercializzazione e' autorizzata in altri Stati ma non sul territorio nazionale, dei medicinali non ancora autorizzati ma sottoposti a sperimentazione clinica e dei medicinali da impiegare per un'indicazione terapeutica diversa da quella autorizzata;

Visto il provvedimento della Commissione unica del farmaco (CUF), del 20 luglio 2000, pubblicato nella Gazzetta Ufficiale della Repubblica italiana n. 219 del 19 settembre 2000 con errata-corrige nella Gazzetta Ufficiale della Repubblica italiana n. 232 del 4 ottobre 2000, concernente l'istituzione dell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale ai sensi della legge 23 dicembre 1996, n. 648;

Vista la determina AIFA 20 gennaio 2010, pubblicata nella Gazzetta Ufficiale della Repubblica italiana n. 22 del 28 gennaio 2010, che ha integrato l'elenco dei medicinali erogabili ai sensi della legge 23 dicembre 1996, n. 648, istituito con il provvedimento della CUF sopra citato, mediante l'aggiunta di una specifica sezione concernente i medicinali che possono essere utilizzati per una o piu' indicazioni terapeutiche diverse da quelle autorizzate con la lista costituente l'Allegato P1, relativa ai farmaci con uso consolidato nel trattamento di patologie cardiache pediatriche;

Vista la determina AIFA 27 luglio 2012, pubblicata nella Gazzetta Ufficiale della Repubblica italiana n. 199 del 27 agosto 2012, che ha integrato la suddetta sezione con le liste costituenti gli Allegati P3-P9, relative ai farmaci con uso consolidato, sulla base dei dati della letteratura scientifica;

Considerate le evidenze scientifiche presenti in letteratura riguardo l'efficacia e la sicurezza nella popolazione pediatrica degli antipsicotici ARIPIPRAZOLO, LITIO PIMOZIDE e RISPERIDONE per il trattamento di disturbi psichici in eta' evolutiva;

Ritenuto opportuno consentire la prescrizione a carico del Servizio sanitario nazionale dei medicinali con uso consolidato ARIPIPRAZOLO, LITIO PIMOZIDE e RISPERIDONE per il trattamento dei disturbi psichiatrici in eta' evolutiva;

Tenuto conto della decisione assunta dalla CTS dell'AIFA nelle riunioni del 13, 14 e 15 novembre 2018, stralcio verbale n. 2;

Determina:

Art. 1

Nell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale, ai sensi della legge 23 dicembre 1996, n. 648, nella specifica sezione relativa ai medicinali che possono essere impiegati per una o piu' indicazioni diverse da quelle autorizzate, nella lista costituente l'Allegato P8 relativa all'uso consolidato, sulla base dei dati della letteratura scientifica, di farmaci per patologie del sistema nervoso e apparato muscolo-scheletrico, sono inseriti i seguenti medicinali con le relative indicazioni terapeutiche:

ARIPIPRAZOLO:

trattamento della schizofrenia a partire dall'eta' di tredici anni;

trattamento, fino a dodici settimane, degli episodi maniacali gravi o moderati nel contesto di una diagnosi del disturbo bipolare di tipo I in pazienti di eta' a partire dai dieci anni;

trattamento a breve termine (fino ad otto settimane) dell'irritabilita' in soggetti con disturbi dello spettro autistico che non abbiano risposto in modo efficace ad interventi psicologici specifici comportamentali ed educativi o per i quali tali interventi non sono disponibili (≥ sei anni);

sindrome di Tourette con una compromissione funzionale da moderata a grave (≥ sei anni);

PIMOZIDE:

sindrome di Tourette con compromissione funzionale da moderata a grave (≥ dodici anni);

RISPERIDONE:

trattamento a breve termine di problemi comportamentali di grado moderato o grave quali irritabilita' ed aggressivita' in soggetti (≥ cinque anni) con disturbi dello spettro autistico che non abbiano risposto in modo efficace ad interventi psicologici specifici comportamentali ed educativi o per i quali tali interventi non sono disponibili;

sindrome di Tourette con compromissione funzionale da moderata a grave (≥ sette anni);

add-on al metilfenidato in soggetti (≥ sette anni) ADHD e disturbo oppositivo-provocatorio, o aggressivita' che non abbiano risposto in modo efficace al solo trattamento con metilfenidato.

FARMACI CON EVIDENZA SCIENTIFICA A SUPPORTO DELL'USO IN PEDIATRIA
PER INDICAZIONI TERAPEUTICHE DIVERSE DA QUELLE AUTORIZZATE

ATC = M-N (Sistema nervoso e apparato muscolo-scheletrico)

Principio attivo	Uso off-label che si vuole autorizzare	Evidenze a sostegno del bisogno terapeutico	Note
ACTH	Add-on: ESES, S. di Lennox-Gastaut, Gravi encefalopatie epilettiche	ESES. Inutsuka, 2006 Tassinari, 2000 report clinici. Pareri di esperti: Meierkord, 2004 Lennox e encefalopatie: pareri di esperti: Schmidt, 2000, Alvarez, 1998; Arnold, 1996, Pisani, 1989; Yamatogi 1979	Non esistono linee guida per queste rare condizioni cliniche
Aripiprazolo	Trattamento della schizofrenia a partire dall'età di 13 anni.	Findling RL. et al, *A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia.* Am J Psychiatry. 2008; 165(11): 1432-41.	
	Trattamento, fino a 12 settimane, degli episodi maniacali gravi o moderati nel contesto di una diagnosi del disturbo bipolare di tipo I in pazienti di età a partire dai 10 anni	Findling RL. et al, *Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study*. Bipolar Disord. 2013; 15(2): 138-49. Findling RL. et al, *Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study.* J Clin Psychiatry. 2009 ; 70(10): 1441-51. Tramontina S. et al, *Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial*. J Clin Psychiatry. 2009; 70(5): 756-64. Mankoski R. et al, *Young mania rating scale line item analysis in pediatric subjects with bipolar disorder treated with aripiprazole in a short-term, double-blind, randomized study.* J Child Adolesc Psychopharmacol. 2011; 21(4): 359-64	
	Trattamento a breve termine (fino a 8 settimane) dell'irritabilità in soggetti con disturbi dello spettro autistico che non abbiano risposto in modo efficace a interventi psicologici specifici comportamentali ed educativi o per i quali tali interventi non sono disponibili (≥6 anni).	Robb AS. et al, *Safety and tolerability of aripiprazolein the treatment of irritabilità associated with autistic disorder in pediatric subjects (6-17 years old): results from a pooled analysis of 2 studies*. Prim Care Companion J Clin Psych. 2011; 13(1): e1-e9. Marcus RN. et al, *Safety and tolerability of*	

Principio attivo	Uso off-label che si vuole autorizzare	Evidenze a sostegno del bisogno terapeutico	Note
		aripiprazole for irritability in pediatric patients with autistic disorder: a 52-week, open-label, multicenter study. J Clin Psychiatry. 2011; 72(9): 1270-6. Marcus RN. et al, *A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder.* J Am Acad Child Adolesc Psychiatry. *2009;* 48(11): 1110-9. Owen R. et al, *Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder.* Pediatrics. 2009; 124(6): 1533-40.	
	Sindrome di Tourette con una compromissione funzionale da moderata a grave (≥6 anni)	Yoo HK. et al, *A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder*. J Clin Psychiatry. 2013; 74(8): e772-80. Ghanizadeh A. et al, *Aripiprazole versus risperidone for treating children and adolescents with tic disorder: a randomized double-blind clinical trial*. Child Psychiatry Hum Dev. 2014; 45(5): 596-603 Ghanizadeh A. et al, *Twice-weekly aripiprazole for treating children and adolescents with tic disorder, a randomized controlled trial*. Ann Gen Psychiatry. 2016; 15(1): 21,	
Clobazam	Epilessie gravi farmacoresistenti maggiori di tre anni di età	Studi in aperto Shimizu 2003; Montenegro 2001; Anon 1991; Keene 1990 ; Guberman 1990; Vajda 1985 Pareri di esperti: Allen 1983; Gastaut 1979	Nelle LG NICE opzione possibile in add on per il trattamento di vari tipi di crisi o s epilettiche
Clozapina	Psicosi acute e croniche nell'adolescente e nel bambino da un'età di >7 anni	°*Mattai AK*, Treatment of early-onset schizophrenia. Curr Opin Psychiatry. 2010;23(4):304-10; ° *Vitiello B, et al.* Antipsychotics in children and adolescents: increasing use, evidence for efficacy and safety concerns. Eur Neuropsychopharmacol. 2009;19(9):629-35; °*Masi G, Liboni F.* Management of schizophrenia in children and adolescents: focus on pharmacotherapy. Drugs. 2011;71(2):179-208	La Clozapina è un "antipsicotico atipico" con una dimostrata efficacia in RCT nel trattamento della schizofrenia nell'adolescente. E' stato pubblicato un solo RCT che ha incluso bambini con età >7 anni. Nelle forme di schizofrenia refrattarie ai trattamenti la clopazina sembra essere più efficace rispetto agli altri antipsicotici. Possibile comparsa di diversi effetti collaterali che vanno monitorati e che a volte richiedono la sospensione del trattamento. L'indicazione all'utilizzo degli antipsicotici atipici e è discussa in letteratura con il richiamo alla necessità di condurre

Principio attivo	Uso off-label che si vuole autorizzare	Evidenze a sostegno del bisogno terapeutico	Note
			ulteriori RCT nel bambino (nelle forme di schizofrenia ad insorgenza precoce) e anche nell'adolescente
Colchicina	Profilassi della febbre familiare mediterranea	°*Kallinich T, et al*. Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. Pediatrics. 2007;119(2):e474-8; °*Lehman TJ,et al.* Long-term colchicine therapy of familial Mediterranean fever. J Pediatr 1978;93:876-78 ; °*Majeed HA, et al.* Long-term colchicine prophylaxis in children with familial Mediterranean fever (recurrent hereditary polyserositis). J Pediatr 1990;116 :997-99; °*Koşan C*. Once-daily use of colchicine in children with familial Mediterranean fever. Clin Pediatr (Phila). 2004;43(7):605-8.	La colchicina è efficace nel 90% dei casi nella prevenzione dei casi di ricorrenza di attacchi di FFM. E' in grado di ridurre anche la complicanza temibile della FFM: l'amiloidosi
Diclofenac	Trattamento dell'artrite idiopatica giovanile (>6 mesi); Trattamento del dolore post operatorio (uso orale o rettale, no i.m)		Il problema riguarda l'assenza in Italia di adeguate formulazioni del farmaco per un uso pediatrico
Etosuccimide	Add-on: ESES, Epileptic Negative Myoclonus	ESES: Inutsuka, 2006; Liukkonen, 2010 Lennox: Schmidt, 2005 report clinici in add on Mioclono negativo . Pareri di esperti: Rubboli, 2006 Capovilla 1999; Oguni 1998; Capovilla 2000 report clinici in add on e monoterapia Pareri di esperti: Glauser, 2004	Non esistono linee guida per queste rare condizioni cliniche
Fentanil	Sia per il neonato sia per il bambino: a) Analgesia per procedure, anche di breve durata ; b) Controllo del dolore postoperatorio c) Sedazione per ventilazione assistita; d) Analgesia epidurale Analgesia in bambini di età > 1 anno (somministrazione di fentanil per via endonasale).	°*Walter-Nicolet E,* Pain management in newborns: from prevention to treatment. Paediatr Drugs. 2010;12(6):353-65 ; Guideline statement: management of procedure-related pain in children and adolescent. J Paediatr Child Health 2006;42:S1–29; *Krauss B, Green SM*. Procedural sedation and analgesia in children. Lancet 2006;367:766-8 ; American Academy of Pediatrics, Committee on Psychosocial Aspects of Child Family Health, Task Force on Pain in Infants, Children, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. Pediatrics 2001;108:793–7 . Graudins A et al. The PICHFORK (Pain in Children Fentanyl or Ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries. Ann Emerg Med. 2015;65:248-254. Murphy A Intranasal fentanyl for the management of	Sono stati pubblicati diversi RCT che dimostrano l'efficacia sedativa/analgesica del farmaco somministrato per via nasale con appositi dispositivi

Principio attivo	Uso off-label che si vuole autorizzare	Evidenze a sostegno del bisogno terapeutico	Note
		acute pain in children. Cochrane Database Syst Rev. 2014 Hippard H et al. Postoperative analgesic and behavioral effects of intranasal fentanyl, intravenous morphine, and intramuscular morphine in pediatric patients undergoing bilateral myringotomy and placement of ventilating tubes. Anesth Analg. 2012;115:356-63. Mudd S. Intranasal fentanyl for pain management in children: a systematic review of the literature. J Pediatr Health Care. 2011;25:316-22. Finn M, Harris D. Intranasal fentanyl for analgesia in the paediatric emergency department. Emerg Med J. 2010 ;27:300-1. Cole J, Shepherd M, Young P. Intranasal fentanyl in 1-3-year-olds: a prospective study of the effectiveness of intranasal fentanyl as acute analgesia. Emerg Med Australas. 2009;21:395-400 . Borland ML, Clark LJ, Esson A. Comparative review of the clinical use of intranasal fentanyl versus morphine in a paediatric emergency department. Emerg Med Australas. 2008;20:515-20.	
Indometacina	Chiusura del dotto arterioso pervio (PDA) nei neonati pretermine	°*Malviya M, et al*. Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003951	Nella PDA esistono numerosi trial randomizzati e revisioni sistematiche sull'uso dell'indometacina che hanno dimostrato l'efficacia nella chiusura del dotto arterioso nei neonati pretermine. Sembra essere parimenti efficace rispetto all'ibuprofene.
Lamotrigina	Monoterapia: > Di 12 anni: sindrome di Janz	Studi in aperto Morris, 2004 Bodenstein-Sachar, 2011 Paereri di esperti: Mantoan 2011; Montouris 2009; Auvin 2008; Verrotti 2006	Considerato di prima scelta nellle LG NICE anche se si specifica che non è autorizzato per questo uso in UK
Levetiracetam	Monoterapia: > Di 12 anni: sindrome di Janz ESES Add-on in Assenze Tipiche	Studi in aperto : Verrotti, 2008 Studi in aperto: Capovilla 2004, Aeby 2005, Atkins 2011 Pareri di esperti: Verrotti 2010, Striano 2008; Montouris, 2009; Di Bonaventura 2005 Pareri di esperti: Mantoan, 2011 Lyseng-	S di Janz: Considerato di prima scelta nelle LG NICE in alternativa al VPA in monoterapia anche se si specifica che è autorizzato solo in add on in questa sindrome in UK ASSENZE: LG NICE: opzione

Principio attivo	Uso off-label che si vuole autorizzare	Evidenze a sostegno del bisogno terapeutico	Note
		Williamson , 2011; Auvin, 2007; Wheless, 2007 ; Verrotti,2006; Di Bonaventura 2005 Sharpe, 2008; Specchio, 2006 ; Specchio 2007; Labate 2006	possibile in add on
Lorazepam	Trattamento dello stato di male epilettico o delle crisi subentranti nel bambino	Lagae L. Clinical practice : The treatment of acute convulsive seizures in children. Eur J Pediatr. 2011 Feb 8. [Epub ahead of print]	Sono stati pubblicati almeno due RCT che hanno dimostrato l'efficacia del lorazepam nel trattamento dello stato convulsivo anche se utilizzato per via nasale con appositi dispositivi Nelle LG NICE considerato opzione di scelta nel trattamento della fase precoce dello SE LG LICE considerato di prima scelta nello SE iniziale
Meloxicam	Trattamento del dolore e/o dello stato infiammatorio nei pazienti >2 anni con artrite idiopatica giovanile intolleranti ad altri FANS		E' stato pubblicato un solo RCT multicentrico. I presunti minori effetti collaterali del meloxicam rispetto ad altri FANS non sono dimostrati. E' possibile la monosomministrazione giornaliera, che non ha chiare evidenze di una maggiore compliance al trattamento in età pediatrica
Midazolam	Trattamento dello stato di male epilettico o delle crisi subentranti > 1 mese di età		Nelle LG NICE opzione possibile nello SE refrattario anche se si specifica che non è autorizzato in UK per l'indicazione
Olanzapina	Schizofrenia e disturbo bipolare nell'adolescente e nel bambino dall'età >7 anni	°*McCormack PL*. Olanzapine: in adolescents with schizophrenia or bipolar I disorder. CNS Drugs. 2010;24(5):443-52; °*Maloney AE, Sikich L.* Olanzapine approved for the acute treatment of schizophrenia or manic/mixed episodes associated with bipolar I disorder in adolescent patients. Neuropsychiatr Dis Treat. 2010;6:749-66; °*Ardizzone I, et al.* Antipsychotic medication in adolescents suffering from schizophrenia: a meta-analysis of randomized controlled trials. Psychopharmacol Bull. 2010;43(2):45-66.	L'olanzapina è un "antipsicotico atipico" con una dimostrata efficacia in RCT nel trattamento della schizofrenia nell'adolescente e nel disturbo bipolare ad insorgenza precoce. L'efficacia del farmaco nelle forme di schizofrenia ad insorgenza precoce (quelle del bambino) è limitata. Possibile comparsa di diversi effetti collaterali che vanno monitorati e che a volte richiedono la sospensione del trattamento. L'indicazione all'utilizzo degli antispicotici atipici è discussa in letteratura con il richiamo alla necessità di condurre ulteriori RCT nel bambino (nelle forme di schizofrenia ad insorgenza precoce) e anche nell'adolescente
Ossicodone	Trattamento del dolore da moderato a severo	°*Ali S, et al* Pain management of musculoskeletal injuries in children: current state and future	

Principio attivo	Uso off-label che si vuole autorizzare	Evidenze a sostegno del bisogno terapeutico	Note
		directions. Pediatr Emerg Care 2010;26(7):518-24	
Pimozide	Sindrome di Tourette con compromissione funzionale da moderata a grave (≥12 anni)	Shapiro E. et al, *Controlled study of haloperidol, pimozide and placebo for the treatment of Gilles del la Tourette's syndrome.* Arch Gen Psychiatry. 1989; 46: 722-730. Sallee FR. et al, *Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder.* Am J Psychiatry.1997; 154: 1057-1062. Bruggeman R. et al, *Risperidone versus pimozide in Tourette's disorder: a comparativedouble-blind parallel-group study*. J Clin Psychiatry. 2001; 62(1): 50-6. Gilbert DL. et al, *Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial.* J Am Acad Child Adolesc Psychiatry. 2004; 43(2): 206-14.	
Quetiapina	Schizofrenia, disturbo bipolare, nell'adolescente (dai 12 anni)	Vedasi Clopazina	La Quetiapina è un "antipsicotico atipico" con una dimostrata efficacia in pochi RCT (prodotti dallo stesso gruppo) nel trattamento della schizofrenia e nel disturbo bipolare ad insorgenza precoce nell'adolescente. Nei RCT non sono stati reclutati pazienti in età pediatrica. L'indicazione all'utilizzo degli antispicotici atipici è discussa in letteratura con il richiamo alla necessità di condurre ulteriori RCT nel bambino (nelle forme di schizofrenia ad insorgenza precoce) e anche nell'adolescente
Risperidone	Trattamento a breve termine di problemi comportamentali di grado moderato o grave quali irritabilità e aggressività in soggetti (≥5 anni) con disturbi dello spettro autistico che non abbiano risposto in modo efficace a interventi psicologici specifici comportamentali ed educativi o per i quali tali interventi non sono disponibili	Nagaraj R. et al, *Risperidone in children with autism: randomized, placebo-controlled, double-blind study.* J Child Neurology. 2006; 21(6): 450-5 McCraken JT. et al, *Research Units on PediatricPsychopharmacology Autism Network. Rispeidone in children with autism and serious behavioral problems*. NEngl J Med. 2002; 347(5): 314-21 Troost PW. et al, *Long-term effects of risperidone in children with autism spectrum disorders: a placebo*	

Principio attivo	Uso off-label che si vuole autorizzare	Evidenze a sostegno del bisogno terapeutico	Note
		discontinuation study. J Am Acad Child Adolesc Psychiatry. 2005; 44: 1137-44. Shea S. et al, *Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders.* Pediatrics. 2004; 114: e634-e641. Pandina GJ. et al, *Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial.* J Autism Dev Disord. 2007 ; 37(2): 367- 73. Miral S. et al, *Risperidone versus haloperidol in children and adolescents with AD: a randomized, controlled, double-blind trial.* Eur Child Adolesc Psychiatry. 2008; 17(1): 1-8.	
	Sindrome di Tourette con compromissione funzionale da moderata a grave (≥7 anni)	Scahill L. et al, *A placebo-controlled trial of risperidone in Tourette syndrome.* Neurology. 2003; 60(7): 1130-5. Gilbert DL. et al, *Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial.* J Am Acad Child Adolesc Psychiatry. 2004; 43(2): 206-14. Bruggeman R. et al, *Risperidone versus pimozide in Tourette's disorder: a comparativedouble-blind parallel-group study*. J Clin Psychiatry .2001; 62(1): 50-6. Gaffney GR. et al, *Risperidone versus cloni dine in the treatment of children and adolescents with Tourette's syndrome*. J Am Acad Child AdolescPsychiatry. 2002; 41(3): 330-6.	
	Add-on al metilfenidato in soggetti (≥7 anni) ADHD e disturbo oppositivo-provocatorio, o aggressività che non abbiano risposto in modo efficace al solo trattamento con metilfenidato	Aman MG. et al, *What does risperidone add to parent training and stimulant for severe aggression in child attention-deficit/ hyperactivity disorder?* J Am Acad Child Adolesc Psychiatry. 2014; 53: 47–60. Farmer CA. et al, *Risperidone added to psychostimulant in children with severe aggression and attention-deficit/ hyperactivity disorder: lack of effect on attention and short–term memory.* J Child	

Principio attivo	Uso off-label che si vuole autorizzare	Evidenze a sostegno del bisogno terapeutico	Note
		Adolesc Psychopharmacol. 2017; 27: 2 (117-124). Findling RL. et al, *The treatment of severe childhood aggression study: 12 weeks of extended, blinded treatment in clinical responders.* J Child Adolesc Psychopharmacol 2017; 27: 1 (52-65). Jahangard L. et al, *Children with ADHD and symptoms of oppositional defiant disorder improved in behavior when treated with methylphenidate and adjuvant risperidone, though weight gain was also observed. Results from a randomized, double-blind, placebo-controlled clinical trial.* Psychiatry Res. 2017; 251: 182-191.	
Rufinamide	Add on in gravi encefalopatie epilettiche > 4 anni	Studi in aperto, terapia aggiuntiva Coppola, 2011. Pareri di esperti : Coppola 2011	
Sumatriptan	Trattamento della crisi di emicrania	°*Eiland LS, Hunt MO*. The use of triptans for pediatric migraines. Paediatr Drugs. 2010;12(6):379-89; °*Barnes N, et al.* Migraine headache in children. Clin Evid. 2006;(15):469-75 °*Lewis D, et al.* American Academy of Neurology Quality Standards Subcommittee; Practice Committee of the Child Neurology Society. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004;63(12):2215-24	L'uso del sumatripan è raccomandato nei casi che non rispondano alla terapia convenzionale della crisi di emicrani che prevede l'uso del paracetamolo o dell'ibuprofene. Nelle LG dell'American Accademy of Neurology viene consigliato l'utilizzo della formulazione per via nasale a partire dai 12 anni di età.
Topiramato	Assenze tipiche farmacoresistenti	Studi clinici: Cross 2002 Pareri di esperti: Ormrod 2001, Cross 2004	Opzione considerata possibile nelle LG NICE. Si specifica che il suo uso non è autorizzato in UK per questa condizione.
Tossina botulinica A	Trattamento del blefarospasmo, spasmo emifacciale, torcicollo spasmodico, spasticità dovuta a paralisi cerebrale; Scialorrea da cause diverse; Trattamento sintomatico del morbo di Hirschsprung	°*Tilton A,* Pharmacologic treatment of spasticity in children.Semin Pediatr Neurol. 2010;17(4):261-7; °*Vaile L, Finlay F.* Is injection of botulinum toxin type A effective in the treatment of drooling in children with cerebral palsy? Arch Dis Child. 2006;91(10):862-3; °*Patrus B, et al.* Intrasphincteric botulinum toxin decreases the rate of hospitalization for postoperative obstructive symptoms in children with Hirschsprung disease. J Pediatr Surg. 2011;46(1):184-7	
Tramadolo	Dolore moderato-severo. Dolore post-operatorio	°*Bozkurt P.* Use of tramadol in children. Paediatr Anaesth. 2005;15(12):1041-7.	Diversi RCT condotti in pazienti in età pediatrica hanno dimostrato l'efficacia ed il profilo di sicurezza

Principio attivo	Uso off-label che si vuole autorizzare	Evidenze a sostegno del bisogno terapeutico	Note
			nel controllo del dolore con un uso per via orale, e.v. e epidurale (nel dolore post-operatorio)
Zonisamide	Gravi encefalopatie epilettiche > 4 anni in add on Assenze tipiche farmacoresistenti	Kelemen, 2011 studio in aperto, casistiche cliniche Pareri di esperti: Arzimanoglou 2006 Studio clinico: Marinas, 2009	Non esistono linee guida per queste rare condizioni cliniche Opzione possibile nelle LG NICE. Si specifica che il suo uso non è autorizzato in UK per questa condizione.

Per ricevere la newsletter iscriversi al seguente indirizzo:
http://www.adhd.marionegri.it/index.php/newsletter/iscrizione-newsletter

link per potersi cancellare dalla mailing list:
http://adhd.marionegri.it/index.php/newsletter/cancellazione-newsletter

Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
(Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI)
Il Progetto è realizzato con il contributo, parziale, della Regione Lombardia
(in attuazione della D.G. sanità n. 3798 del 08/05/2014, n. 778 del 05/02/2015, n. 5954 del 05/12/2016, N. 1077 del 02/02/2017 N. 1938 del 15/02/2019) Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia"
"*Percorsi diagnostico-terapeutici per l'ADHD*".

IRCCS ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI
DIPARTIMENTO DI SALUTE PUBBLICA
Laboratorio per la Salute Materno Infantile
Via Mario Negri, 2 - 20156 Milano MI - Italia - www.marionegri.it
tel +39 02 39014.511 fax +39 02 3550924 - mother_child@marionegri.i