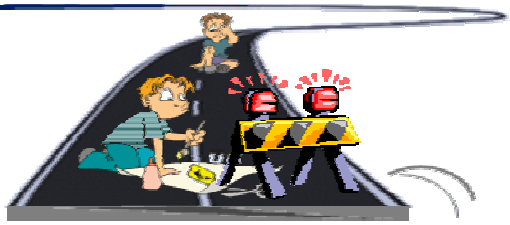
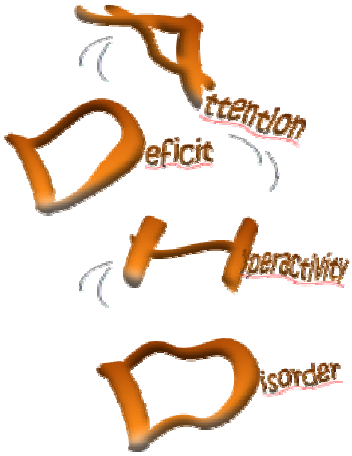
NEWSLETTER





INDICE:

BIBLIOGRAFIA ADHD GENNAIO 2013

ADHD Atten Deficit Hyperact Disord. 2013;5:41-46.

THE EFFECTIVENESS OF COGNITIVE-BEHAVIOURAL PLAY THERAPY ON THE SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AGED 7-9 YEARS .

Abdollahian E, Mokhber N, Balaghi A, et al.

Attention-deficit/hyperactivity disorder (ADHD) is considered to be the most prevalent disorder of childhood and adolescence, and a variety of methods have been used in its diagnosis and treatment. This study was conducted to study the efficacy of play therapy on the symptoms of ADHD in children aged 7-9 years. Using a clinical trial design, we selected 30 study participants among individuals who had been referred to the Ebne-sina hospital, child and adolescent outpatient clinic, Mashhad, Iran, and who had been diagnosed with ADHD by psychiatrists. The 30 study participants were then divided into two groups, experimental and control, based on similar characteristics (Birth order, parents' educational level, parents' occupation and average of last year school marks). Pre-tests (the Rutter Parental Questionnaire and the Rutter Children Behaviour Questionnaire for teachers) were performed prior to play therapy, and all patients in both groups had been receiving medication. Following play therapy, post-tests were also conducted for both groups. Eight sessions of sham play therapy has been performed for case group. (Cognitive-behavioural play therapy has not been performed basically.) All results were evaluated using an independent t test and a comparative test. Play therapy appeared to significantly reduce the symptoms of ADHD. The significant differences found between the experimental and control groups indicate that play therapy could be used as an effective treatment method for children with ADHD.

……

……

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.

ADHD Atten Deficit Hyperact Disord. 2013;5:1-8.

EPIDEMIOLOGY OF ADHD IN CHILEAN CHILDREN AND ADOLESCENTS.

de la Barra FE, Vicente B, Saldivia S, et al.

ADHD prevalence, associated factors, comorbidity and service use are reported for a sample of 1,558 children and adolescents, belonging to four provinces in Chile. The sample is weighted in each step for selection bias. Psychiatric disorders and impairment are assessed with computerized in-home DISC-IV interviews, and a questionnaire regarding socioeconomic and family variables and service use. Estimates of prevalence rates are obtained by means of STATA 11. 0 software, with complex sample design. Multivariate logistic regression is used to determine which factors were the best predictors for mental disorders. Participation rate is 82. 4 %. The prevalence of ADHD is 10 %, and the most prevalent subtype is the hyperactive/impulsive, with no gender differences. Both hyperactive/impulsive and combined subtypes are more prevalent in children 4-11 than in adolescents. The most prevalent comorbidities are anxiety disorders and oppositional disorder. Anxiety is the more prevalent comorbid disorder in girls and correlated with a combined subtype. Perception of good family functioning, adolescent age and school dropout have a negative association with ADHD diagnosis, while maltreatment shows a positive correlation. Over 50 % of children and adolescents diagnosed with ADHD have used services in the last year. This is the first comprehensive community study of psychiatric disorders in children and adolescents in a South American country. It yields information for child and adolescent mental health programmes in Chile and contributes to cross-cultural epidemiological research.

……

ADHD Atten Deficit Hyperact Disord. 2013;5:29-40.

A RANDOMIZED CONTROLLED MULTICENTRE TRIAL ON THE TREATMENT FOR ADHD IN MOTHERS AND CHILDREN: ENROLMENT AND BASIC CHARACTERISTICS OF THE STUDY SAMPLE.

Jans T, Graf E, Jacob C, et al.

Parental ADHD may be a significant barrier to a successful treatment for the child's ADHD. The objective of our randomized controlled trial was to evaluate whether the treatment for maternal ADHD improves the efficacy of a behavioural parent training for children's ADHD. Patient enrolment and a description of the full analysis set (FAS) of mother-child pairs with non-missing baseline data are presented. One hundred and forty-four mother-child pairs were randomized to two treatments for maternal ADHD: cognitive behavioural group psychotherapy plus open methylphenidate treatment or control treatment (supportive counselling). After 3 months of treatment for maternal ADHD, mother-child pairs participated in a behavioural parent-child training. Assessment for eligibility included standardized instruments. After pre-screening out of 444 mother-child pairs, 206 were evaluated for trial participation and 144 were randomized. The FAS was built up by 143 dyads (children: mean age 9. 4 years, 73 % males; mothers: mean age: 38. 3 years). Fifty-two per cent of the children and 66 % of the mothers had combined ADHD subtype. Current axis-I co-morbidity rates were 48 % in children and 31 % in mothers. Maternal axis-II co-morbidity was 20. 1 %. Fifty-seven per cent of the mothers lived together with the father of the index-child, and 29 % were single mothers. Sixty-two per cent had part-time or full-time employment. There was a selection bias excluding mothers with lack of time and effort for participation and mothers affected by coexisting mental and physical illness. Nevertheless, for our trial we were able to collect a sample comparable to routine psychiatric outpatient settings (registration: CCT-ISRCTN73911400, funding: BMBF-01GV0605).

……

ADHD Atten Deficit Hyperact Disord. 2013;5:21-28.

COMORBID ADHD AND MENTAL HEALTH DISORDERS: ARE THESE CHILDREN MORE LIKELY TO DEVELOP READING DISORDERS?

Levy F, Young DJ, Bennett KS, et al.

While attention-deficit/hyperactivity disorder (ADHD) has been associated with both internalizing and externalizing childhood behaviour disorders, the specific relationship of these comorbid disorders to ADHD and reading problems is less well defined. The present study analysed data from the Australian Twin

ADHD Project, which utilized DSM-IV-based ratings of ADHD, separation anxiety disorder, generalized anxiety disorder, depression, conduct disorder, and oppositional defiant disorder for twins and siblings aged 6 to 18 years. While differences between children with and without ADHD were demonstrated for those with separation anxiety disorder, generalized anxiety disorder, depression, conduct disorder, oppositional defiant disorder and a reading disorder, for all age groups, regression analysis of ADHD diagnostic subtypes by age and reading disorder showed that only generalized anxiety disorder remained significant after controlling for ADHD subtypes. Analysis of the mean reading disorder scores in children with and without ADHD showed that children with conduct disorder had significantly more reading problems, as did children with multiple comorbid disorders. In summary, both age and ADHD diagnosis were associated with variations in these comorbid disorders, and multiple comorbid disorders were associated with greater reading impairment.

……

ADHD Atten Deficit Hyperact Disord. 2013;5:9-20.

SEPARATE AND OVERLAPPING RELATIONSHIPS OF INATTENTION AND HYPERACTIVITY/IMPULSIVITY IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Smith LC, Tamm L, Hughes CW, et al.

There is debate regarding the dimensional versus categorical nature of attention-deficit/hyperactivity disorder (ADHD). This study utilized confirmatory factor analysis to examine this issue. ADHD symptoms rated on interviews and rating scales from a large sample of individuals (ages 3-17, 74 % male, 75 % Caucasian) with ADHD were examined (n = 242). Four potential factor structures were tested to replicate prior findings in a sample with a wide age range and included only participants who met DSM-IV-TR diagnostic criteria for ADHD. Correlations with executive function measures were performed to further assess the separability and validity of the derived factors. The data support a bifactor model with a general ADHD factor and two specific factors, inattention and hyperactivity/impulsivity. Importantly, the individual factors were also differentially correlated with executive functioning measures. This study adds to a growing literature suggesting both a general component to ADHD, as well as dimensional traits of inattention and hyperactivity/impulsivity, associated with distinct executive functioning profiles. The presence of a general underlying factor contraindicates separating the inattentive and combined subtypes of ADHD into distinct disorders.

……

Alcohol Clin Exp Res. 2013;37:507-16.

THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ON PSYCHOPATHOLOGY AND BEHAVIOR.

Ware AL, O'Brien JW, Crocker N, et al.

Background: This study examined prevalence of psychiatric disorders and behavioral problems in children with and without prenatal alcohol exposure (AE) and attention-deficit/hyperactivity disorder (ADHD).

Methods: Primary caregivers of 344 children (8 to 16 years, M=12.28) completed the Computerized Diagnostic Interview Schedule for Children-IV (C-DISC-4.0) and the Child Behavior Checklist (CBCL). Subjects comprised 4 groups: AE with ADHD (AE+, n=85) and without ADHD (AE-, n=52), and nonexposed with ADHD (ADHD, n=74) and without ADHD (CON, n=133). The frequency of specific psychiatric disorders, number of psychiatric disorders (comorbidity), and CBCL behavioral scores were examined using chi-square and analysis of covariance techniques.

Results: Clinical groups had greater frequency of all psychiatric disorders, except for anxiety, where the AE- and CON groups did not differ. There was a combined effect of AE and ADHD on conduct disorder. For comorbidity, children with ADHD had increased psychiatric disorders regardless of AE, which did not have an independent effect on comorbidity. For CBCL scores, there were significant main effects of AE and ADHD on all scores and significant AE null ADHD interactions for Withdrawn/Depressed, Somatic Complaints, Attention, and all Summary scores. There was a combined effect of AE and ADHD on Externalizing, Total Problems, and Attention Problems.

Conclusions: Findings indicate that ADHD diagnosis elevates children's risk of psychiatric diagnoses, regardless of AE, but suggest an exacerbated relation between AE and ADHD on conduct disorder and externalizing behavioral problems in children. Findings affirm a poorer behavioral prognosis for alcohol-exposed children with ADHD and suggest that more than 1 neurobehavioral profile may exist for individuals with AE.

……

Am J Med Genet Part B Neuropsychiatr Genet. 2011;156:28-35.

EFFECT OF DOPAMINE TRANSPORTER GENOTYPE ON CAUDATE VOLUME IN CHILDHOOD ADHD AND CONTROLS.

Shook D, Brady C, Lee PS, et al.

Polymorphism of the dopamine transporter genotype (DAT1) confers a small but significant susceptibility to attention deficit hyperactivity disorder (ADHD). We examined whether the volume of the head of caudate, a striatal structure with high DAT expression that is important for inhibitory function, differs by DAT1 in children diagnosed with the disorder relative to age and IQ matched controls. Volume of the head of caudate was delineated in the right and left hemisphere and compared between 7- and 13-year-old children with and without ADHD (combined type) who were carriers of two (10/10) or one (9/10) copy of the 10-repeat DAT1 allele. Caudate volumes were overall smaller in 10/10 than 9/10 children, particularly in the left than right hemisphere. While DAT1 effects did not vary by ADHD diagnosis, overall caudate volumes were smaller in ADHD relative to control children. Altered caudate development associated with 10-repeat homozygosity of DAT1 may contribute susceptibility to ADHD.

……

Ann Saudi Med. 2012;32:462-68.

PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY SYMPTOMS IN FEMALE SCHOOLCHILDREN IN SAUDI ARABIA.

Jenahi E, Khalil MS, Bella H.

BACKGROUND AND OBJECTIVES: Attention deficit hyperactivity disorder (ADHD) is the most commonly seen developmental disorder, with significant impacts on the child's social, psychological, and scholastic functioning. The aim of this study was to determine the prevalence and sociodemographic correlates of ADHD in female primary schoolchildren.

DESIGN AND SETTING: A cross-sectional study conducted in Al-Khobar Town, Eastern Saudi Arabia.

METHODS: A random sample of six primary schools for girls was chosen, from which samples of 1009 students were selected by systematic random sampling, with ages ranging between 6 and 15 years (mean and standard deviation, 9.2 [1.9]). All subjects were screened for different types of ADHD using the Attention Deficit Disorders Evaluation Scale.

RESULTS: The overall prevalence of ADHD was 3.5%. The prevalence of children with ADHD/inattentive type was 2.1% and the prevalence of children with ADHD/hyperactive-impulsive type was 5.6%. This rate decreased significantly with increase in age. The prevalence was higher in government school students, among Saudi citizens, later born siblings, higher number of siblings, and lower parental education.

CONCLUSIONS: It was concluded that the prevalence of ADHD in female primary schoolchildren is comparable with what has been reported in other studies. Some demographic factors should be taken into consideration when interpreting this result. Implications and recommendations to the concerned authorities are outlined to improve the health and educational care services to help these children.

……

Anthropol Med. 2013.

THE SOCIAL AND CULTURAL CONSTRUCTION OF PSYCHIATRIC KNOWLEDGE: AN ANALYSIS OF NICE GUIDELINES ON DEPRESSION AND ADHD.

Moncrieff J, Timimi S.

The current paper presents an analysis of the NICE guidelines on depression and attention deficit hyperactivity disorder (ADHD) from the perspective of the philosophy of science, guided particularly by

Foucault's notion of the symbiosis of knowledge and power. It examines how data that challenged the orthodox position on the validity and drug treatment of these conditions was managed in the process of guideline development. The depression guideline briefly considered the complexity and heterogeneity of depression, and numerous methodological problems with evaluating treatments, including antidepressants. However, the guideline recommendations made no reference to these issues and ignored evidence that questioned the analysis of antidepressant trials. The guideline on ADHD reviewed validity, but did not consider evidence from the critical literature, and overlooked inconsistencies in the data. The guideline identified that drug trials have shown no long-term benefit in ADHD, but still recommended treatment with stimulant drugs for children with severe symptoms and for all adults claiming consensus for this position. Both guidelines demonstrate how contradictory data are managed so as not to jeopardise the currently predominant view that ADHD and depression are valid and un-contentious medical conditions that should be treated with drugs. The subjective nature of guideline formation that is revealed illustrates Foucault's suggestion that the authority of medicine operates to promote a technological view of the nature of certain human problems, which in turn strengthens medical hegemony over these areas.

……

Asian J Psychiatry. 2013.

OPPOSITIONAL DEFIANT DISORDER: PREVALENCE BASED ON PARENT AND TEACHER RATINGS OF MALAYSIAN PRIMARY SCHOOL CHILDREN.

Gomez R, Hafetz N, Gomez RM.

Background: This study examined the prevalence rate of Oppositional Defiant Disorder (ODD) in Malaysian primary school children.

Methods: In all 934 Malaysian parents and teachers completed ratings of their children using a scale comprising DSM-IV-TR ODD symptoms.

Results: Results showed rates of 3.10%, 3.85%, 7.49% and 0.64% for parent, teacher, parent or teacher ("or-rule"), and parent and teacher ("and-rule") ratings, respectively. When the functional impairment criterion was not considered, the rate reported by parents was higher at 13.28%.

Discussion: The theoretical, diagnostic and cultural implications of the findings are discussed.

……

Aust New Zealand J Psychiatry. 2013;47:89-91.

POLITICS VS PRACTICE: COMMENTARY ON THE ADHD DEBATE.

Levy F.

……

Basic Clin Neurosci. 2013;4:50-56.

CLOCK FACE DRAWING TEST PERFORMANCE IN CHILDREN WITH ADHD.

Ghanizadeh A, Safavi S, Berk M.

Introduction: The utility and discriminatory pattern of the clock face drawing test in ADHD is unclear. This study therefore compared Clock Face Drawing test performance in children with ADHD and controls.

Methods: 95 school children with ADHD and 191 other children were matched for gender ratio and age. ADHD symptoms severities were assessed using DSM-IV ADHD checklist and their intellectual functioning was assessed. The participants completed three clock-drawing tasks, and the following four functions were assessed: Contour score, Numbers score, Hands setting score, and Center score

Results: All the subscales scores of the three clock drawing tests of the ADHD group were lower than that of the control group. In ADHD children, inattention and hyperactivity/ impulsivity scores were not related to free drawn clock test scores. When pre-drawn contour test was performed, inattentiveness score was statistically associated with Number score while none of the other variables of age, gender, intellectual functioning, and hand use preference were associated with that kind of score. In pre-drawn clock, no

association of ADHD symptoms with any CDT subscales found significant. In addition, more errors are observed with free drawn clock and Pre-drawn contour than pre-drawn clock.
Discussion: Putting Numbers and Hands setting are more sensitive measures to screen ADHD than Contour and Center drawing. Test performance, except Hands setting, may have already reached a developmental plateau. It is probable that Hand setting deficit in children with ADHD may not decrease from age 8 to 14 years. Performance of children with ADHD is associated with complexity of CDT.

……

BMC Psychiatry. 2012;12.
PERSISTENCE OF PHARMACOLOGICAL TREATMENT INTO ADULTHOOD, IN UK PRIMARY CARE, FOR ADHD PATIENTS WHO STARTED TREATMENT IN CHILDHOOD OR ADOLESCENCE.
McCarthy S, Wilton L, Murray ML, et al.
Background: ADHD guidelines in the UK suggest that children and adults who respond to pharmacological treatment should continue for as long as remains clinically effective, subject to regular review. To what extent patients persist with treatment from childhood and adolescence into adulthood is not clear. This study aims to describe, in UK primary care, the persistence of pharmacological treatment for patients with ADHD who started treatment aged 6-17 years and to estimate the percentage of patients who continued treatment from childhood and adolescence into adulthood.
Methods: The Health Improvement Network (THIN) database was used to identify patients with ADHD who received their first prescription for methylphenidate/ dexamfetamine/atomoxetine, aged 6-17 years. Patients were monitored until their 'censored date' (the earliest of the following dates: date the last prescription coded in the database ended, end of the study period (31st December 2008), date at which they transferred out of their practice, date of death, the last date the practice contributed data to the database). Persistence of treatment into adulthood was estimated using Kaplan Meier analysis.
Results: 610 patients had follow-up data into adulthood. 213 patients (93.4% male) started treatment between 6-12 years; median treatment duration 5.9 years. 131 (61.5%) stopped before 18 years, 82 (38.5%) were still on treatment age (greater-than or equal to)18 years. 397 patients (86.4% male) started treatment between 13-17 years; median treatment duration was 1.6 years. 227 (57.2%) stopped before 18 years, 170 (42.8%) were still on treatment age (greater-than or equal to)18 years. The number of females in both age categories was too small to formally test for differences between genders in persistence of treatment.
Conclusion: Persistence of treatment into adulthood is lower (~40%) compared with published rates of persistence of the condition (~65% when symptomatic definition of remission used). Due to the limited number of patients with data past 18 years, it is important that ongoing monitoring of prescribing into later adulthood is undertaken, particularly to observe the effects of recommendations in new guidelines.

……

BMC Psychiatry. 2013;13.
TRANSITION TO ADULT MENTAL HEALTH SERVICES FOR YOUNG PEOPLE WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD): A QUALITATIVE ANALYSIS OF THEIR EXPERIENCES.
Swift KD, Hall CL, Marimuttu V, et al.
Background: There is little research on the process of transition between child and adolescent mental health services (CAMHS) and adult mental health services (AMHS). More recently, there is growing recognition that Attention Deficit/Hyperactivity Disorder (ADHD) may persist into adulthood requiring services beyond age 18. However, despite National Institute for Health and Clinical Excellence (NICE) Guidance which recommends specialist services for adults with ADHD, there is currently a lack of such services in the UK. The aim of the current study is to explore the experiences of young people with ADHD during transition from CAMHS to AMHS.
Method: Semi-structured qualitative interviews with ADHD patients accessing CAMHS clinics in Nottinghamshire were analysed using thematic analysis.

Results: Ten semi-structured interviews were transcribed and analysed. We found that patients' relationships with their clinician were a key factor in both their reported experience of CAMHS and the transition process. Perceived responsibility of care was also pivotal in how the transition process was viewed. Nature and severity of problems and patients expectations of adult services were also contributing factors in the transition process. The need for continued parental support was openly accepted and thought to be required by the majority of young people with ADHD during transition.
Conclusions: Timely preparation, joint working, good clinician relationships and parental support serve to facilitate the process of transition for young people with ADHD. Nature and severity of problems are perceived to impede or facilitate transition, with predominantly more 'complex presentations' with associated mental health problems more familiar to AMHS (e.g. self-harm, depression) making for smoother transitions to adult services. Transitions to AMHS were more difficult when ADHD was viewed as the main or sole clinical problem. Further exploration of young people's experiences of transition and their engagement with and experience of adult services is required to provide an overall picture of facilitators to successful transition and integration into adult services.

……

Child Adolesc Ment Health. 2013.
ADHD AND FUNCTIONAL SOMATIC SYMPTOMS: STRUCTURAL EQUATIONS OF A CONCEPTUAL MODEL.
Giacobo RS, Jane MC, Bonillo A, et al.
Aims: To examine the effect of anxiety and parental overprotection on functional somatic symptoms (FSS) in children with attention deficit hyperactivity disorder (ADHD).
Method: Seventy-six children and adolescents (aged 6-17) with ADHD and their parents completed a clinical interview about psychiatric and somatic symptoms. Parents also reported about parenting styles. Structural equation modeling (SEM) was used.
Results: The generalized anxiety, overprotection, and specific phobia variables each had a direct effect on FSS.
Conclusions: Anxiety symptoms and parental overprotection may play a role in the development of FSS in children with ADHD. Further research is necessary to corroborate our findings.

……

Child Care Health Dev. 2013 Mar;39:202-12.
HOME ENVIRONMENT: ASSOCIATION WITH HYPERACTIVITY/IMPULSIVITY IN CHILDREN WITH ADHD AND THEIR NON-ADHD SIBLINGS.
Mulligan A, Anney R, Butler L, et al.
Objective: We wished to ascertain if there is an association between symptoms of attention-deficit/hyperactivity disorder (ADHD) and home environment in children with ADHD and non-ADHD siblings, controlling for other environmental measures.
Methods: 96 children with ADHD combined type (ADHD-CT) and their siblings participated in the study. Parent and teacher Conners' rating scales were completed and home environment was assessed using the middle childhood and early adolescent Home Observation for Measurement of the Environment (HOME). ADHD symptoms were assessed for correlation with HOME in children with ADHD-CT and non-ADHD siblings and multiple regression analysis was used to control for gender, socio-economic status, exposure to nicotine, exposure to alcohol in utero, birth weight, gestational age, pregnancy and perinatal risk factors. The presence of oppositional disorders was assessed for association with HOME score in those with ADHD-CT. The multiple regression analysis was repeated controlling for environmental factors and for oppositional disorders in those with ADHD-CT. Oppositional symptoms were assessed for correlation with HOME score in non-ADHD siblings.
Results: Teacher-rated hyperactive/impulsive scores correlated with HOME ($r=-0.27$, $P<0.01$) in children with ADHD-CT. This association remained significant when other environmental factors and oppositional disorders were controlled for. Environmental factors and gender contributed to 30% of the variance of ADHD symptoms in ADHD-CT. Parent-rated hyperactive/impulsive scores also correlated with HOME (r=-

0.28, P<0.05) for non-ADHD siblings. An association between HOME and diagnosis of oppositional defiant disorder or conduct disorder was found for children with ADHD-CT and between HOME and oppositional symptoms in non-ADHD siblings.
Conclusions: The home environment has a small but significant association with hyperactive/impulsive symptoms in children with ADHD-CT and non-ADHD siblings. This association remained when other environmental factors were taken into account. Oppositional symptoms are associated with home environment in ADHD-CT and in non-ADHD siblings.

……

Child Care Health Dev. 2013 Mar;39:268-76.
SCREENING FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): CAN HIGH-RISK CHILDREN BE IDENTIFIED IN FIRST GRADE?
Holmberg K, Sundelin C, Hjern A.
Aim: Recent studies have demonstrated the beneficial long-term effects of an indicated parent support programme for acting out behaviour in pre-school children with attention-deficit/hyperactivity disorder (ADHD) traits. In this study we wanted to assess different thresholds for screening with the Conners scale for hyperactive-inattentive behaviours in first grade for ADHD in grade four.
Method: The study population consisted of 422 first graders (6- to 7-year-olds) in one municipality in Stockholm County who were screened with Conners 10-item scale and followed up by ADHD assessment in grade four. Sensitivity, specificity, likelihood ratios, and positive predictive value (PPV) of the screening by parents and teachers in first grade for being diagnosed with ADHD in fourth grade were calculated.
Results: The prevalence of pervasive and situational ADHD was 5.7% and 5.9% respectively. A score =10 on the Conners scale in first grade in teachers' reports identified 63% [95% confidence interval (CI): 43-79] of children diagnosed with pervasive ADHD in grade four (P<0.001) with a PPV of 29% and a positive likelihood ratio (LR+) of 6.72. Parental reports of a score =10 yielded a lower sensitivity (29%; 95% CI: 15-49), PPV of 20% and LR+ of 4.24 for pervasive ADHD. The best predictor was a combination of parent and teacher scores =10 with a PPV of 50% and LR+ of 16.63. Associations with situational ADHD were weak with LR+ of 1.81 and 2.49, respectively, for teachers' and parental scores =10.
Conclusions: This study indicates a strong association between a teacher's report of a score =10 on the Conners scale in first grade and pervasive ADHD in grade four, while parental reports were less predictive.

……

Cortex: A Journal Devoted to the Study of the Nervous System and Behavior. 2013 Jan;49:340-47.
TOPOGRAPHY OF SLEEP SLOW WAVE ACTIVITY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Ringli M, Souissi S, Kurth S, et al.
Introduction: Sleep slow wave activity (SWA, EEG power between 1 and 4.5 Hz) is a major characteristic of non-rapid eye movement (NREM) sleep, which seems to be critically involved in cortical plasticity. Studies using high-density electroencephalography (hd-EEG) showed that the topographical distribution of SWA mirrors cortical maturation, expressing a local maximum that is characteristic for a certain age range. We compared the sleep EEG of children with attention-deficit/hyperactivity disorder (ADHD) with healthy controls to explore differences in sleep SWA.
Methods: All-night hd-EEG recordings (128 electrodes) were performed in a group of nine children diagnosed with ADHD and nine age- and sex-matched healthy controls. SWA topography was calculated and contrasted between the groups.
Results: We found a local increase of SWA in a cluster of six electrodes over central regions in children with ADHD compared to control children (¦ 17% ¦ 6% SE, p<.01). This group difference was specific for the SWA range and stable across the night.
Conclusions: Children with ADHD showed a less mature topographical SWA distribution in comparison to healthy children of the same age and sex. This neuromaturational delay in ADHD is in accordance with

neuroimaging and behavioral studies. Thus, our study supports the use of sleep SWA topography as a reliable imaging tool for the study of cortical plasticity.

……

Depression Anxiety. 2013.

COMPARISON OF BEHAVIORAL PROFILES FOR ANXIETY-RELATED COMORBIDITIES INCLUDING ADHD AND SELECTIVE MUTISM IN CHILDREN.

Levin-Decanini T, Connolly SD, Simpson D, et al.

Background: Elucidating differences in social-behavioral profiles of children with comorbid presentations, utilizing caregiver as well as teacher reports, will refine our understanding of how contextual symptoms vary across anxiety-related disorders.

Methods: In our pediatric anxiety clinic, the most frequent diagnoses and comorbidities were mixed anxiety (MA; (greater-than or equal to) 1 anxiety disorder; N=155), anxiety with comorbid attention-deficit hyperactivity disorder (MA/ADHD, N=47) and selective mutism (SM, N=48). Behavioral measures (CPRS, CTRS) were analyzed using multiple one-way multivariate analyses of covariance tests. Differences between the three diagnostic groups were examined using completed parent and teacher reports (N=135, 46, and 48 for MA, MA/ADHD, and SM groups, respectively).

Results: Comparisons across the MA, MA/ADHD, and SM groups indicate a significant multivariate main effect of group for caregiver and teacher responses (P<0.01). Caregivers reported that children with SM are similar in profile to those with MA, and both groups were significantly different from the MA/ADHD group. Teachers reported that children with SM had more problems with social behaviors than with the MA or MA/ADHD groups. Further comparison indicates a significant main effect of group (P<0.001), such that children with SM have the greatest differences in behavior observed by teachers versus caregivers.

Conclusions: Clinical profiles between MA/ADHD, MA, and SM groups varied, illustrating the importance of multi-rater assessment scales to capture subtle distinctions and to inform treatment planning given that comorbidities occur frequently in children who present with anxiety.

……

Dev Cognitive Neurosci. 2013;5:71-85.

NEUROPHYSIOLOGICAL RESPONSES TO FACES AND GAZE DIRECTION DIFFERENTIATE CHILDREN WITH ASD, ADHD AND ASD + ADHD.

Tye C, Mercure E, Ashwood KL, et al.

Children with autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) demonstrate face processing abnormalities that may underlie social impairment. Despite substantial overlap between ASD and ADHD, ERP markers of face and gaze processing have not been directly compared across pure and comorbid cases. Children with ASD (n=19), ADHD (n=18), comorbid ASD + ADHD (n=29) and typically developing (TD) controls (n=26) were presented with upright/inverted faces with direct/averted gaze, with concurrent recording of the P1 and N170 components. While the N170 was predominant in the right hemisphere in TD and ADHD, children with ASD (ASD/ASD+ADHD) showed a bilateral distribution. In addition, children with ASD demonstrated altered response to gaze direction on P1 latency and no sensitivity to gaze direction on midline-N170 amplitude compared to TD and ADHD. In contrast, children with ADHD (ADHD/ASD + ADHD) exhibited a reduced face inversion effect on P1 latency compared to TD and ASD. These findings suggest children with ASD have specific abnormalities in gaze processing and altered neural specialisation, whereas children with ADHD show abnormalities at early visual attention stages. Children with ASD + ADHD are an additive co-occurrence with deficits of both disorders. Elucidating the neural basis of the overlap between ASD and ADHD is likely to inform aetiological investigation and clinical assessment.

……

Dev Med Child Neurol. 2013.

THE IMPACT OF METHYLPHENIDATE ON SEIZURE FREQUENCY AND SEVERITY IN CHILDREN WITH ATTENTION-DEFICIT-HYPERACTIVITY DISORDER AND DIFFICULT-TO-TREAT EPILEPSIES.

Santos K, Palmini A, Radziuk AL, et al.

Aim: Difficult-to-treat epilepsies and attention-deficit-hyperactivity disorder (ADHD) often co-occur. Because of concerns about the use of stimulants in children with this comorbidity, the impact of ADHD treatment on seizure frequency and severity is not known. This pilot study evaluated the safety and efficacy of methylphenidate in this population.

Method: After a 3 month period in which antiepileptic drugs were adjusted, 22 patients recruited from a specialist outpatient clinic for severe epilepsy (16 males, six females; mean age 11y 2mo, SD 3y 2mo) received methylphenidate for 3 months in an open label, non-controlled trial; four with generalized or multifocal (symptomatic/cryptogenic) epilepsy, one with generalized (idiopathic) epilepsy, 17 with partial (symptomatic/cryptogenic) epilepsy; five with partial seizures only, 17 with primarily or secondarily generalized seizures). Epilepsy, ADHD symptoms, and side effects were assessed using the Swanson, Nolan, and Pelham Questionnaire, the Child Behavior Checklist, the Hague Seizure Severity Scale, and the Side Effects Rating Scale.

Results: Methylphenidate significantly improved ADHD. After 3 months of treatment, 73% of patients no longer had clinically significant symptoms. Methylphenidate also reduced seizure severity (9-point median decrease on the Hague Seizure Severity Scale). Seizure frequency increased in four out of 22 patients, but only one patient withdrew from the study for this reason. Most patients experienced no major side effects.

Interpretation: These data are among the first showing that low doses of methylphenidate are safe and effective to treat ADHD symptoms in patients with difficult-to-treat epilepsies. Randomized controlled trials are needed to replicate the findings. Please also see the Commentary on this paper by Shalev.

……

Drug Test Anal. 2013;5:191-95.

SWEAT TESTING FOR THE DETECTION OF ATOMOXETINE FROM PAEDIATRIC PATIENTS WITH ATTENTION DEFICIT/ HYPERACTIVITY DISORDER: APPLICATION TO CLINICAL PRACTICE.

Marchei E, Papaseit E, Garcia-Algar O, et al.

Atomoxetine (ATX) is a selective norepinephrine reuptake inhibitor approved since 2002 for the treatment of attention deficit hyperactivity disorder (ADHD) in children, adolescents, and adults as an alternative treatment to methylphenidate. Within the framework of a project evaluating the use of alternative biological matrices for therapeutic monitoring of psychoactive drugs in paediatric and non-paediatric individuals, the excretion of ATX and its principal metabolites has been recently studied in oral fluid and hair. The aim of this study was to describe the excretion profile of ATX and its metabolites 4-hydroxyatomoxetine (4-OH-ATX) and N-desmethylatomoxetine (N-des-ATX) in sweat following the administration of different dosage regimens (60, 40, 35, and 18mg/day) of ATX to six paediatric patients. Sweat patches were applied to the back of each participant and removed at timed intervals. ATX and its metabolites were measured in patches using a previously validated liquid chromatography-tandem mass spectrometric (LC-MS/MS) method. Independently from the administered dose, ATX appeared in the sweat patches 1h post administration and reached its maximum concentration generally at 24h. Peak ATX concentrations ranged between 2.31 and 40.4ng/patch and did not correlate with the administered drug dose, or with body surface area. Total ATX excreted in sweat ranged between 0.008 and 0.121mg, corresponding to 0.02 and 0.3% of the administered drug. Neither 4-OH-ATX, nor N-des-ATX was detected in either of the collected sweat patches. Measuring ATX in sweat patches can provide information on cumulative drug use from patch application until removal.

……

Dusunen Adam. 2012;25:353-57.

COMPARISON OF HIGH SCHOOL ENTRANCE EXAM SCORES OF CHILDREN WITH HYPERACTIVITY DISORDER BEFORE AND AFTER TREATMENT: A RETROSPECTIVE EVALUATION.

Gokcen C, Gulec M.

Objective: In this study, we aimed to investigate the effect of the treatment in children with Attention Deficit Hyperactivity Disorder (ADHD) on High School Entrance Exam scores.

Method: Forty five students of seventh and eighth grades, who referred to our clinic in the academic year of 2009-2010 and diagnosed with ADHD were included in this study. ADHD diagnoses had been made with the help of family interviews, child interviews, family and teacher questionnaires and DSM-IV. Results were obtained via examination of the records retrospectively.

Results: We have found that 32 of 35 cases (91.4%) had increased scores and 3 cases (8.6%) had decreased scores after medication. High School Entrance Exam average scores was 371.6 before the treatment and 401.9 after, and the difference between the two scores was statistically significant. The average treatment duration was 4.4 months.

Discussion: Our study shows ADHD treatment has positive effects on High School Entrance Exam scores. Also, we found that ADHD treatment has positive impact on academic progress and child, family and educators must be aware about this situation.

……

Early Hum Dev. 2013;89:199-207.

BEHAVIOURAL OUTCOMES AND PSYCHOPATHOLOGY DURING ADOLESCENCE.

Johnson S, Wolke D.

Preterm birth is associated with a high risk of residual neurodevelopmental disability and cognitive impairment. These problems are closely associated with psychiatric disorders and thus it is unsurprising that preterm birth also confers high risk for poor long term mental health. The risk associated with preterm birth is not a general one, but appears to be specific to symptoms and disorders associated with anxiety, inattention and social and communication problems, and manifest in a significantly higher prevalence of emotional disorders, ADHD and Autism. Adolescence is a key period for mental health and studies have shown that problems evident in childhood persist over this time and are more stable amongst preterm individuals than term-born peers. There is also modest evidence for an increased prevalence of psychotic symptoms in preterm adolescents. The high prevalence of psychiatric disorders, present in around 25% of preterm adolescents, requires long term screening and intervention.

……

Early Intervent Psychiatry. 2013.

MEMORY-GUIDED SACCADES IN YOUTH-ONSET PSYCHOSIS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

White T, Mous S, Karatekin C.

Aim: Working memory deficits have been shown to be present in children and adolescents with schizophrenia and attention deficit hyperactivity disorder. Considering the differences in clinical characteristics between these disorders, it was the goal of this study to assess differences in the specific components of working memory in children and adolescents with psychosis and attention deficit hyperactivity disorder.

Methods: Children and adolescents (age range 8-20 years) with either a non-affective psychotic disorder (n=25), attention deficit hyperactivity disorder (n=33) and controls (n=58) were administered an oculomotor delayed-response task using both a recall and a control condition. Memory-guided saccades were measured during delay periods of 2, 8 and 20s.

Results: Although both clinical groups were less accurate than controls, there was no evidence of a disproportionate impairment in recall. In addition, there was no evidence of a delay-dependent impairment in psychosis; however, there was a delay-dependent impairment in attention deficit hyperactivity disorder when corrective saccades were included. Speed of information processing was correlated with distance

errors in psychosis, suggesting that speed of encoding the stimulus location may have constrained the accuracy of the saccades.
Conclusions: Our findings support impairments during encoding in the psychosis group and a delay-dependent deficit in the attention deficit hyperactivity disorder group.

……

Egypt J Neurol , Psychiatr Neurosurg. 2013;50:61-66.
PRAGMATIC SKILLS IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD).
Safwat RF, Hamid AA, Salam AA, et al.
Background: Attention Deficit Hyperactivity Disorder (ADHD) is the most frequent reported psychiatric disease for children with language disorder. ADHD can create problems in accessing language and using language appropriately, the difficulties in language are secondary to the attentional difficulties.
Objective: To study the pragmatic language deficit in ADHD children.
Methods: This study included 62 consecutive newly diagnosed ADHD children according to Diagnostic and Statistical Manual of mental disorders IV-TR criteria, their age ranged from 6- 8 year. Then they were referred to the Phoniatric unit, Kasr Al-Aini for pragmatic assessment. Forty four normal control children (age and sex matched), were included in the study. The included samples were subjected to the protocol of language and pragmatic assessment applied in Kasr Al-Aini. Twenty-four children with ADHD were excluded as they had history of delayed language development. Four control children were also excluded because of phonetic errors. The 38 ADHD children and 40 controls were subjected to the following psychiatric assessment: Semi-structured interview to confirm that the patients have ADHD, Wechsler Intelligence scale for children (WISC), and Conner's' Parent Rating Scale-Revised: long version (CPRS-R: L).
Results: ADHD children got less significant scores in intention, narrative, conversation and total pragmatic scores than controls. There was significant negative correlation between inattention Conners' subscale with intention and narrative pragmatic subscales. Also, significant negative correlation between social problems Conners' subscale and intention and conversation.
Conclusion: ADHD children have pragmatic deficits than controls.

……

Epilepsy Behav. 2013.
QUESTIONNAIRE-BASED ASSESSMENT OF BEHAVIORAL PROBLEMS IN JAPANESE CHILDREN WITH EPILEPSY.
Kobayashi K, Endoh F, Ogino T, et al.
Behavioral problems in Japanese children with epilepsy were investigated by means of a questionnaire for parents consisting of three checklists: the Child Behavior Checklist (CBCL)/4-18 Japanese Edition, the High-Functioning Autism Spectrum Screening Questionnaire (ASSQ), and the Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scale-IV (ADHD-RS) for parents. The participants were the parents of 108 children aged 6-18 years with apparently normal intelligence. The CBCL indicated abnormal behavior in 10.5 to 35.6% of the children, and T scores on both the internalizing and externalizing scales had a significant positive relation with scores on the ASSQ and ADHD-RS. It was revealed through multivariate logistic regression analysis that the persistence of seizures was significantly related with abnormality on the externalizing scale of the CBCL ($p = 0.010$, odds ratio: 3.48, 95% confidence interval: 1.34-9.02). Future studies are needed to determine whether seizure freedom improves behavior in children with epilepsy.

……

Eur Child Adolesc Psychiatry. 2013;1-10.

RELATIONSHIP BETWEEN ANXIETY, ANXIETY SENSITIVITY AND CONDUCT DISORDER SYMPTOMS IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Bilgic A, Turkoglu S, Ozcan O, et al.

Attention-deficit hyperactivity disorder (ADHD) is often comorbid with anxiety disorders and previous studies observed that anxiety could have an impact on the clinical course of ADHD and comorbid disruptive behavioral disorders (conduct disorders and oppositional-defiant disorders). Anxiety sensitivity (AS) is a different concept from anxiety per se and it is believed to represent the constitutionally based sensitivity of individuals to anxiety and anxiety symptoms. We aimed to assess the associations between anxiety, AS and symptoms of disruptive behavioral disorders (DBD) in a clinical sample of children and adolescents with ADHD. The sample consisted of 274 treatment naive children with ADHD aged 8-17 years. The severity of ADHD symptoms and comorbid DBD were assessed via parent rated Turgay DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S), Conners' Parent Rating Scale (CPRS), and Conners' Teacher Rating Scale (CTRS). AS and severity of anxiety symptoms of children were evaluated by self-report inventories. The association between anxiety, AS, and DBD was evaluated using structural equation modeling. Analyses revealed that AS social subscale scores negatively predicted symptoms of conduct disorder (CD) reported in T-DSM-IV-S. On the other hand, CD symptoms positively predicted severity of anxiety. No direct relationships were detected between anxiety, AS and oppositional-defiant behavior scores in any scales. These results may suggest a protective effect of AS social area on the development of conduct disorder in the presence of a diagnosis of ADHD, while the presence of symptoms of CD may be a vulnerability factor for the development of anxiety symptoms in children and adolescents with ADHD.

……

Eur Child Adolesc Psychiatry. 2013;1-10.

A SMALL-SCALE RANDOMIZED CONTROLLED TRIAL OF THE SELF-HELP VERSION OF THE NEW FOREST PARENT TRAINING PROGRAMME FOR CHILDREN WITH ADHD SYMPTOMS.

Daley D, O'Brien M.

The efficacy of a self-help parent training programme for children with attention deficit hyperactivity disorder (ADHD) was evaluated. The New Forest Parenting Programme Self-help (NFPP-SH) is a 6-week written self-help psychological intervention designed to treat childhood ADHD. Forty-three children were randomised to either NFPP-SH intervention or a waiting list control group. Outcomes were child ADHD symptoms measured using questionnaires and direct observation, self-reported parental mental health, parenting competence, and the quality of parent-child interaction. Measures of child symptoms and parental outcomes were assessed before and after the intervention. ADHD symptoms were reduced, and parental competence was increased by self-help intervention. Forty-five percent of intervention children showed clinically significant reductions in ADHD symptoms. Self-help intervention did not lead to improvements in parental mental health or parent-child interaction. Findings provide support for the efficacy of self-help intervention for a clinical sample of children with ADHD symptoms. Self-help may provide a potentially cost-effective method of increasing access to evidence-based interventions for clinical populations.

……

Eur Child Adolesc Psychiatry. 2013;1-10.

WHAT INFLUENCES CLINICIANS' DECISIONS ABOUT ADHD MEDICATION? INITIAL DATA FROM THE INFLUENCES ON PRESCRIBING FOR ADHD QUESTIONNAIRE (IPAQ).

Kovshoff H, Vrijens M, Thompson M, et al.

Despite evidence for its efficacy and effectiveness, the use of medication for the treatment of ADHD remains controversial. Little is known about the factors that influence clinicians' decisions to use medication for ADHD. Here, we present initial data on the attitudes of prescribing clinicians from the Influences on Prescribing for ADHD Questionnaire (IPAQ)-a new clinician-completed, 40-item scale. The eight IPAQ

subscales cover attitudes towards (1) treatment outcome optimisation, (2) the use of rule based over more informal approaches, (3) side effects, (4) symptoms control as the primary goal of treatment, (5) the influence of external pressure on medication-related decisions, (6) the value of taking the child's views into account, (7) long-term medication use and (8) the value of psychosocial approaches for the treatment of ADHD. Sixty-eight clinicians from Belgium and the UK took part. All subscales had acceptable levels of internal reliability (Chronbach's alpha = 0.62-0.78). Overall, clinicians reported taking a rule-based approach to prescribing with a focus on treatment optimisation, taking the child's view into account and valuing psycho-social approaches. They focused on treating broader patterns of impairment, but were wary of the potential side effects and long-term treatment. Psychiatrists scored high on their focus on symptom control and preference for long-term medication use, while paediatricians reported using more rule-based approaches. We identified four distinctive response profiles: (1) pro-psychosocial; (2) medication focused; (3) unsystematic; and (4) response optimizers. Future larger scale studies are required to replicate these profiles and to explore their relationship with prescribing behaviour and treatment outcomes.

……

Eur Child Adolesc Psychiatry. 2013;1-14.

AN INVENTORY OF EUROPEAN DATA SOURCES FOR THE LONG-TERM SAFETY EVALUATION OF METHYLPHENIDATE.

Murray ML, Insuk S, Banaschewski T, et al.

To compile an inventory of European healthcare databases with potential to study long-term effects of methylphenidate (MPH) in patients with attention deficit hyperactivity disorder (ADHD). Potential databases were identified through expert opinion, the website of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, and literature search. An online survey was conducted among database providers/coordinators to ascertain the databases' appropriateness for inclusion into the inventory. It included questions about database characteristics, sample size, availability of information on drug exposure, clinical data and accessibility. Forty-two databases from 11 countries were identified and their coordinators invited to participate; responses were obtained for 22 (52.4 %) databases of which 15 record ADHD diagnoses. Eleven had sufficient data on ADHD diagnosis, drug exposure, and at least one type of outcome information (symptoms/clinical events, weight, height, blood pressure, heart rate) to assess MPH safety. These were Aarhus University Prescription Database, Danish National Birth Cohort (Denmark); German Health Interview and Examination Survey for Children and Adolescents; Health Search Database Thales, Italian ADHD Register, Lombardy Region ADHD Database (Italy); Avon Longitudinal Study of Parents and Children, General Practice Research Database, The Health Improvement Network, QResearch (UK) and IMS Disease Analyzer (UK, Germany, France). Of the 20 databases with no responses, information on seven from publications and/or websites was obtained; Pedianet and the Integrated Primary Care Information database were considered suitable. Many European healthcare databases can be used for multinational long-term safety studies of MPH. Methodological research is underway to investigate the feasibility of their pooling and analysis.

……

Eur J Paediatr Neurol. 2013.

TOURETTE SYNDROME AND COMORBID ADHD: CURRENT PHARMACOLOGICAL TREATMENT OPTIONS.

Rizzo R, Gulisano M, Cali PV, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is the most common co-morbid condition encountered in people with tics and Tourette Syndrome (TS). The co-occurrence of TS and ADHD is associated with a higher psychopathological, social and academic impairment and the management may represent a challenge for the clinicians.

Aim: To review recent advances in management of patients with tic, Tourette Syndrome and comorbid Attention Deficit Hyperactivity Disorder.

Methods: We searched peer reviewed and original medical publications (PUBMED 1990-2012) and included randomized, double-blind, controlled trials related to pharmacological treatment for tic and TS used in children and adolescents with comorbid ADHD. "Tourette Syndrome" or "Tic" and "ADHD", were

cross referenced with the words "pharmacological treatment", "(alpha)-agonist", "psychostimulants", "selective norepinephrine reuptake inhibitor", "antipsychotics".
Results: Three classes of drugs are currently used in the treatment of TS and comorbid ADHD: (alpha)-agonists (clonidine and guanfacine), stimulants (amphetamine enantiomers, methylphenidate enantiomers or slow release preparation), and selective norepinephrine reuptake inhibitor (atomoxetine). It has been recently suggested that in a few selected cases partial dopamine agonists (aripiprazole) could be useful.
Conclusion: Level A of evidence supported the use of noradrenergic agents (clonidine). Reuptake inhibitors (atomoxetine) and stimulants (methylphenidate) could be, also used for the treatment of TS and comorbid ADHD. Taking into account the risk-benefit profile, clonidine could be used as the first line treatment. However only few studies meet rigorous quality criteria in terms of study design and methodology; most trials have low statistical power due to small sample size or short duration. Treatment should be "symptom targeted" and personalized for each patient.

……

Eur J Paediatr Neurol. 2013.
NEUROCOGNITIVE EFFECTS OF METHYLPHENIDATE ON ADHD CHILDREN WITH DIFFERENT DAT GENOTYPES: A LONGITUDINAL OPEN LABEL TRIAL.
Pasini A, Sinibaldi L, Paloscia C, et al.
The variable number of tandem repeat polymorphism in the 3'-untranslated region of the dopamine transporter gene (DAT) may influence the variability of the therapeutic response to methylphenidate (MPH) in Attention Deficit/Hyperactivity Disorder (ADHD). For this reason we evaluated the neuropsychological functioning after a prolonged period of MPH treatment and after a specific time from MPH suspension. Relationship between DAT VNTR genotypes and neurocognitive response to MPH was analyzed in a sample of 108 drug-naive ADHD patients. The performance of children with ADHD on measures of working memory, inhibition and planning was assessed at 4, 8 and 24 weeks and at 8 weeks after MPH withdrawal. Patients with 9/9 genotype evidenced an improvement in response inhibition and working memory only at 4 weeks of treatment, in planning at 24 weeks of therapy and after 8 weeks of MPH suspension. Patients with 9/10 showed an improvement in response inhibition at 4, 8 and 24 weeks of treatment, in planning at 24 weeks and after 8 weeks of MPH suspension. Patients with 10/10 evidenced an improvement in response inhibition and working memory at 4, 8 and 24 weeks of treatment and in planning at 4, 8 and 24 weeks of treatment and after 8 weeks of suspension. These results indicate that the 9/9 ADHD genotype has a different response at 24 weeks treatment with MPH. 10/10 DAT allele seems to be associated with an increased expression level of the dopamine transporter and seems to mediate the MPH treatment response in ADHD patients.

……

Eur Neuropsychopharmacol. 2013;23:33-45.
REWARD CIRCUIT CONNECTIVITY RELATES TO DELAY DISCOUNTING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Costa Dias TG, Wilson VB, Bathula DR, et al.
Attention-deficit/hyperactivity disorder (ADHD) is a prevalent psychiatric disorder that has poor long-term outcomes and remains a major public health concern. Recent theories have proposed that ADHD arises from alterations in multiple neural pathways. Alterations in reward circuits are hypothesized as one core dysfunction, leading to altered processing of anticipated rewards. The nucleus accumbens (NAcc) is particularly important for reward processes; task-based fMRI studies have found atypical activation of this region while the participants performed a reward task. Understanding how reward circuits are involved with ADHD may be further enhanced by considering how the NAcc interacts with other brain regions. Here we used the technique of resting-state functional connectivity MRI (rs-fcMRI) to examine the alterations in the NAcc interactions and how they relate to impulsive decision making in ADHD. Using rs-fcMRI, this study: examined differences in functional connectivity of the NAcc between children with ADHD and control children; correlated the functional connectivity of NAcc with impulsivity, as measured by a delay discounting

task; and combined these two initial segments to identify the atypical NAcc connections that were associated with impulsive decision making in ADHD. We found that functional connectivity of NAcc was atypical in children with ADHD and the ADHD-related increased connectivity between NAcc and the prefrontal cortex was associated with greater impulsivity (steeper delayed-reward discounting). These findings are consistent with the hypothesis that atypical signaling of the NAcc to the prefrontal cortex in ADHD may lead to excessive approach and failure in estimating future consequences; thus, leading to impulsive behavior.

……

Front Syst Neurosci. 2013;1-31.

DISTINCT NEURAL SIGNATURES DETECTED FOR ADHD SUBTYPES AFTER CONTROLLING FOR MICRO-MOVEMENTS IN RESTING STATE FUNCTIONAL CONNECTIVITY MRI DATA.

Fair DA, Nigg JT, Iyer S, et al.

In recent years, there has been growing enthusiasm that functional magnetic resonance imaging (MRI) could achieve clinical utility for a broad range of neuropsychiatric disorders. However, several barriers remain. For example, the acquisition of large-scale datasets capable of clarifying the marked heterogeneity that exists in psychiatric illnesses will need to be realized. In addition, there continues to be a need for the development of image processing and analysis methods capable of separating signal from artifact. As a prototypical hyperkinetic disorder, and movement-related artifact being a significant confound in functional imaging studies, ADHD offers a unique challenge. As part of the ADHD-200 Global Competition and this special edition of Frontiers, the ADHD-200 Consortium demonstrates the utility of an aggregate dataset pooled across five institutions in addressing these challenges. The work aimed to (1) examine the impact of emerging techniques for controlling for "micro-movements," and (2) provide novel insights into the neural correlates of ADHD subtypes. Using support vector machine (SVM)-based multivariate pattern analysis (MVPA) we show that functional connectivity patterns in individuals are capable of differentiating the two most prominent ADHD subtypes. The application of graph-theory revealed that the Combined (ADHD-C) and Inattentive (ADHD-I) subtypes demonstrated some overlapping (particularly sensorimotor systems), but unique patterns of atypical connectivity. For ADHD-C, atypical connectivity was prominent in midline default network components, as well as insular cortex; in contrast, the ADHD-I group exhibited atypical patterns within the dlPFC regions and cerebellum. Systematic motion-related artifact was noted, and highlighted the need for stringent motion correction. Findings reported were robust to the specific motion correction strategy employed. These data suggest that resting-state functional connectivity MRI (rs-fcMRI) data can be used to characterize individual patients with ADHD and to identify neural distinctions underlying the clinical heterogeneity of ADHD.

……

Genes, Brain & Behavior. 2013 Feb;12:56-69.

DENSE-MAP GENOME SCAN FOR DYSLEXIA SUPPORTS LOCI AT 4Q13, 16P12, 17Q22; SUGGESTS NOVEL LOCUS AT 7Q36.

Field LL, Shumansky K, Ryan J, et al.

Analysis of genetic linkage to dyslexia was performed using 133,165 array-based SNPs genotyped in 718 persons from 101 dyslexia-affected families. Results showed five linkage peaks with lod scores >2.3 (4q13.1, 7q36.1-q36.2, 7q36.3, 16p12.1, and 17q22). Of these five regions, three have been previously implicated in dyslexia (4q13.1, 16p12.1, and 17q22), three have been implicated in attention-deficit hyperactivity disorder (ADHD, which highly co-occurs with dyslexia; 4q13.1, 7q36.3, 16p12.1) and four have been implicated in autism (a condition characterized by language deficits; 7q36.1-q36.2, 7q36.3, 16p12.1, and 17q22). These results highlight the reproducibility of dyslexia linkage signals, even without formally significant lod scores, and suggest dyslexia predisposing genes with relatively major effects and locus heterogeneity. The largest lod score (2.80) occurred at 17q22 within the MSI2 gene, involved in neuronal stem cell lineage proliferation. Interestingly, the 4q13.1 linkage peak (lod 2.34) occurred immediately upstream of the LPHN3 gene, recently reported both linked and associated with ADHD.

Separate analyses of larger pedigrees revealed lods >2.3 at 1-3 regions per family; one family showed strong linkage (lod 2.9) to a known dyslexia locus (18p11) not detected in our overall data, demonstrating the value of analyzing single large pedigrees. Association analysis identified no SNPs with genome-wide significance, although a borderline significant SNP (P = 6 Î 10[sup]-7[/sup]) occurred at 5q35.1 near FGF18, involved in laminar positioning of cortical neurons during development. We conclude that dyslexia genes with relatively major effects exist, are detectable by linkage analysis despite genetic heterogeneity, and show substantial overlapping predisposition with ADHD and autism.

……

Gent Test and Mol Biomarkers. 2013;17:178-82.

ASSOCIATION BETWEEN HTR1A GENE POLYMORPHISMS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN KOREAN CHILDREN.

Park YH, Lee KK, Kwon HJ, et al.

Attention deficit hyperactivity disorder (ADHD) is a common disorder of the school age population. ADHD has been shown to be familial, and genetic studies estimate its heritability at 80%-90%. The aim of the present study was to investigate the association between the genetic type and alleles for the HTR1A gene in Korean children with ADHD. The sample consisted of 142 ADHD children and 139 control children. We diagnosed ADHD according to the Diagnostic and Statistical Manual of Mental Disorders-4th edition. ADHD symptoms were evaluated with Conners' Parent Rating Scales and Dupaul Parent ADHD Rating Scales. Blood samples were taken from the 281 subjects, DNA was extracted from blood lymphocytes, and polymerase chain reaction was performed for HTR1A polymorphism. Alleles and genotype frequencies were compared using the chi-square test. We compared the allele and genotype frequencies of HTR1A gene polymorphism in the ADHD and control groups. This study showed that there was a significant correlation among the frequencies of the rs10042486 (OR=1.55, 95% CI=1.02-2.30, p=0.041), rs1423691(OR=1.55, 95% CI=1.02-2.30, p=0.041),and rs878567(OR=1.60, 95% CI=1.06-2.43, p=0.027) alleles of HTR1A, but the final conclusions are not definite. Follow-up studies with larger patient or pure subgroups are expected. These results suggested that HTR1A might be related to ADHD symptoms.

……

JAMA Pediatr. 2013;167:282-88.

RECENT TRENDS IN CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Getahun D, Jacobsen SJ, Fassett MJ, et al.

Objective: To examine trends in attention-deficit/ hyperactivity disorder (ADHD) by race/ethnicity, age, sex, and median household income.

Design: An ecologic study of trends in the diagnosis of ADHD using the Kaiser Permanente Southern California (KPSC) health plan medical records. Rates of ADHD diagnosis were derived using Poisson regression analyses after adjustments for potential confounders.

Setting: Kaiser Permanente Southern California, Pasadena.

Participants: All children who received care at the KPSC from January 1, 2001, through December 31, 2010 (n=842 830).

Main Exposure: Period of ADHD diagnosis (in years).

Main Outcome Measures: Incidence of physiciandiagnosed ADHD in children aged 5 to 11 years.

Results: Rates ofADHDdiagnosis were 2.5% in 2001 and 3.1% in 2010, a relative increase of 24%. From 2001 to 2010, the rate increased among whites (4.7%-5.6%; relative risk [RR]=1.3; 95% CI, 1.2-1.4), blacks (2.6%- 4.1%; RR=1.7; 95% CI, 1.5-1.9), and Hispanics (1.7%-2.5%; RR=1.6; 95% CI, 1.5-1.7). Rates for Asian/Pacific Islander and other racial groups remained unchanged over time. The increase inADHDdiagnosis among blacks was largely driven by an increase in females (RR=1.9; 95% CI, 1.5-2.3). Although boys were more likely to be diagnosed as having ADHD than girls, results suggest the sex gap for blacks may be closing over time. Children living in high-income households were at increased risk of diagnosis.

Conclusions: The findings suggest that the rate ofADHD diagnosis among children in the health plan notably has increased over time.Weobserved disproportionately high ADHD diagnosis rates among white children and notable increases among black girls.

……

JAMA Psychiatry. 2013;70:311-18.

DEVELOPMENTAL TWIN STUDY OF ATTENTION PROBLEMS: HIGH HERITABILITIES THROUGHOUT DEVELOPMENT.

Chang Z, Lichtenstein P, Asherson PJ, et al.

Context: The genetic and environmental link between attention-deficit/ hyperactivity disorder in childhood and the adult manifestation of the disorder is poorly understood because of a lack of longitudinal studies with crossinformant data.

Objective: To explore the relative contribution of genetic and environmental influences on symptoms of attention problems from childhood to early adulthood.

Design: Analysis was conducted using longitudinal structural equation modeling with multiple informants.

Setting: The Swedish Twin Study of Child and Adolescent Development.

Participants: One thousand four hundred eighty twin pairs were prospectively followed up from childhood to young adulthood.

Main Outcome Measures: Symptoms were obtained using parent and self-ratings of the Attention Problems Scale at ages 8 to 9, 13 to 14, 16 to 17, and 19 to 20 years.

Results: The best-fitting model revealed high heritability of attention problems as indexed by parent and selfratings from childhood to early adulthood (h2=0.77- 0.82). Genetic effects operating at age 8 to 9 years continued, explaining 41%, 34%, and 24% of the total variance at ages 13 to 14, 16 to 17, and 19 to 20 years. Moreover, new sets of genetic risk factors emerged at ages 13 to 14, 16 to 17, and 19 to 20 years.

Conclusions: The shared view of self- and informantrated attention problems is highly heritable in childhood, adolescence, and early adulthood, suggesting that the previous reports of low heritability for attentiondeficit/ hyperactivity disorder in adults are best explained by rater effects. Both genetic stability and genetic innovation were present throughout this developmental stage, suggesting that attention problems are a developmentally complex phenotype characterized by both continuity and change across the life span.

……

J Abnorm Child Psychol. 2013 Jan;41:27-41.

YOUNG ADULT EDUCATIONAL AND VOCATIONAL OUTCOMES OF CHILDREN DIAGNOSED WITH ADHD.

Kuriyan AB, Pelham WEJr, Molina BSG, et al.

Decreased success at work and educational attainment by adulthood are of concern for children with ADHD given their widely documented academic difficulties; however there are few studies that have examined this empirically and even fewer that have studied predictors and individual variability of these outcomes. The current study compares young adults with and without a childhood diagnosis of ADHD on educational and occupational outcomes and the predictors of these outcomes. Participants were from the Pittsburgh ADHD Longitudinal Study (PALS), a prospective study with yearly data collection. Significant group differences were found for nearly all variables such that educational and occupational attainment was lower for adults with compared to adults without histories of childhood ADHD. Despite the mean difference, educational functioning was wide-ranging. High school academic achievement significantly predicted enrollment in post-high school education and academic and disciplinary problems mediated the relationship between childhood ADHD and post-high school education. Interestingly, ADHD diagnosis and disciplinary problems negatively predicted occupational status while enrollment in post-high school education was a positive predictor. Job loss was positively predicted by a higher rate of academic problems and diagnosis of ADHD. This study supports the need for interventions that target the child and adolescent predictors of later educational and occupational outcomes in addition to continuing treatment of ADHD in

young adulthood targeting developmentally appropriate milestones, such as completing post-high school education and gaining and maintaining stable employment.

……

J Abnorm Child Psychol. 2013 Jan;41:71-80.

EARLY CHILDHOOD ASSESSMENTS OF COMMUNITY PEDIATRIC PROFESSIONALS PREDICT AUTISM SPECTRUM AND ATTENTION DEFICIT HYPERACTIVITY PROBLEMS.

Jaspers M, de Winter AF, Buitelaar JK, et al.

For clinically referred children with Autism Spectrum Disorder (ASD) or Attention Deficit/Hyperactivity Disorder (ADHD) several early indicators have been described. However, knowledge is lacking on early markers of less severe variants of ASD and ADHD from the general population. The aim of the present study is to identify early indicators of high risk groups for ASD and ADHD problems based on routine data from community pediatric services between infancy and age four. Data are from 1,816 participants who take part in Tracking AdolescentsÆ Individual Lives Survey (TRAILS), a longitudinal study. Information on early developmental factors was extracted from charts of routine Preventive Child Healthcare (PCH) visits. To assess ASD and ADHD problems, respectively, we used the ChildrenÆs Social Behavior Questionnaire (CSBQ) and the Child Behavior Checklist (CBCL), filled out by parents three times between the ages of 11 and 17. Note that these are parent ratings and not diagnostic instruments performed by trained clinicians. Male gender, low birth weight, low level of education of the mother, social, behavioral, language, psychomotor and eating problems significantly predicted ASD problems (odds ratios (OR) between 1.34 and 2.41). ADHD problems were also predicted by male gender and low level of education of the mother and by maternal smoking during pregnancy, good gross motor skills in first year, early attention and hyperactivity problems, and absence of parent-reported positive behavior (ORs between 1.36 and 1.74). Routine data on early childhood from PCH services are predictive for ASD and ADHD problems in adolescents in the general population. The PCH services are a useful setting to identify high risk groups, and to monitor them subsequently.

……

J Abnorm Psychol. 2012;121:360-71.

EVALUATING VIGILANCE DEFICITS IN ADHD: A META-ANALYSIS OF CPT PERFORMANCE.

Huang-Pollock CL, Karalunas SL, Tam H, et al.

We meta-analytically review 47 between-groups studies of continuous performance test (CPT) performance in children with attention-deficit/hyperactivity disorder (ADHD). Using a random effects model and correcting for both sampling error and measurement unreliability, we found large effect sizes ((delta)) for overall performance, but only small to moderate (delta) for performance over time in the handful of studies that reported that data. Smaller (delta)s for performance over time are likely attributable, in part, to the extensive use of stimuli for which targets and distractors are quite easily differentiated. Artifacts accounted for a considerable proportion of variance among observed (delta)s. Effect sizes reported in previous reviews were significantly attenuated because of the presence of uncorrected artifacts and highlight the necessity of accounting for artifactual variance in future work to determine the amount of true neurocognitive heterogeneity within ADHD. Signal detection theory and diffusion modeling analyses indicated that the ADHD-related deficits were because of decreased perceptual sensitivity (d(delta)) and slower drift rates (v). Results are interpreted the context of several recent models of ADHD.

……

Journal of Attention Disorders. 2013 Feb;17:141-51.
Exasperating or exceptional? Parent's interpretations of their child's ADHD behavior.
Lench HC, Levine LJ, Whalen CK.
Objective: Attention Deficit/Hyperactivity Disorder (ADHD) is a commonly diagnosed childhood disorder associated with parentùchild conflict and parental stress. This investigation explored whether parentsÆ interpretation of symptomatic behavior predicted negative interactions with and perceptions of their child.
Method: We recruited parents of 7-12 year old children who were diagnosed with ADHD (n=41), were diagnosed with ADHD but whose parents construed symptomatic behavior positively (Indigo children; n=36), and had no diagnosis (n=26). Parents completed a questionnaire about their experiences with their child.
Results: Relative to parents who used only the ADHD label for childrenÆs behavior, parents who also perceived symptomatic behavior as a sign of positive characteristics reported less frequent negative experiences with their child and less intense negative emotions during those experiences. They also viewed their children as more self-efficacious and as more likely to have a positive future.
Conclusion: Positive perceptions of child symptomatic behavior appeared to buffer the impact of ADHD symptoms on parents and parent-child relationships.

……

Journal of Attention Disorders. 2013 Feb;17:152-62.
THE SWAN CAPTURES VARIANCE AT THE NEGATIVE AND POSITIVE ENDS OF THE ADHD SYMPTOM DIMENSION.
Arnett AB, Pennington BF, Friend A, et al.
Objective: The Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Rating Scale differs from previous parent reports of ADHD in that it was designed to also measure variability at the positive end of the symptom spectrum.
Method: The psychometric properties of the SWAN were tested and compared with an established measure of ADHD, the Disruptive Behavior Rating Scale (DBRS).
Results: The SWAN demonstrates comparable validity, reliability, and heritability to the DBRS. Furthermore, plots of the SWAN and DBRS reveal heteroscedasticity, which supports the SWAN as a preferred measure of positive attention and impulse regulation behaviors.
Conclusion: The ability of the SWAN to measure additional variance at the adaptive end of the ADHD symptom dimensions makes it a promising tool for behavioral genetic studies of ADHD.

……

Journal of Attention Disorders. 2013 Feb;17:128-40.
ASSESSING ADHD IN LATINO FAMILIES: EVIDENCE FOR MOVING BEYOND SYMPTOMATOLOGY.
Gerdes AC, Lawton KE, Haack LM, et al.
Objective: In an effort to combat the mental health disparities that exist among Latinos, the current study aimed to add to our knowledge related to culturally appropriate assessments for Latino children presenting with ADHD.
Method: As part of a larger study, a community sample of 68 Spanish-speaking, Latino parents completed the Spanish translation of the Disruptive Behavior Disorders Rating Scale (DBD-S), a commonly used, parent-report measure of ADHD.
Results: Results suggest that although both the Inattentive and Hyperactive/Impulsive subscales of the DBD-S are psychometrically sound, the Hyperactive/Impulsive subscale may not be culturally appropriate with some Latino families, particularly those who are less acculturated. This was further supported by preliminary evidence suggesting that this subscale also was not diagnostically useful with the current, community sample.

Conclusion: The potential problems associated with the overemphasis on symptomatology when working with Latino families, the importance of examining functional impairment as part of a culturally appropriate assessment, and the need to replicate the current findings with a clinical sample are discussed.

……

J Autism Dev Disord. 2013;1-7.

SYSTEMATIC REVIEW AND META-ANALYSIS OF PHARMACOLOGICAL TREATMENT OF THE SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN WITH PERVASIVE DEVELOPMENTAL DISORDERS.

Reichow B, Volkmar FR, Bloch MH.

Many children with pervasive developmental disorders (PDD) exhibit behaviors and symptoms of attention-deficit/hyperactivity disorder (ADHD). We sought to determine the relative efficacy of medications for treating ADHD symptoms in children with PDD by identifying all double-blind, randomized, placebo-controlled trials examining the efficacy of medications for treating ADHD symptoms in children with PDD. We located seven trials involving 225 children. A random effects meta-analysis of four methylphenidate trials showed methylphenidate to be effective for treating ADHD symptoms in children with PDD (ES=.67). Several adverse events were greater for children were taking methylphenidate compared to placebo. An individual trial of clonidine and two trials of atomoxetine suggest these agents may also be effective in treating ADHD symptoms in children with PDD.

……

J Child Adolesc Psychopharmacol. 2013;23:11-21.

A LONG-TERM OPEN-LABEL SAFETY AND EFFECTIVENESS TRIAL OF LISDEXAMFETAMINE DIMESYLATE IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Findling RL, Cutler AJ, Saylor K, et al.

Objective: Information on psychostimulant treatment in long-term studies for attention-deficit/hyperactivity disorder (ADHD) in adolescents is limited. This study aimed to assess the safety and effectiveness of lisdexamfetamine dimesylate (LDX) over 52 weeks in adolescents with ADHD.

Methods: This open-label multicenter study enrolled eligible participants after their participation in a randomized, double-blind, placebo-controlled 4 week trial in adolescents with ADHD. Following a 4 week dose-optimization phase, participants were maintained on treatment for up to ~48 weeks on an optimal dose. Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, laboratory findings, and electrocardiograms. Effectiveness measures included the ADHD Rating Scale IV (ADHD-RS-IV; primary) and Clinical Global Impressions-Improvement (CGI-I). The Youth Quality of Life-Research Version (YQOL-R) was also included in this study; raw scores are transformed to a 0-100 point scale.

Results: Of 269 enrolled (from the antecedent study), 265 (98.5%) were in the safety population and effectiveness population. Common TEAEs ((greater-than or equal to)5%) with LDX included upper respiratory tract infection (21.9%), decreased appetite (21.1%), headache (20.8%), decreased weight (16.2%), irritability (12.5%), insomnia (12.1%), nasopharyngitis (7.2%), influenza (6.8%), dizziness (5.3%), and dry mouth (5.3%). At end point, for all LDX doses in the overall safety population, mean (SD) increase from baseline in systolic blood pressure was 2.3 (10.53) mm Hg, diastolic blood pressure was 2.5 (8.37) mm Hg, and pulse rate was 6.3 (12.74) bpm. No clinically meaningful electrocardiogram or vital sign changes were observed. At end point with LDX treatment, the ADHD-RS-IV mean (SD) total score change from antecedent study baseline was -26.2 (9.75) ($p<0.001$); 87.2% of participants were improved (CGI-I=1 or 2). Baseline (antecedent study) mean (SD) YQOL-R perceptual total score was 79.8 (11.28) and increased by 3.9 (9.73) at end point ($p<0.001$).

Conclusions: LDX demonstrated a long-term safety profile similar to that of other long-acting psychostimulants and was effective, as indicated by improvements in ADHD symptoms and participant-perceived YQOL, in adolescents with ADHD.

……

J Child Adolesc Psychopharmacol. 2013;23:22-27.

TWO DIFFERENT SOLICITATION METHODS FOR OBTAINING INFORMATION ON ADVERSE EVENTS ASSOCIATED WITH METHYLPHENIDATE IN ADOLESCENTS: A 12-WEEK MULTICENTER, OPEN-LABEL STUDY.

Lee MS, Lee SI, Hong SD, et al .

Objective: We explored two different methods of determining adverse events (AEs) among methylphenidate (MPH)-treated adolescents with attention-deficit/ hyperactivity disorder (ADHD).

Methods: We performed a 12-week open label study of osmotic-release oral system (OROS) MPH in adolescents with ADHD who were recruited from four child and adolescent psychiatric outpatient clinics. The AEs were evaluated via a two-step procedure at weeks 1, 3, 6, and 12. The first step was to ask a general question to subjects and their parents regarding AEs. The second step included an AE evaluation process by the investigators, which was performed using a drug-specific checklist. One-way repeated measures ANOVA were used to compare the number of AEs reported by patients and their parents compared with the number reported by clinicians. This statistical technique was also used to compare the number of AEs reported by various sources (i.e., patients, parents, and clinicians) at weeks 1, 3, 6, and 12.

Results: Of the 55 participants (43 males, 12 females) between the ages of 12 and 18 enrolled in this study, 47 participants completed the trial. When the number of AEs reported by patients, parents and clinicians were compared, there were no statistically significant differences. When the numbers of AEs obtained from the three different information sources at each study visit were compared, we noted differences. At week 6, the number of AEs evaluated by clinical investigators was higher than those reported by patients and their parents ($p=0.003$). Although the results did not reach statistical significance, the number of AEs reported by clinical investigators appeared to be greater than those obtained from patients or parents at weeks 3 and 12. The number of AEs reported by patients and their parents were similar at every visit. There were some differences in the pattern of AEs reported between patients and their parents.

Conclusions: Clinicians should supplement the subjective report on AEs from patients or their parents with a more drug-specific checklist to obtain drug side effects more effectively. As there are some differences in the pattern of AEs reported by patients and their parents, it is generally recommended that clinicians obtain information from both parties when possible.

……

J Child Adolesc Psychopharmacol. 2013;23:3-10.

NWP06, AN EXTENDED-RELEASE ORAL SUSPENSION OF METHYLPHENIDATE, IMPROVED ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS COMPARED WITH PLACEBO IN A LABORATORY CLASSROOM STUDY.

Wigal SB, Childress AC, Belden HW, et al.

Objective: The purpose of this study was to determine the efficacy of NWP06, a novel extended-release (ER) liquid formulation of methylphenidate (MPH), compared with placebo in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children in a laboratory school.

Methods: A total of 45 subjects ages 6-12 years were enrolled in this dose-optimized, randomized, double-blind, placebo-controlled, crossover laboratory school study. Following open-label dose optimization, subjects received 2 weeks of double-blind treatment (1 week of NWP06 and 1 week of placebo). The treatment sequence (NWP06/placebo or placebo/NWP06) was randomly assigned with the last day of each week-long treatment occurring on the laboratory school test day. Efficacy measures included Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) Rating Scale-Combined and Permanent Product Measure of Performance (PERMP) mathematics tests measured at pre-dose and at 0.75, 2, 4, 8, 10, and 12 hours post-dose on each laboratory classroom day. Safety assessments included physical examination, screening electrocardiogram (ECG), vital signs, clinical laboratory tests, adverse event measures, and assessment of suicidality with the Columbia Suicide Severity Rating Scale.

Results: NWP06 resulted in significant ($p<0.0001$) improvements in the SKAMP-Combined score at 4 hours post-dose (mean=7.12) as compared with placebo (mean=19.58) in the completers (n=39). Significant separation from placebo occurred at each time point tested (0.75, 2, 4, 8, 10, 12 hours), with onset of action of NWP06 at 45 minutes post-dose and duration of efficacy extending to 12 hours post-dose. Adverse events (AEs) and changes in vital signs following NWP06 treatment were generally mild and consistent with the known safety profile of MPH. The most common AEs in the open-label phase were

decreased appetite (55.6%), upper abdominal pain (42.2%), affect lability (26.7%), initial insomnia (22.2%), insomnia (17.8%), and headache (17.8%).
Conclusions: NWP06 treatment effectively reduced symptoms of ADHD in children beginning at 45 minutes and continuing for 12 hours post-dose. NWP06 was well tolerated.

……

J Child Adolesc Psychopharmacol. 2013;23:28-35.
PARENT-REPORTED EXECUTIVE FUNCTION BEHAVIORS AND CLINICIAN RATINGS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN CHILDREN TREATED WITH LISDEXAMFETAMINE DIMESYLATE.
Findling RL, Adeyi B, Dirks B, et al.
Objective: The purpose of this article was to describe the relationships between parent-rated executive function (EF) and clinician-rated attention-deficit/hyperactivity disorder (ADHD) symptoms before and after lisdexamfetamine dimesylate (LDX) treatment in children with and without EF deficit.
Methods: In post-hoc analyses of children with ADHD who participated in a 7 week open-label, dose-optimized (LDX 20-70 mg/day) trial, ADHD Rating Scale-IV (ADHD-RS-IV) change scores were compared (using two-sample t tests) between youth with and without clinically significant EF impairment at baseline. Clinically significant impairment was defined as parent-rated Behavior Rating Inventory of EF (BRIEF) Global Executive Composite (GEC) t scores (greater-than or equal to)65. Relationships between baseline and endpoint BRIEF and ADHD-RS-IV scores were examined using Pearson correlations and generalized effect linear model. Safety assessment included treatment-emergent adverse events (TEAEs).
Results: At baseline, 265/315 participants (84.1%) had a clinically significant BRIEF score. Their mean (SD) ADHD-RS-IV total score at baseline was 42.1 (6.64) for those with, and 36.5 (6.67) for those without, clinically significant BRIEF. At endpoint, ADHD-RS-IV total and subscale scores were significantly improved ($p<0.0001$) for both those with and those without clinically significant baseline BRIEF scores. Moderately strong, positive Pearson correlations were observed between BRIEF and ADHD-RS-IV total and subscale scores. In the generalized effect linear model, ADHD-RS-IV change scores were significantly correlated with endpoint BRIEF scores ($r2=0.35$, (beta)=0.73, $p<0.0001$). In the subgroup without clinically significant BRIEF t scores at endpoint, parents and clinicians rated 90% and 95%, respectively, as improved. In the subgroup with clinically significant BRIEF t scores at endpoint, parents and clinicians rated 69% and 78%, respectively, as improved. TEAEs were experienced by 269/318 (84.9%) participants; most (82.7%) experienced events mild to moderate in intensity. A total of 12/318 (4.1%) participants discontinued because of TEAEs.
Conclusion: Clinically significant impairment of EF behaviors in children with ADHD was associated with more severe ADHD symptoms. LDX therapy improved ADHD symptom severity, and at endpoint, fewer participants displayed impairment of EF behaviors (versus baseline). The parent-rated BRIEF may describe clinically important EF behaviors not assessed by the 18-item ADHD-RS-IV.

……

Journal of Child Psychology and Psychiatry. 2013 Mar;54:260-70.
A NEUROPHYSIOLOGICAL MARKER OF IMPAIRED PREPARATION IN AN 11-YEAR FOLLOW-UP STUDY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).
Doehnert M, Brandeis D, Schneider G, et al.
Background: This longitudinal electrophysiological study investigated the course of multiple impaired cognitive brain functions in attention-deficit/hyperactivity disorder (ADHD) from childhood to adulthood by comparing developmental trajectories of individuals with ADHD and typically developing controls.
Methods: Subjects with ADHD (N=11) and normal controls (N=12) diagnosed in childhood [mean age ADHD/CTRL=10.9 years [SD 1.72]/10.0 years (SD 1.03)] were followed up after 1.1 and 2.4 years, and as young adults [ADHD/CTRL: 21.9 years (SD 1.46)/21.1 years (SD 1.29)]. At all four times, event-related potential (ERP) maps were recorded during a cued continuous performance test (CPT). We focused on residual deficits as adults, and on developmental trajectories (time and time Î group effects) for CPT

performance and attentional (Cue P300), preparatory (CNV: contingent negative variation) and inhibitory (NoGo P300) ERP components.
Results: All ERP components developed without significant time Î group interactions. Only the CNV remained reduced in the ADHD group, although 8/11 individuals no longer met a full ADHD diagnosis as adults. Cue P300 and NoGo P300 group differences became nonsignificant in early adulthood. The CNV parameters correlated with reaction time (RT) and RT-SD. Perceptual sensitivity improved and the groupsÆ trajectories converged with development, while RT-SD continued to be elevated in adult ADHD subjects.
Conclusions: Attentional and preparatory deficits in ADHD continue into adulthood, and the attenuated CNV appears to reflect a particularly stable ADHD marker. Although some deficit reductions may have gone undetected due to small sample size, the findings challenge those developmental lag models postulating that most ADHD-related deficits become negligible with brain maturation.

……

Journal of Child Psychology and Psychiatry. 2013 Mar;54:227-46.
PRACTITIONER REVIEW: CURRENT BEST PRACTICE IN THE MANAGEMENT OF ADVERSE EVENTS DURING TREATMENT WITH ADHD MEDICATIONS IN CHILDREN AND ADOLESCENTS.
Cortese S, Holtmann M, Banaschewski T, et al.
Background: Medication is an important element of therapeutic strategies for ADHD. While medications for ADHD are generally well-tolerated, there are common, although less severe, as well as rare but severe adverse events AEs during treatment with ADHD drugs. The aim of this review is to provide evidence- and expert-based guidance concerning the management of (AEs) with medications for ADHD.
Methods: For ease of use by practitioners and clinicians, the article is organized in a simple question and answer format regarding the prevalence and management of the most common AEs. Answers were based on empirical evidence from studies (preferably meta-analyses or systematic reviews) retrieved in PubMed, Ovid, EMBASE and Web of Knowledge through 30 June 2012. When no empirical evidence was available, expert consensus of the members of the European ADHD Guidelines Group is provided. The evidence-level of the management recommendations was based on the SIGN grading system.
Results: The review covers monitoring and management strategies of loss of appetite and growth delay, cardiovascular risks, sleep disturbance, tics, substance misuse/abuse, seizures, suicidal thoughts/behaviours and psychotic symptoms.
Conclusion: Most AEs during treatment with drugs for ADHD are manageable and most of the times it is not necessary to stop medication, so that patients with ADHD may continue to benefit from the effectiveness of pharmacological treatment.

……

J Consult Clin Psychol. 2012;80:1041-51.
PROSPECTIVE FOLLOW-UP OF GIRLS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER INTO EARLY ADULTHOOD: CONTINUING IMPAIRMENT INCLUDES ELEVATED RISK FOR SUICIDE ATTEMPTS AND SELF-INJURY.
Hinshaw SP, Owens EB, Zalecki C, et al.
Objective: We performed a 10-year prospective follow-up of a childhood-ascertained (6-12 years), ethnically and socioeconomically diverse sample of girls with attention-deficit/hyperactivity disorder (ADHD; N=140: combined type [ADHD-C] n = 93; inattentive type [ADHD-I] n=47) plus a matched comparison group (N=88). Girls were recruited from schools, mental health centers, pediatric practices, and via advertisements; extensive evaluations confirmed ADHD versus comparison status.
Method: Ten-year outcomes (age range 17-24 years; retention rate=95%) included symptoms (ADHD, externalizing, internalizing), substance use, eating pathology, self-perceptions, functional impairment (global, academic, service utilization), self-harm (suicide attempts, self-injury), and driving behavior.
Results: Participants with childhood-diagnosed ADHD continued to display higher rates of ADHD and comorbid symptoms, showed more serious impairment (both global and specific), and had higher rates of suicide attempts and self-injury than the comparison sample, with effect sizes from medium to very large;

yet the groups did not differ significantly in terms of eating pathology, substance use, or driving behavior. ADHD-C and ADHD-I types rarely differed significantly, except for suicide attempts and self-injury, which were highly concentrated in ADHD-C. Domains of externalizing behavior, global impairment, service utilization, and self-harm (self-injury and suicide attempts) survived stringent control of crucial childhood covariates (age, demographics, comorbidities, IQ).
Conclusions: Girls with childhood ADHD maintain marked impairment by early adulthood, spreading from symptoms to risk for serious self-harm. Our future research addresses the viability of different diagnostic conceptions of adult ADHD and their linkages with core life impairments.

……

J Consult Clin Psychol. 2012;80:139-50.
DIAGNOSING ADHD IN ADOLESCENCE.
Sibley MH, Pelham J, Molina BSG, et al.
Objective: This study examines adolescent-specific practical problems associated with current practice parameters for diagnosing attention-deficit/ hyperactivity disorder (ADHD) to inform recommendations for the diagnosis of ADHD in adolescents. Specifically, issues surrounding the use of self-versus informant ratings, diagnostic threshold, and retrospective reporting of childhood symptoms were addressed.
Method: Using data from the Pittsburgh ADHD Longitudinal Study (PALS), parent, teacher, and self-reports of symptoms and impairment were examined for 164 adolescents with a childhood diagnosis of ADHD (age M=14.74 years) and 119 demographically similar non-ADHD controls (total N=283).
Results: Results indicated that 70% of the well-diagnosed childhood ADHD group continued to meet Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; American Psychiatric Association, 2000) diagnostic criteria for ADHD in adolescence; however, an additional 17% possessed clinically significant impairment in adolescence but did not qualify for a current ADHD diagnosis. The optimal source of information was combined reports from the parent and a core academic teacher. Adolescents with ADHD met criteria for very few symptoms of hyperactivity/impulsivity, suggesting a need to revisit the diagnostic threshold for these items. Additionally, emphasis on impairment, rather than symptom threshold, improved identification of adolescents with a gold-standard childhood diagnosis of ADHD and persistent ADHD symptoms. Parent retrospective reports of baseline functioning, but not adolescent self-reports, were significantly correlated with reports collected at baseline in childhood.
Conclusions: Recommendations are offered for diagnosing ADHD in adolescence based on these findings.

……

J Consult Clin Psychol. 2012;80:239-44.
TREATMENT OF COMORBID ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND ANXIETY IN CHILDREN: A MULTIPLE BASELINE DESIGN ANALYSIS.
Jarrett MA, Ollendick TH.
Objective: The present study evaluated a 10-week psychosocial treatment designed specifically for children with attention-deficit/hyperactivity disorder (ADHD) and a comorbid anxiety disorder.
Method: Using a nonconcurrent multiple baseline design, the authors treated 8 children ages 8-12 with ADHD, combined type, and at least 1 of 3 major anxiety disorders (separation anxiety disorder, generalized anxiety disorder, social phobia). The integrated treatment protocol involved parent management training for ADHD and family-based cognitive-behavioral therapy for anxiety. Pretreatment assessments included semistructured diagnostic interviews and other standardized measures to determine study eligibility. Children were randomized to 1 of 3 baseline control conditions (i.e., 2, 3, or 4 weeks) and subsequently treated in a university-based psychosocial treatment clinic. Weekly assessments of ADHD and anxiety disorder symptoms occurred throughout treatment and comprehensive assessments were obtained at pretreatment, 1-week posttreatment, and 6-months posttreatment.
Results: Single-case results supported greater success in the treatment phase relative to the baseline phase for both ADHD and anxiety symptoms, and ADHD and anxiety symptoms appeared to change

concurrently. Pre-post group analyses revealed significant and clinically meaningful improvements in ADHD and anxiety symptoms at 1-week posttreatment, but only anxiety symptoms moved into the subclinical range. At 6-months follow-up, treatment effects were maintained with new movement into the subclinical range for ADHD.
Conclusions: The present study provides initial data on an integrated treatment protocol for ADHD and anxiety. Further replication and evaluation are needed. Implications of the findings are discussed.

……

J Consult Clin Psychol. 2012;80:611-23.
A FAMILY-SCHOOL INTERVENTION FOR CHILDREN WITH ADHD: RESULTS OF A RANDOMIZED CLINICAL TRIAL.
Power TJ, Mautone JA, Soffer SL, et al.
Objective: Accumulating evidence highlights the importance of using psychosocial approaches to intervention for children with attention-deficit/ hyperactivity disorder (ADHD) that target the family and school, as well as the intersection of family and school. This study evaluated the effectiveness of a family-school intervention, Family-School Success (FSS), designed to improve the family and educational functioning of students in Grades 2-6 who meet criteria for ADHD combined and inattentive types. Key components of FSS were conjoint behavioral consultation, daily report cards, and behavioral homework interventions.
Method: FSS was provided over 12 weekly sessions, which included 6 group sessions, 4 individualized family sessions, and 2 school-based consultations. Participating families were given the choice of placing their children on medication; 43% of children were on medication at the time of random assignment. Children (n =199) were randomly assigned to FSS or a comparison group controlling for non-specific treatment effects (Coping With ADHD Through Relationships and Education [CARE]). Outcomes were assessed at post-intervention and 3-month follow-up. The analyses controlled for child medication status.
Results: FSS had a significant effect on the quality of the family-school relationship, homework performance, and parenting behavior.
Conclusions: The superiority of FSS was demonstrated even though about 40% of the participants in FSS and CARE were on an optimal dose of medication and there were significant time effects on each measure. This relatively brief intervention produced effect sizes comparable to those of the more intensive Multimodal Treatment Study of Children With ADHD (MTA) behavioral intervention.

……

J Dev Behav Pediatr. 2013 Feb;34:72-82.
THE PSYCHOMETRIC PROPERTIES OF THE VANDERBILT ATTENTION-DEFICIT HYPERACTIVITY DISORDER DIAGNOSTIC PARENT RATING SCALE IN A COMMUNITY POPULATION.
Bard DE, Wolraich ML, Neas B, et al.
Objective: To examine the psychometric properties of the Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS) using a community-based sample of primarily elementary and middle school-aged children.
Method: Participants were initially recruited from 41 elementary schools in 5 Oklahoma school districts including urban, suburban, and rural students. Vanderbilt rating scales were obtained from all teachers (n = 601) and sampled parents (n = 587) of the participating children. Construct validity was assessed by confirmatory factor analysis of the 45 items that made up the 4 scales of inattention, hyperactivity, conduct/oppositional problems, and anxiety/depression problems. Reliability was evaluated from internal consistency, test-retest, and interrater agreement perspectives. Criterion validity was evaluated via comparisons to a structured psychiatric interview with the parents using the Diagnostic Interview Schedule for Children-IV.
Results: A 4-factor model (inattention, hyperactivity, conduct/oppositional problems, and anxiety/depression problems) fit the data well once discarding conduct items that were infrequently endorsed. The estimates of coefficient alpha ranged from .91 to .94 and the analogous KR20 coefficient for a binary item version of the scale ranged from .88 to .91. Test-retest reliability exceeded .80 for all summed

scale scores. The VADPRS produced a sensitivity of .80, specificity of .75, positive predictive value of .19, and negative predictive value of .98 when predicting an attention-deficit hyperactivity disorder (ADHD) case definition that combined teacherÆs Vanderbilt ADHD Diagnostic Teacher Rating Scale and parent diagnostic interview responses.
Conclusion: The confirmation of the construct and concurrent criterion validities found in this study further support the utility of the VADPRS as a diagnostic rating scale for ADHD.

……

J Dev Behav Pediatr. 2013 Feb;34:138-40.
'WHEN THE PRESCRIPTION PAD IS NOT ENOUGH': ATTENTION-DEFICIT HYPERACTIVITY DISORDER MANAGEMENT 2.0.
Radesky J, Reddy A, Steiner N, et al.
This article first describes the case of Jose, a 13-year-old boy who presents to his primary care provider after struggling in school for many years. When he was in the first grade, he was diagnosed at a tertiary center with attention-deficit hyperactivity disorder (ADHD). Multiple medication trials have produced few benefits and many side effects. He comes now for his annual physical and the parents report that the school is threatening that he be retained in the seventh grade. They have brought their own and his advisorÆs VanderbiltÆs, which each endorse 7 of 9 inattentive symptoms. Several familial, sociocultural, and school-level issues in the case are briefly presented. The family is very concerned about the possibility of retention, but the parents do not want to try another medication. The current authors discuss their recommendations for intervention. These include several nonpharmacological approaches to treatment, including behavior modification, parent management training programs, and computer attention training based on cognitive training or neurofeedback. The authors also recommend psychoeducational evaluation for comorbid learning disabilities or emotional problems, as well as seeking support from the school and educational accommodations if necessary. These commentaries demonstrate that when the family is resistant to continuing medication, partnering with the family and exploring with them other options is critical to therapeutic success.

……

J Indian Assoc Child Adolesc Ment Health. 2013;9:1-4.
TREATMENT NEEDS OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER BEYOND SYMPTOM CONTROL.
Agarwal V, Dhanasekaran S.

……

J Neuroimmunol. 2013.
ANTI-PURKINJE CELL ANTIBODY AS A BIOLOGICAL MARKER IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A PILOT STUDY.
Passarelli F, Donfrancesco R, Nativio P, et al.
An autoimmune hypothesis has been suggested for several disorders in childhood. The aim of the study was to clarify the role of the cerebellum in ADHD and to evaluate the possible association between anti-Yo antibodies and ADHD. The presence/absence of antibodies was tested by indirect immunofluorescence assay on 30 combined subtype ADHD children, on 19 children with other psychiatric disorders (Oppositional-defiant and Conduct Disorders, Dyslexia) and 27 healthy controls. Results showed a significant positive response to the anti-Yo antibody immunoreactivity in the Purkinje cells of the cerebellum of ADHD children, compared with the control group and the psychiatric non-ADHD children. This association points to an immune dysregulation and the involvement of the cerebellum in ADHD.

……

J Neurother. 2013;17:35-42.

THE EFFECTS OF NEUROFEEDBACK IN THE DEFAULT MODE NETWORK: PILOT STUDY RESULTS OF MEDICATED CHILDREN WITH ADHD.

Russell-Chapin L, Kemmerly T, Liu WC, et al.

Children with attention deficit hyperactivity disorder (ADHD) have difficulty activating the Default Mode Network (DMN) in a resting or quiet state. The DMN function assists in processing and understanding a person's internal, reflective world and the world of self and others. Neurofeedback (NFB), a type of EEG operant conditioning, trains self-regulation skills using a brain-computer interface. The hardware and software have audio/video capabilities to correct irregular brainwave patterns and regional cerebral blood flow associated with mental health and cognitive concerns. Individual treatment sessions usually last approximately 20 min; to gain the largest overall treatment effect, NFB users need to experience about 30 to 40 sessions. This study randomly assigned 12 children diagnosed with ADHD and currently on a stimulant medication to a treatment or control group. Subjects in the treatment group completed 40 NFB sessions. Pre- and posttest fMRIs were administered on the treatment and control groups. Evidence showed that the forty 20-min sessions of Sensory Motor Rhythm NFB consolidated the DMN allowing for appropriate activation in the posterior cingulate, precuneus, the temporoparietal junction and the cerebellar tonsils. In addition to regulating and increasing SMR at 12-15 Hz, our research results showed activation of the DMN in a resting state after 40 NFB sessions. Assisting children with ADHD to appropriately activate the DMN may help them be more adaptive and reflective and to better understand their own internal world and the world of others.

……

J Pediatr Gastroenterol Nutr. 2013;56:211-14.

FREQUENCY OF CELIAC DISEASE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Gungor S, Celiloglu OS, Ozcan OO, et al.

OBJECTIVE: Although it is well known that celiac disease (CD) is associated with neurologic disorders, association with psychiatric problems is not well defined. In this report, we aimed to detect CD prevalence in patients with attention-deficit hyperactivity disorder (ADHD).

METHODS: A total of 362 patients between the ages 5 and 15 years with the diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria and 390 sex- and age-matched healthy children were included in the present study. Serum levels of tissue transglutaminase (tTg) immunoglobulin (Ig) A and IgG were studied in both groups. Serum IgA levels were also studied in patients with positive tTG IgG for the exclusion of selective IgA deficiency. Endoscopic duodenal biopsy was provided in seropositive patients, whose parents approved the procedure. Biopsy samples were evaluated according to Marsh-Oberhuber classification.

RESULTS: tTg IgA was positive in 4 patients with ADHD (1.1%). Endoscopic duodenal biopsy was suggestive of CD in one of them (0.27%). tTg IgA was positive in 3 of control group patients (0.8%). Duodenal biopsy of the only patient from control group, who underwent upper gastrointestinal endoscopy, revealed normal intestinal mucosa.

CONCLUSIONS: The seropositivity rates for CD were found similar in ADHD and control groups. Thus, neither routine screening for CD nor empirical recommendation of gluten-free diet seems necessary in children with ADHD.

……

J Pediatr. 2013;162:543-51.

EXERCISE IMPROVES BEHAVIORAL, NEUROCOGNITIVE, AND SCHOLASTIC PERFORMANCE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Pontifex MB, Saliba BJ, Raine LB, et al.

Objective: To examine the effect of a single bout of moderate-intensity aerobic exercise on preadolescent children with attention-deficit/hyperactivity disorder (ADHD) using objective measures of attention, brain neurophysiology, and academic performance.

Study design: Using a within-participants design, task performance and event-related brain potentials were assessed while participants performed an attentional-control task following a bout of exercise or seated reading during 2 separate, counterbalanced sessions.
Results: Following a single 20-minute bout of exercise, both children with ADHD and healthy match control children exhibited greater response accuracy and stimulus-related processing, with the children with ADHD also exhibiting selective enhancements in regulatory processes, compared with after a similar duration of seated reading. In addition, greater performance in the areas of reading and arithmetic were observed following exercise in both groups.
Conclusion: These findings indicate that single bouts of moderately intense aerobic exercise may have positive implications for aspects of neurocognitive function and inhibitory control in children with ADHD.

……

J Psychiatr Res. 2013;47:505-12.
1H MRSI OF MIDDLE FRONTAL GYRUS IN PEDIATRIC ADHD.
Tafazoli S, O'Neill J, Bejjani A, et al.
Neuroimaging studies in multiple modalities have implicated the left or right dorsolateral prefrontal cortex (here, middle frontal gyrus) in attentional functions, in ADHD, and in dopamine agonist treatment of ADHD. The far lateral location of this cortex in the brain, however, has made it difficult to study with magnetic resonance spectroscopy (MRS). We used the smaller voxel sizes of the magnetic resonance spectroscopic imaging (MRSI) variant of MRS, acquired at a steep coronal-oblique angle to sample bilateral middle frontal gyrus in 13 children and adolescents with ADHD and 13 age- and sex-matched healthy controls. Within a subsample of the ADHD patients, aspects of attention were also assessed with the Trail Making Task. In right middle frontal gyrus only, mean levels of N-acetyl-aspartate + N-acetyl-aspartyl-glutamate (tNAA), creatine + phosphocreatine (Cr), choline-compounds (Cho), and myo-inositol (mI) were significantly lower in the ADHD than in the control sample. In the ADHD patients, lower right middle frontal Cr was associated with worse performance on Trails A and B (focused attention, concentration, set-shifting), while the opposite relationship held true for the control group on Trails B. These findings add to evidence implicating right middle frontal cortex in ADHD. Lower levels of these multiple species may reflect osmotic adjustment to elevated prefrontal cortical perfusion in ADHD and/or a previously hypothesized defect in astrocytic production of lactate in ADHD resulting in decelerated energetic metabolism (Cr), membrane synthesis (Cho, mI), and acetyl-CoA substrate for NAA synthesis. Lower Cr levels may indicate attentional or executive impairments.

……

J Psychopathol Behav Assess. 2013;35:10-19.
AN INTENSIVE SUMMER TREATMENT PROGRAM FOR ADHD REDUCES PARENT-ADOLESCENT CONFLICT.
Sibley MH, Ross JM, Gnagy EM, et al.
There are currently almost no treatment efforts to reduce parent-adolescent conflict in adolescents with ADHD. As such, this study investigated the effect of an intensive Summer Treatment Program for Adolescents with ADHD (STP-A) on parent-adolescent conflict. Twenty adolescents and their parents completed the 8 week behavioral treatment program, which included 320 hours of adolescent-directed treatment, 15 hours of parent behavior management training, and daily feedback from staff on parent implementation of a home-based behavioral contract. Results indicated that 70-85 % of adolescents who attended the STP-A demonstrated reliable improvement in parent-adolescent conflict from baseline to post-treatment. Treatment response was associated with higher levels of conflict at baseline, but not adolescent ODD severity or parent ADHD severity. Several patterns of treatment non-response were detected through visual examination of weekly conflict scores during the STP-A. Discussion suggests that intensive, parent-involved treatment programs may be necessary to improve home-conflict in adolescents with ADHD.

……

J Sleep Res. 2013.

CLINICAL IMPLICATIONS OF DAYTIME SLEEPINESS FOR THE ACADEMIC PERFORMANCE OF MIDDLE SCHOOL-AGED ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Langberg JM, Dvorsky MR, Marshall S, et al.

This study investigated the relative impact of total time slept per night and daytime sleepiness on the academic functioning of 100 middle school-aged youth (mean age = 11.9) with attention deficit hyperactivity disorder (ADHD). The primary goal of the study was to determine if total time slept per night and/or daytime sleepiness, as measured by youth self-report on the Pediatric Daytime Sleepiness Scale (PDSS), predicted academic functioning above and beyond symptoms of ADHD and relevant covariates, such as intelligence, achievement scores and parent education level. Self-reported daytime sleepiness but not self-reported total time slept per night was associated significantly with all academic outcomes. When examined in a hierarchical regression model, self-reported daytime sleepiness significantly predicted parent-rated homework problems and academic impairment and teacher-rated academic competence above and beyond symptoms of ADHD and relevant covariates, but did not predict grade point average or teacher-rated academic impairment. The implications of these findings for understanding more clearly the association between ADHD and sleep and the functional implications of this relationship are discussed.

……

Journal of the American Academy of Child & Adolescent Psychiatry. 2013 Mar;52:264-278e2.

THE PRESCHOOL ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATMENT STUDY (PATS) 6-YEAR FOLLOW-UP.

Riddle MA, Yershova K, Lazzaretto D, et al.

Objective: To describe the clinical course of attention-deficit/hyperactivity disorder (ADHD) symptom severity and diagnosis from ages 3 to 5 up to 9 to 12 years during a 6-year follow-up after the original Preschool ADHD Treatment Study (PATS).

Method: A total of 207 participants (75% male) from the original PATS, assessed at baseline (mean age, 4.4 years, when all met criteria for ADHD) and 3 months later (before medication treatment), were re-evaluated in three follow-up assessment visits (year 3, mean age 7.4 years; year 4, 8.3 years; and year 6, 10.4 years). Parents and teachers rated symptom severity, and clinicians established psychiatric diagnoses. Analyses examined longitudinal changes in symptom severity and ADHD diagnosis.

Results: Parent- and teacher-rated symptom severity decreased from baseline to year 3 but remained relatively stable and in the moderate-to-severe clinical range through year 6. Girls showed generally steeper decreases in symptom T-scores. At year 6, 89% (160/180) of remaining participants met ADHD symptom and impairment diagnostic criteria. Comorbidity of oppositional defiant disorder and/or conduct disorder was associated with a 30% higher risk of having an ADHD diagnosis at year 6 in the multiple logistic model. Medication status during follow-up, on versus off, did not predict symptom severity change from year 3 to year 6 after adjustment for other variables.

Conclusions: ADHD in preschoolers is a relatively stable diagnosis over a 6-year period. The course is generally chronic, with high symptom severity and impairment, in very young children with moderate-to-severe ADHD, despite treatment with medication. Development of more effective ADHD intervention strategies is needed for this age group.

……

Journal of the American Academy of Child & Adolescent Psychiatry. 2013 Mar;52:309-18.

LATE PRETERM BIRTH, MATERNAL DEPRESSION, AND RISK OF PRESCHOOL PSYCHIATRIC DISORDERS.

Rogers CE, Lenze SN, Luby JL.

Objective: Preterm children are at greater risk for psychiatric disorders, including anxiety disorders and attention-deficit/hyperactivity disorder (ADHD), than their term-born peers. Prior research has focused primarily on children born at early gestational ages. Less is known about the rate of psychiatric disorders among late preterm or early term children. In addition, whether a history of maternal depression also associated with prematurity has an impact on the risk for psychiatric disorders remains underexplored.

Method: Preschoolers between ages 3 and 6 years (N=306) were recruited for a study examining preschool depression that included healthy and disruptive preschoolers. Preschoolers were placed in the following groups: late preterm (34-36 weeks, n=39), early term (37-39 weeks, n=78), and full term (40-41 weeks, n = 154). DSM-IV psychiatric disorders were assessed via the Preschool Age Psychiatric Assessment. Maternal history of psychiatric disorders was assessed using the Family Interview for Genetic Studies.
Results: Late preterm children had higher rates of any Axis I psychiatric diagnosis (odds ratio = 3.18, 95% confidence interval=1.09-4.76) and of any anxiety disorder (odds ratio=3.74, 95% confidence interval=1.59-8.78) than full term children after adjusting for gender, ethnicity, family income, and IQ. There were no differences in rates of psychiatric diagnoses between early term and full term children. A history of maternal depression mediated the relationship between late preterm birth and anxiety disorders in preschoolers.
Conclusions: Late preterm children were at increased risk for anxiety disorders at preschool age. A history of maternal depression mediated this association. Findings confirm the extension of the risk of psychiatric disorders associated with prematurity to the late preterm group, and suggest that maternal depression may play a key role in this risk trajectory.

……

Journal of the American Academy of Child & Adolescent Psychiatry. 2013 Mar;52:228-30.
FINDING THE TOOLS FOR EFFECTIVE EARLY INTERVENTION FOR PRESCHOOL ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Gleason MM.
The rapid development across all developmental domains in early childhood offers opportunities for early intervention to mitigate risks and promote healthy development. Existing data are clear that early intervention promotes healthy brain development and positive caregiving environments and lowers the costs associated with high-risk child, family, and community factors. A growing empirical literature moves beyond risk factors to characterize clinically impairing early childhood mental health problems, including attention-deficit/hyperactivity disorder (ADHD), and examine the efficacy of treatments. Together, the promise of effective interventions and the current gaps in available treatments highlight the need for studies to define effective early intervention strategies. Young children, their families, and clinicians depend on studies designed to address relevant clinical questions with developmentally specific approaches. We must redouble our efforts to identify enhanced or alternative interventions for preschool ADHD and to ensure that those treatments are accessible to young children with impairing ADHD.

……

Journal of the American Academy of Child & Adolescent Psychiatry. 2013 Mar;52:225-27.
DO STIMULANTS PREVENT SUBSTANCE USE AND MISUSE AMONG YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER? THE ANSWER IS STILL MAYBE.
Goldstein BI.
The association of substance-use disorders (SUDs) with attention-deficit/hyperactivity disorder (ADHD) and its treatment with stimulants has been the subject of much research and much debate. Previous studies have shown that ADHD is associated with an increased risk of subsequent SUD. However, those studies have been constrained by a limited emphasis on substance use below the threshold for SUD and by limited detail regarding the developmental course of SUD in youth with ADHD. Many clinicians believe that by treating ADHD, most effectively with stimulants, we may be doing the dual good service of decreasing current symptoms and impairment and indirectly preventing substance misuse. Based on the extant literatureùit would be inaccurate to characterize stimulants as a globally effective inoculation against substance misuse. Nonetheless, it remains likely that there is a subset of youth for whom ongoing stimulant treatment may prevent the academic impairment, peer difficulties, family conflict, and impulsive decisions that plant the seeds of substance misuse. For now, we cannot tell which youth will derive this benefit. Can we be content telling youth and parents that, in addition to improving symptoms, stimulants may decrease the risk of substance misuse for some youth with ADHD? For now, we may have to be.

……

Journal of the American Academy of Child & Adolescent Psychiatry. 2013 Mar;52:250-63.

ADOLESCENT SUBSTANCE USE IN THE MULTIMODAL TREATMENT STUDY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) (MTA) AS A FUNCTION OF CHILDHOOD ADHD, RANDOM ASSIGNMENT TO CHILDHOOD TREATMENTS, AND SUBSEQUENT MEDICATION.

Molina BSG, Hinshaw SP, Arnold LE, et al.

Objective: To determine long-term effects on substance use and substance use disorder (SUD), up to 8 years after childhood enrollment, of the randomly assigned 14-month treatments in the multisite Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA; n=436); to test whether medication at follow-up, cumulative psychostimulant treatment over time, or both relate to substance use/SUD; and to compare substance use/SUD in the ADHD sample to the non-ADHD childhood classmate comparison group (n=261).

Method: Mixed-effects regression models with planned contrasts were used for all tests except the important cumulative stimulant treatment question, for which propensity score matching analysis was used.

Results: The originally randomized treatment groups did not differ significantly on substance use/SUD by the 8-year follow-up or earlier (mean age =17 years). Neither medication at follow-up (mostly stimulants) nor cumulative stimulant treatment was associated with adolescent substance use/SUD. Substance use at all time points, including use of two or more substances and SUD, were each greater in the ADHD than in the non-ADHD samples, regardless of sex.

Conclusions: Medication for ADHD did not protect from, or contribute to, visible risk of substance use or SUD by adolescence, whether analyzed as randomized treatment assignment in childhood, as medication at follow-up, or as cumulative stimulant treatment over an 8-year follow-up from childhood. These results suggest the need to identify alternative or adjunctive adolescent-focused approaches to substance abuse prevention and treatment for boys and girls with ADHD, especially given their increased risk for use and abuse of multiple substances that is not improved with stimulant medication.

……

J Am Acad Child Adolesc Psychiatry. 2013;52:264-78.

THE PRESCHOOL ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATMENT STUDY (PATS) 6-YEAR FOLLOW-UP.

Riddle MA, Yershova K, Lazzaretto D, et al.

Objective: To describe the clinical course of attention-deficit/ hyperactivity disorder (ADHD) symptom severity and diagnosis from ages 3 to 5 up to 9 to 12 years during a 6-year follow-up after the original Preschool ADHD Treatment Study (PATS).

Method: A total of 207 participants (75% male) from the original PATS, assessed at baseline (mean age, 4.4 years, when all met criteria for ADHD) and 3 months later (before medication treatment), were re-evaluated in three follow-up assessment visits (year 3, mean age 7.4 years; year 4, 8.3 years; and year 6, 10.4 years). Parents and teachers rated symptom severity, and clinicians established psychiatric diagnoses. Analyses examined longitudinal changes in symptom severity and ADHD diagnosis.

Results: Parent- and teacher-rated symptom severity decreased from baseline to year 3 but remained relatively stable and in the moderate-to-severe clinical range through year 6. Girls showed generally steeper decreases in symptom T-scores. At year 6, 89% (160/180) of remaining participants met ADHD symptom and impairment diagnostic criteria. Comorbidity of oppositional defiant disorder and/or conduct disorder was associated with a 30% higher risk of having an ADHD diagnosis at year 6 in the multiple logistic model. Medication status during follow-up, on versus off, did not predict symptom severity change from year 3 to year 6 after adjustment for other variables.

Conclusions: ADHD in preschoolers is a relatively stable diagnosis over a 6-year period. The course is generally chronic, with high symptom severity and impairment, in very young children with moderate-to-severe ADHD, despite treatment with medication. Development of more effective ADHD intervention strategies is needed for this age group.

……

J Am Acad Child Adolesc Psychiatry. 2013;52:250-63.

ADOLESCENT SUBSTANCE USE IN THE MULTIMODAL TREATMENT STUDY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) (MTA) AS A FUNCTION OF CHILDHOOD ADHD, RANDOM ASSIGNMENT TO CHILDHOOD TREATMENTS, AND SUBSEQUENT MEDICATION.

Molina BSG, Hinshaw SP, Eugene Arnold L, et al.

Objective: To determine long-term effects on substance use and substance use disorder (SUD), up to 8 years after childhood enrollment, of the randomly assigned 14-month treatments in the multisite Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA; n=436); to test whether medication at follow-up, cumulative psychostimulant treatment over time, or both relate to substance use/SUD; and to compare substance use/SUD in the ADHD sample to the non-ADHD childhood classmate comparison group (n=261).

Method: Mixed-effects regression models with planned contrasts were used for all tests except the important cumulative stimulant treatment question, for which propensity score matching analysis was used.

Results: The originally randomized treatment groups did not differ significantly on substance use/SUD by the 8-year follow-up or earlier (mean age = 17 years). Neither medication at follow-up (mostly stimulants) nor cumulative stimulant treatment was associated with adolescent substance use/SUD. Substance use at all time points, including use of two or more substances and SUD, were each greater in the ADHD than in the non-ADHD samples, regardless of sex.

Conclusions: Medication for ADHD did not protect from, or contribute to, visible risk of substance use or SUD by adolescence, whether analyzed as randomized treatment assignment in childhood, as medication at follow-up, or as cumulative stimulant treatment over an 8-year follow-up from childhood. These results suggest the need to identify alternative or adjunctive adolescent-focused approaches to substance abuse prevention and treatment for boys and girls with ADHD, especially given their increased risk for use and abuse of multiple substances that is not improved with stimulant medication.

……

Med J Aust. 2013;198:29-32.

GROWTH AND PUBERTAL DEVELOPMENT OF ADOLESCENT BOYS ON STIMULANT MEDICATION FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Poulton AS, Melzer E, Tait PR, et al.

Objective: To investigate the growth and pubertal attainment of boys with attention deficit hyperactivity disorder (ADHD) on stimulant medication.

Design, setting and participants: Longitudinal study of boys aged 12.00-15.99 years at recruitment in 2005-2011, with stimulant-treated ADHD for at least 3 years, attending three paediatric practices (subjects), compared with longitudinal data from 174 boys from the Nepean longitudinal study (controls).

Main outcome measures: Subjects' growth parameters before treatment were compared with controls aged 7 or 8 years; growth parameters and longitudinal changes on treatment to ages 12.00-13.99 and 14.00-15.99 years were compared with controls reviewed at 13 and 15 years of age, respectively. The subjects' pubertal staging and height velocity were related to their treatment history.

Results: Sixty-five subjects were recruited; mean duration of treatment was 6.3 (plus or minus) 1.9 years. At baseline, their growth parameters were not significantly different from those of the controls after adjusting for age. Compared with the controls, after adjusting for current age and baseline growth parameter z score, subjects aged 12.00-13.99 years had significantly lower weight and body mass index ($P< 0.01$), and those aged 14.00-15.99 years had significantly lower height and weight ($P< 0.05$). At 12.00-13.99 years of age, the subjects were comparable to the controls in their pubertal development adjusted for age, but those aged 14.00-15.99 years reported significant delay (mean Tanner stage, 3.6 for subjects v 4.0 for controls; $P< 0.05$). The dose of medication was inversely correlated with the height velocity from baseline to 14.00-15.99 years of age ($P<0.05$).

Conclusions: Prolonged treatment (more than 3 years) with stimulant medication was associated with a slower rate of physical development during puberty. To maintain adequate height velocity during puberty, we recommend keeping the dose as low as possible.

……

NeuroMol Med. 2013;15:122-32.

GENETIC EVIDENCE FOR THE ASSOCIATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS WITH ADHD AND METHYLPHENIDATE TREATMENT RESPONSE.

Fortier ME, Sengupta SM, Grizenko N, et al.

Exposure to stressors results in a spectrum of autonomic, endocrine, and behavioral responses. A key pathway in this response to stress is the hypothalamic-pituitary-adrenal (HPA) axis, which results in a transient increase in circulating cortisol, which exerts its effects through the two related ligand-activated transcription factors: the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Genetic polymorphisms in these receptors have been shown to influence HPA axis reactivity, and chronic dysregulation of the HPA axis has been associated with the development of several psychiatric disorders. The objective of the study was to test the association between four functional polymorphisms in NR3C1 (encoding GR: ER22/23EK-rs6189, N363S-rs6195, BclI-rs41423247, A3669G-rs6198) and two in NR3C2 (encoding MR: 215G/C-rs2070951, I180 V-rs5522) with childhood ADHD. Family-based association tests (FBAT) were conducted with the categorical diagnosis of ADHD, behavioral and cognitive phenotypes related to ADHD, as well as with treatment response assessed in a 2-week, double-blind, placebo-controlled trial with methylphenidate. A specific haplotype (G:A:G:G; ER22/23EK- N363S- BclI- A3669G) of NR3C1 showed a significant association with behaviors related to ADHD (particularly thought and attention problems, aggressive behavior), comorbidity with oppositional defiant disorder, and executive function domains. An association was also observed with treatment response (assessed by the Conners'-Teachers and Restricted Academic Situation Scale). In contrast, MR gene polymorphisms were not associated with any of the variables tested. To the best of our knowledge, this is the first report showing an association between functional polymorphisms in NR3C1 and ADHD, providing genetic evidence for involvement of the HPA axis in the disorder and treatment response.

……

Neuropsychiatr Dis Treat. 2013;9:211-18.

RESPONSE TO METHYLPHENIDATE BY ADULT AND PEDIATRIC PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE SPANISH MULTICENTER DIHANA STUDY.

Valdizan-Uson JR, Canovas-Martinez A, de Lucas-Taracena MT, et al.

Background: The purpose of this multicenter Spanish study was to evaluate the response to immediate-release methylphenidate by children and adults diagnosed with attention-deficit/hyperactivity disorder (ADHD), as well as to obtain information on current therapy patterns and safety characteristics.

Methods: This multicenter, observational, retrospective, noninterventional study included 730 patients aged 4-65 years with a diagnosis of ADHD. Information was obtained based on a review of medical records for the years 2002-2006 in sequential order.

Results: The ADHD predominantly inattentive subtype affected 29.7% of patients, ADHD predominantly hyperactive-impulsive was found in 5.2%, and the combined subtype in 65.1%. Overall, a significant lower Clinical Global Impression (CGI) score and mean number of DSM-IV TR (Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision) symptoms by subtype were found after one year of treatment with immediate-release methylphenidate; CGI decreased from 4.51 to 1.69, symptoms of inattention from 7.90 to 4.34, symptoms of hyperactivity from 6.73 to 3.39, and combined subtype symptoms from 14.62 to 7.7. Satisfaction with immediate-release methylphenidate after one year was evaluated as "very satisfied" or "satisfied" by 86.90% of the sample; 25.75% of all patients reported at least one adverse effect. At the end of the study, 41.47% of all the patients treated with immediate-release methylphenidate were still receiving it, with a mean time of 3.80 years on therapy.

Conclusion: Good efficacy and safety results were found for immediate-release methylphenidate in patients with ADHD.

……

Neuropsychiatry. 2013;3:17-21.

PSYCHOSIS IN A BOY WITH ADHD TREATED WITH STIMULANTS AND ACUTE LYMPHOCYTIC LEUKEMIA TREATED WITH CHEMOTHERAPY AND STEROIDS.

Hechtman L, Russell RC, Young LJ.

This article describes the case of a 14-year-old boy who presented at the emergency room with acute psychotic symptoms, ADHD treated with stimulants and acute lymphocytic leukemia treated with chemotherapy and steroids. The stimulants were discontinued and not reinstated; the course of chemotherapy and steroids were continued; and the psychosis was treated with risperidone. The psychotic symptoms resolved and the risperidone was discontinued. The patient presented again as a psychiatric emergency 1 month later with acute anxiety and paranoia after he began a further course of chemotherapy and steroids. The risperidone course was again initiated and the symptoms resolved. As the chemotherapy and steroids would be continued almost on a monthly basis to treat the leukemia, a prophylactic protocol was established. Very small dosages of risperidone were administered prophylactically a day before the steroids and chemotherapy course began and were continued throughout the course (5-6 days). This treatment approach has been repeated over several months of treatment and there has been no recurrence of the acute psychosis. This case report highlights the possibility of developing steroid psychosis and the potential effectiveness of intermittent small doses of risperidone in preventing the recurrence of the steroid-associated psychotic symptoms.

……

Neuropsychology. 2012;26:684-94.

DECOMPOSING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)-RELATED EFFECTS IN RESPONSE SPEED AND VARIABILITY.

Karalunas SL, Nigg JT, Huang-Pollock CL.

Objective: Slow and variable reaction times (RTs) on fast tasks are such a prominent feature of attention-deficit/hyperactivity disorder (ADHD) that any theory must account for them. However, this has proven difficult because the cognitive mechanisms responsible for this effect remain unexplained. Although speed and variability are typically correlated, it is unclear whether single or multiple mechanisms are responsible for group differences in each. RTs are a result of several semi-independent processes, including stimulus encoding, rate of information processing, speed-accuracy trade-offs, and motor response, which have not been previously well characterized.

Method: A diffusion model was applied to RTs from a forced-choice RT paradigm in two large, independent case-control samples (NCohort 1=214 and NCohort 2=172). The decomposition measured three validated parameters that account for the full RT distribution and assessed reproducibility of ADHD effects.

Results: In both samples, group differences in traditional RT variables were explained by slow information processing speed, and unrelated to speed-accuracy trade-offs or nondecisional processes (e.g., encoding, motor response).

Conclusions: RT speed and variability in ADHD may be explained by a single information processing parameter, potentially simplifying explanations that assume different mechanisms are required to account for group differences in the mean and variability of RTs.

……

Neuropsychology. 2012;26:278-87.

EXECUTIVE FUNCTIONS IN GIRLS WITH ADHD FOLLOWED PROSPECTIVELY INTO YOUNG ADULTHOOD.

Miller M, Ho J, Hinshaw SP.

Objective: We prospectively followed an ethnically and socioeconomically diverse sample of girls with ADHD (n=140) and a matched comparison group (n=88) into young adulthood (Mage=19.6), 10 years after childhood initial assessments, to evaluate neuropsychological functioning. We hypothesized that neuropsychological deficits would persist through young adulthood for those with ADHD, and that those with continuing ADHD symptomatology in young adulthood would show the largest impairments.

Method: Neuropsychological measures at follow-up emphasized executive functions (EF) including planning, organization, inhibitory control, sustained attention, working memory, and set shifting.
Results: Parallel to findings from childhood and adolescence, the girls with childhood-diagnosed ADHD displayed medium to large deficits in EF relative to comparisons at follow-up, even with statistical control of baseline demographic and comorbidity variables. The addition of IQ as a covariate attenuated differences but several remained significant. Comparisons between the inattentive and combined subtypes of ADHD yielded nonsignificant results with small effect sizes. EF impairments were evident in both participants whose ADHD diagnoses persisted and in those whose ADHD symptoms had remitted to a nondiagnosable level; both subgroups had more EF deficits than those who did not meet criteria for ADHD in either childhood or young adulthood.
Conclusions: Those in both the persistent and remitted ADHD groups showed impairments in EF relative to comparisons and generally did not differ from each other. Overall, childhood ADHD in girls portends neuropsychological/EF deficits that persist for at least 10 years.

……

Neuropsychology. 2013 Mar;27:193-200.
ADHD PERFORMANCE REFLECTS INEFFICIENT BUT NOT IMPULSIVE INFORMATION PROCESSING: A DIFFUSION MODEL ANALYSIS.
Metin B, Roeyers H, Wiersema JR, et al.
Objective: Attention-deficit/hyperactivity disorder (ADHD) is associated with performance deficits across a broad range of tasks. Although individual tasks are designed to tap specific cognitive functions (e.g., memory, inhibition, planning, etc.), these deficits could also reflect general effects related to either inefficient or impulsive information processing or both. These two components cannot be isolated from each other on the basis of classical analysis in which mean reaction time (RT) and mean accuracy are handled separately.
Method: Seventy children with a diagnosis of combined type ADHD and 50 healthy controls (between 6 and 17 years) performed two tasks: a simple two-choice RT (2-CRT) task and a conflict control task (CCT) that required higher levels of executive control. RT and errors were analyzed using the Ratcliff diffusion model, which divides decisional time into separate estimates of information processing efficiency (called ôdrift rateö) and speed-accuracy tradeoff (SATO, called ôboundaryö). The model also provides an estimate of general nondecisional time.
Results: Results were the same for both tasks independent of executive load. ADHD was associated with lower drift rate and less nondecisional time. The groups did not differ in terms of boundary parameter estimates.
Conclusion: RT and accuracy performance in ADHD appears to reflect inefficient rather than impulsive information processing, an effect independent of executive function load. The results are consistent with models in which basic information processing deficits make an important contribution to the ADHD cognitive phenotype.

……

Neuropsychology. 2013 Mar;27:201-09.
BEHAVIORAL CORRELATES OF REACTION TIME VARIABILITY IN CHILDREN WITH AND WITHOUT ADHD.
Antonini TN, Narad ME, Langberg JM, et al.
Objective: Reaction time (RT) variability is often purported to indicate behavioral attention. This study seeks to examine whether RT variability in children with Attention Deficit Hyperactivity Disorder (ADHD) is associated with observed behavioral indicators of attention.
Method: One-hundred 47 participants with and without ADHD completed five computerized neuropsychological tasks and an analog math task. Linear mixed models were utilized to examine the relationship between observations of behavioral inattention during the analog task and measures of RT variability from the neuropsychological tasks.

Results: Significant associations were observed between RT variability and mean duration of on-task behavior on the analog math task. Secondary analyses indicated that on-task behavior during the math task was also related to accuracy on the neuropsychological tasks.
Conclusions: RT variability, especially the portion of RT variability characterized by long RTs, appears to measure a cognitive phenomenon that relates to successful on-task academic behavior across children with and without ADHD. The relationship between RT variability and on-task behavior is present across multiple neuropsychological tasks and does not appear to be moderated by age, sex, or the presence of anxiety or depression.

……

Neuropsychopharmacology. 2013 Jan;38:250-51.
FRACTIONATING THE IMPULSIVITY CONSTRUCT IN ADOLESCENCE.
Whelan R, Garavan H.
The teenage years are often associated with 'impulsive' behavior; that is, behavior with diminished regard to potential negative consequences. Adolescent impulsivity, while often adaptive, can manifest itself in a range of sub-optimal behaviors, including use of nicotine, alcohol, or illicit substances, symptoms associated with attention deficit hyperactivity disorder (ADHD), or poorer performance on laboratory assays of impulse control. Although these maladaptive behaviors are often co-morbid, their correlation is not perfect. It is therefore increasingly recognized that impulsivity is multi-dimensional, with some predicting that 'what is generally denoted as impulsivity will be fractionated into distinct forms that may, however, often coexist in the same individual'. Understanding the neural correlates of impulsivity subtypes is important because it yields insights into the etiology of maladaptive impulsive behaviors. Disentangling the biological basis of substance misuse and ADHD symptoms has proven difficult previously because, for example, adult substance misusers are more likely to retrospectively endorse childhood ADHD symptoms. A goal of future research will be to shed more light on the structural, functional, neurochemical, and genetic under-pinnings of the various impulsivity brain networks.

……

Neurosci Behav Physiol. 2013;1-5.
ATTENTION DEFICIT HYPERACTIVITY DISORDER: SELECTION OF THE OPTIMUM DURATION OF MEDICAL TREATMENT.
Zavadenko NN, Suvorinova NY.
A total of 32 children aged 6-12 years with attention deficit hyperactivity disorder (ADHD) were monitored during prolonged (6-8 months) treatment with Pantogam (homopantothenic acid) at daily doses of 500-1000 mg. Treatment results were assessed using the DSM-IV core ADHD symptom scales and the WFIRS-P (parental) scale every two months. Decreases in core symptoms on the DSM-IV core ADHD symptom scale were seen at two months of treatment. Significant changes on the WFIRS-P scale took longer: improvements in self-concept, socialization, and social activity were seen at four months and in behavior and schoolwork, basic life skills, along with decreases in risk-associated behavior, at six months. Thus, in contrast to regression of core ADHD symptoms, overcoming impairments in social-psychological adaptation required longer treatment periods.

……

Obes Facts. 2012;5:856-68.
THE HYPERACTIVITY/INATTENTION SUBSCALE OF THE STRENGTHS AND DIFFICULTIES QUESTIONNAIRE PREDICTS SHORT-AND LONG-TERM WEIGHT LOSS IN OVERWEIGHT CHILDREN AND ADOLESCENTS TREATED AS OUTPATIENTS.
Van Egmond-Froehlich A, Bullinger M, Holl RW, et al.
Objective: The success of treatment for pediatric obesity is variable and often unsatisfactory. This study elucidates the influence of inattention and hyperactivity/impulsivity on short-and long-term weight loss and maintenance after outpatient treatment.

Methods: We included 8-to 16-year-old overweight and obese participants treated in 17 multidisciplinary outpatient treatment centers in a nationwide observational study. All treatment centers that reported long-term (1-year) follow-up weight data of at least 60% of the participants were included. At the beginning and end of treatment and at 1 year follow-up weight and height were measured at the center. Inattention and hyperactivity/impulsivity were assessed with the hyperactivity/inattention subscale (HI) of the parent-rated Strengths and Difficulty Questionnaire (SDQ). General linear models were used with the standard deviation scores of the BMI (BMI-SDS) as dependent variable and HI scores as main independent variable adjusting for age, sex, baseline BMI-SDS, and center.
Results: 394 participants were included (57% female, age: 11.7(plus or minus) 2.0 years, baseline BMI-SDS 2.32 (plus or minus).46 kg/m2). HI scores were significantly associated with short-and long-term BMI-SDS ($p < 0.0005$), with higher baseline HI scores predicting less weight loss.
Conclusions: Our results indicate that inattention and hyperactivity/impulsivity are linearly associated with reduced short-and long-term weight loss. Implications for treatment are discussed.

……

Obes Facts. 2013;6:109-15.

SUCCESSFUL TREATMENT WITH ATOMOXETINE OF AN ADOLESCENT BOY WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER, EXTREME OBESITY, AND REDUCED MELANOCORTIN 4 RECEPTOR FUNCTION.

Pott W, Albayrak O, Hinney A, et al.

Objective: Recent case reports suggest a link between reduced melanocortinergic tone and both obesity and attention deficit / hyperactivity disorder (ADHD). We present the case of a 13-year-old, male, obese MC4R mutation carrier with ADHD.
Case Report: The boy carries a heterozygous mutation in the melanocortin 4 receptor gene (MC4R; Met281Val), that leads to a reduced receptor function. Dominant mutations of this type represent major gene effects for obesity. He participated in a lifestyle intervention program for obesity and received treatment with the selective norepinephrine re-uptake inhibitor atomoxetine for 31 months. The boy markedly reduced his BMI from 47.2 to 29.6 kg/m.
Conclusion: Atomoxetine proved to efficiently reduce weight in a severely obese MC4R mutation carrier with ADHD. We briefly discuss possible mechanisms for our observation, including evidence for the functional connectivity between melanocortinergic, dopaminergic, and norepinephrinergic brain circuitries.

……

Pediatrics. 2013;131:S50-S59.

DO PARENT PERCEPTIONS PREDICT CONTINUITY OF PUBLICLY FUNDED CARE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Zima BT, Bussing R, Tang L, et al.

OBJECTIVE: To examine whether parent perceptions about care (barriers, disorder knowledge, treatment willingness) vary among children who drop out of or stay in publicly funded care for attention-deficit/ hyperactivity disorder (ADHD) and to explore whether parent perceptions are predictive of staying in care over time.
METHODS: A longitudinal cohort study of 529 children ages 5 to 11 years receiving care for ADHD in primary care or specialty mental health clinics in a large, countywide, managed-care Medicaid program. Multiple logistic regression analyses were performed to identify parent perceptions associated with the likelihood of staying in care across three 6-month time intervals, controlling for child and parent demographic characteristics, parental distress, clinical need, and recent special education use.
RESULTS: At least three-fourths of children had at least 1 contact for any mental health care during a 6-month time interval (75%, 85%, 76%). Parent-perceived barriers, ADHD knowledge, and counseling willingness did not predict staying in care, whereas willingness for medication treatment was predictive at baseline. Minority status, nonmarried parent, parental distress, clinical need, and special education use were predictive of staying in care, but mostly during only one 6-month time interval, and their influence varied over time.

CONCLUSIONS: Parent willingness for medication treatment along with several demographic and need factors predicted staying in care but not consistently over time. Future research is needed to develop practical tools for clinicians to elicit parent priorities about ADHD treatment and to integrate them into quality-improvement interventions targeted to improving shared decision-making for longer term ADHD care.

……

Pediatr Int. 2013;55:24-29.

KINEMATIC PERFORMANCE OF FINE MOTOR CONTROL IN ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER: THE EFFECTS OF COMORBID DEVELOPMENTAL COORDINATION DISORDER AND CORE SYMPTOMS.

Lee IC, Chen YJ, Tsai CL.

Background The aims of this study were: (i) to determine whether differences exist in the fine motor fluency and flexibility of three groups (children with attention-deficit/hyperactivity disorder [ADHD], children in whom ADHD is comorbid with developmental coordination disorder [DCD] [denoted as ADHD+DCD], and a typically developing control group); and (ii) to clarify whether the degree of severity of core symptoms affects performance.

Methods The Peabody Picture Vocabulary Test-Revised, the Beery-Buktenica Development Test of Visual-Motor Integration and the Movement Assessment Battery for Children were used as prescreening tests. The Integrated Visual and Auditory+Plus test was utilized to assess subjects' attention. The redesigned fine motor tracking and pursuit tasks were administered to evaluate subjects' fine motor performance.

Results No significant difference was found when comparing the performance of the Children with ADHD and the typically developing group. Significant differences existed between children in whom ADHD is comorbid with DCD and typically developing children.

Conclusions Children with ADHD demonstrated proper fine motor fluency and flexibility, and deficient performance occurred when ADHD was comorbid with developmental coordination disorder. Children with ADHD had more difficulty implementing closed-loop movements that required higher levels of cognitive processing than those of their typically developing peers. Also, deficits in fine motor control were more pronounced when ADHD was combined with movement coordination problems. The severity of core symptoms had a greater effect on children with ADHD's fine motor flexibility than did fluency performance. In children with pure ADHD, unsmooth movement performance was highly related to the severity of core symptoms.

……

PLoS ONE. 2013;8.

CORRELATION BETWEEN EPILEPSY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: A POPULATION-BASED COHORT STUDY.

Chou IC, Chang YT, Chin ZN, et al.

Background: This study presents an evaluation of the bidirectional correlation between attention deficit hyperactivity disorder (ADHD) and epilepsy using 2 cohorts from the same population database.

Methods: We used data from the Taiwan National Health Insurance Research Database to establish 2 separate cohort studies with participants <19 years old. We subdivided Cohort 1 in 2 groups: (1) 2468 patients initially diagnosed with epilepsy during the period 1999-2008, and (2) 9810 randomly selected sex- and age-matched non-epileptic controls. We subdivided Cohort 2 into 2 groups: (1) 3664 patients with newly diagnosed ADHD and (2) 14 522 sex- and age-matched non-ADHD patients. We evaluated the risk of subsequent ADHD in relationship to epilepsy and vice versa in the 2 cohorts at the end of 2008.

Results: The ADHD incidence in Cohort 1 was 7.76 in patients with epilepsy and 3.22 in those without epilepsy (per 1000 person-years) after a median follow-up of 7-7.5 years. The adjusted hazard ratio (HR) for ADHD was 2.54 (95% CI 2.02-3.18) in the epilepsy group compared to the non-epilepsy group. In Cohort 2, the incidence of epilepsy was 3.24 in patients with ADHD and 0.78 in those without ADHD (per 1000 person-years) after a median follow-up of 3-3.5 years and an HR of 3.94 (95% CI 2.58-6.03).

Conclusion: This study shows a bidirectional association between ADHD and epilepsy in the 2 cohort studies. Causative factors may be common between these 2 disorders, leading to a cascade of transcriptional changes in the brain that alter behavior or cognition prior to seizures.

……

Psychiatr Genet. 2013;23:90-91.

ASSOCIATION OF THE CATECHOL-O-METHYLTRANSFERASE GENE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: RESULTS FROM AN EPIDEMIOLOGICAL STUDY OF ADOLESCENTS OF MEXICO CITY.

Martinez-Levy GA, Benjet C, Perez-Molina A, et al.

……

Psychiatry Clin Neurosci. 2013;67:83-91.

WECHSLER INTELLIGENCE SCALE FOR CHILDREN 4TH EDITION-CHINESE VERSION INDEX SCORES IN TAIWANESE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Yang P, Cheng CP, Chang CL, et al.

Aim The Wechsler Intelligence Scale for Children 4th edition-Chinese version (WISC-IV-Chinese) has been in clinical use in Taiwan since 2007. Research is needed to determine how the WISC-IV, modified from its earlier version, will affect its interpretation in clinical practice in a Mandarin-speaking context.

Methods We attempted to use WISC-IV-Chinese scores to identify the cognitive strengths and weaknesses in 334 Taiwanese children with attention-deficit/hyperactivity disorder (ADHD). Comparison of cognitive profiles of WISC-IV-Chinese scores between subtypes of ADHD was also performed.

Results The results indicated that the four-factor model of the WISC-IV-Chinese fitted well for Taiwanese children with ADHD. The profiles showed that performance in the index score of the Processing Speed Index was the weakness domain for the Taiwanese children with ADHD, as confirmed by two different kinds of analytic methods. Cognitive profile analysis of ADHD subtypes revealed children with inattentive subtypes to have a greater weakness in processing speed performance.

Conclusion The implications of the profiles of the index scores on the WISC-IV-Chinese version for Taiwanese children with ADHD were explored.

……

Psychiatr Invest. 2013;10:384-90.

EFFECT OF METHYLPHENIDATE ON SLEEP PARAMETERS IN CHILDREN WITH ADHD.

Lee SH, Seox WS, Sung HM, et al.

Objective: The primary aim of this study was to investigate the acute impact of methylphenidate (MPH) on sleep parameters in attention-deficit/hyperactivity disorder (ADHD) children. The second aim was to investigate the different effects of intermediate- and longacting MPH on sleep parameters. The third aim was to test the different effects of dose and age on sleep parameters.

Methods: Ninety-three ADHD children were enrolled and randomized to two different MPH preparations. Baseline and daily sleep diaries were evaluated for four weeks after taking medication. Weekday and weekend bedtimes, wake-up times, sleep latencies and total sleep times were compared by weeks.

Results: After taking MPH, there was a significant delay in bedtimes and a significant reduction of total sleep time (TST) both on weekdays and at weekends. There was also a significant delay in wake-up time on weekdays. However, the difference was applied to younger age group children only. There was no difference in changes of TST between metadate-CD and OROS-MPH. There also was no difference in changes of TST with different doses of MPH.

Conclusion: MPH had negative impacts on sleep among young ADHD children, but different preparations and doses did not affect the result.

……

Psychopharmacology. 2013;225:895-902.

A HIGH DENSITY LINKAGE DISEQUILIBRIUM MAPPING IN 14 NORADRENERGIC GENES: EVIDENCE OF ASSOCIATION BETWEEN SLC6A2, ADRA1B AND ADHD.

Hawi Z, Matthews N, Barry E, et al.

Pharmacological evidence suggests the importance of noradrenergic and other monoaminergic neurotransmitters in the aetiology and treatment of attention deficit hyperactivity disorder (ADHD). Until recently, the genes of the noradrenergic pathway were not intensively investigated in ADHD compared to dopaminergic and serotonergic candidates. In this study, 91 SNP markers of 14 noradrenergic genes (an average density of one SNP per 4.5 kbp) were examined in ADHD samples from Ireland and Australia. Although suggestive evidence of association (nominal p (less-than or equal to) 0.05) with the genes SLC6A2, ADRA1A, ADRA1B and ADRA2B was observed, none remained significant after permutation adjustments. In contrast, haplotype analyses demonstrated a significant association between ADHD and a SLC6A2 haplotype comprising the markers rs36009, rs1800887, rs8049681, rs2242447 and rs9930182 ((chi)2 = 9.39, p-corrected = 0.019, OR = 1.51). A rare ADRA1B haplotype made of six SNPs (rs2030373, rs6884105, rs756275, rs6892282, rs6888306 and rs13162302) was also associated ((chi)2 =7.79, p-corrected =0.042 OR =2.74) with the disorder. These findings provide evidence of a contribution of the noradrenaline system to the genetic aetiology of ADHD. The observed haplotype association signals may be driven by as yet unidentified functional risk variants in or around the associated regions. Functional genomic analysis is warranted to determine the biological mechanism of the observed association.

……

Res Dev Disabil. 2013;34:1581-94.

MATERNAL PARENTING STYLES AND MOTHER-CHILD RELATIONSHIP AMONG ADOLESCENTS WITH AND WITHOUT PERSISTENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Gau SSF, Chang JPC.

We investigated mothering and mother-child interactions in adolescents with and without persistent attention-deficit/hyperactivity disorder (ADHD) in a sample of 190 adolescents with persistent DSM-IV ADHD, 147 without persistent ADHD, and 223 without ADHD. Both participants and their mothers received psychiatric interviews for diagnosis of ADHD and other mental disorders; and reported on the Parental Bonding Instrument about mother's parenting style, the Social Adjustment Inventory for Children and Adolescents for interactions with mothers and home behavioral problems. The mothers also reported on their ADHD and neurotic/depressive symptoms. Our results based on both informants showed that both ADHD groups obtained less affection/care and more overprotection and control from the mothers, and perceived less family support than those without ADHD. Child's inattention and comorbidity, and maternal depression were significantly correlated with decreased maternal affection/care and increased maternal controls; child's hyperactivity-impulsivity and maternal neurotic trait were significantly correlated with maternal overprotection; and child's inattention and comorbidity, and maternal neurotic/depressive symptoms were significantly correlated with impaired mother-child interactions and less family support. Our findings suggested that, regardless of persistence, childhood ADHD diagnosis, particularly inattention symptoms and comorbidity, combining with maternal neurotic/depressive symptoms was associated with impaired maternal process.

……

Res Dev Disabil. 2013;34:1434-45.

THE DEVELOPMENTAL TRAJECTORIES OF EXECUTIVE FUNCTION OF CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Qian Y, Shuai L, Chan RCK, et al.

This study examined the developmental trajectories of executive function (EF) of children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD) in Han Chinese. Five hundred and fifteen children and adolescents with ADHD and 249 healthy controls took part in this study. All of them were administered four EF tests capturing inhibition, working memory, shifting and planning components. The participants were

further divided into four age groups, 7-8, 9-10, 11-12, and 13-15 years old, respectively, for developmental trajectories comparison. The performance of the typical developing children and adolescents aged 7-15 were reported to get stable at age 11-12 for inhibition, working memory and planning, and kept developing till age 13-15 for shifting. For inhibition and shifting, participants with ADHD displayed similar performance to the healthy controls who were 2 years younger whereas they did poorer than the healthy controls of their same age. And at age 13-15, such poorer performance disappeared for inhibition but maintained for shifting. No significant differences were found between participants with and without ADHD in working memory and planning across all age groups. The current findings suggested, compared with healthy controls, Han Chinese children and adolescents with ADHD displayed delayed developmental trajectories on inhibition and shifting, whereas they showed similar trend of development on working memory and planning.

……

Res Dev Disabil. 2013;34:1700-09.

CAREGIVER SURVEY OF PHARMACOTHERAPY TO TREAT ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN INDIVIDUALS WITH WILLIAMS SYNDROME.

Martens MA, Seyfer DL, Andridge RR, et al.

Williams syndrome (WS) is a genetic condition characterized by a unique neurocognitive and behavioral profile, including increased incidence of attention deficit/hyperactivity disorder (ADHD). The purpose of the present study was to examine the perceived helpfulness and side effects of medications used to treat ADHD (methylphenidate class, amphetamine class, atomoxetine) in individuals with WS. This was accomplished with a survey of parents/caregivers of individuals with WS through the Williams Syndrome Association. Five-hundred twelve (512) parents/caregivers responded to the survey regarding their child's/adult child's use of ADHD medications. Twenty-seven percent (27%) of the individuals had been prescribed a medication for ADHD, most commonly a methylphenidate class medication. OROS-methylphenidate was reported as the most helpful methylphenidate class formulation, with 74% reporting it at least somewhat helpful. Survey participants reported similar side effects as typically developing controls, but to a greater degree. Irritability was the most commonly endorsed side effect of an ADHD medication (38%). Individuals reported use of stimulant medications in the presence and absence of underlying cardiac conditions, with 56% of ADHD medication users reporting supravalvular aortic stenosis, 36% pulmonary artery stenosis, and 25% systemic hypertension. Individuals taking ADHD medications were more likely to report dental problems (p=0.004). Additional studies are needed to further investigate these findings and examine short-versus long-acting stimulant medications and dosage effects.

……

Rev Psiquiatr Salud Ment. 2013.

COST-EFFECTIVENESS OF PHARMACOLOGICAL TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: QUALITATIVE SYNTHESIS OF SCIENTIFIC EVIDENCE.

Catala-Lopez F, Ridao M, Sanfelix-Gimeno G, et al.

Objective: To describe the cost-effectiveness analyses of medications launched in Spain for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents.

Material and methods: Systematic review of the literature without meta-analysis. A search was made in, PubMed/MEDLINE, SCOPUS, databases of the Centre for Reviews and Dissemination, and the websites of technology assessment agencies from Canada, the United Kingdom and the Spanish Platform AUnETS. Only full economic evaluations were included, considering at least methylphenidate or atomoxetine as pharmacological treatment alternatives in children and/or adolescents with ADHD.

Results: Eleven studies published in 9 articles or reports were included. The most frequent characteristics were: cost-utility analysis (82%), health system perspective (82%), short-term horizon (91%), and private funding (50%). Methylphenidate was included in all studies, and atomoxetine in 4 studies. Methylphenidate and atomoxetine are cost-effective alternatives compared to placebo or no treatment, although incremental

cost-effectiveness ratios are variable. The few direct treatment-comparisons between methylphenidate and atomoxetine provided contradictory and potentially biased results.
Conclusions: The pharmacological treatment of ADHD in children and adolescents, with the reservations arising from the generalization of results to different settings, is probably cost-effective in the short term. The existing studies do not allow the relative efficiency of different treatments to be established, either in the long-term treatment or in patient subgroups with specific characteristics or comorbidities.

……

School Psychology Quarterly. 2013 Mar;28:25-36.
EDUCATIONAL OUTCOMES OF A COLLABORATIVE SCHOOL-HOME BEHAVIORAL INTERVENTION FOR ADHD.
Pfiffner LJ, Villodas M, Kaiser N, et al.
This study evaluated educationally relevant outcomes from a newly developed collaborative school-home intervention (Collaborative Life Skills Program [CLS]) for youth with attention and/or behavior problems. Participants included 17 girls and 40 boys in second through fifth grades (mean age = 8.1 years) from diverse ethnic backgrounds. CLS was implemented by 10 school-based mental health professionals at their schools and included 3 integrated components over 12 weeks: group behavioral parent training, classroom behavioral intervention, and a child social and independence skills group. Parent and teacher ratings of attention-deficit/hyperactivity disorder (ADHD) symptoms, organizational skills, and homework problems, and teacher-rated academic skills, report card grades, academic achievement, and classroom observations of student engagement were measured before and after treatment. Significant pre-post improvement was found for all measures, with large effect sizes for ADHD symptoms, organizational skills, and homework problems, and medium to large effects for teacher-rated academic skills, report card grades, academic achievement, and student engagement. Improvements in organizational skills mediated the relationship between improvement in ADHD symptoms and academic skills. Significant improvement in both ratings and objective measures (achievement testing, report cards, classroom observations) suggests that improvement exceeded what might be accounted for by expectancy or passage of time. Findings support the focus of CLS on both ADHD symptom reduction and organizational skill improvement and support the feasibility of a model which utilizes school-based mental health professionals as providers.

……

Social Psychiatry and Psychiatric Epidemiology. 2013 Feb;48:337-44.
ESTIMATING THE COSTS OF ONGOING CARE FOR ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Telford C, Green C, Logan S, et al.
Purpose: Attention-deficit hyperactivity disorder (ADHD) is associated with increased use of health, social and education services. There is a lack of data to quantify the economic burden of ADHD in the UK. The aim of this study was to estimate additional education, health and social care costs amongst adolescents in the UK diagnosed with ADHD.
Methods: Participants were 143, 12- to 18-year-olds from the Cardiff longitudinal ADHD study. Service use relating to mental health over the previous year was measured using the children's service interview. Individual resource use was combined with unit cost data, from national sources, to calculate costs per patient and subsequently the mean cost per patient. Mean costs, 95 % confidence intervals and median use were calculated using nonparametric boot-strapping methods.
Results: The mean cost per adolescent for NHS, social care and education resources used in a 12-month period related to ADHD was £5,493 (£4,415.68, £6,678.61) in 2010 prices and the median was £2,327. Education and NHS resources accounted for approximately 76 and 24 %, respectively. Estimated annual total UK costs are £670 million.

Conclusions: The additional costs to the NHS and education system of treating adolescents remain substantial for several years after the initial ADHD diagnosis. There exists a need to develop and evaluate early interventions which have the potential to reduce the longer-term burden, particularly on education resource use.

……

Wisc Med J. 2013;112:13-17.

THE POTENTIAL FOR SOCIOCULTURAL FACTORS IN THE DIAGNOSIS OF ADHD IN CHILDREN.

Reyes N, Baumgardner DJ, Simmons DH, et al.

Purpose: The nongenetic contributors to attention deficit/hyperactivity disorder (ADHD) remain to be identified. A previous study in eastern Wisconsin (prevalence 13.5%) suggested that male gender, white race, lower block group median household income and population density, and greater distance to the nearest park were factors predictive of ADHD diagnosis. We performed a similar study in Dane County, Wisconsin.

Methods: Cross sectional study of children age 5-17, with and without ADHD diagnosis, who received well child care in Dane County UW Family Medicine clinics (N=7954) 2007-2008. Street addresses were geocoded to 2000 Census block group. Univariate analysis was done by chi-square test or Mann-Whitney U test, multivariate analysis by logistic regression.

Results: ADHD diagnosis was present in 309 (3.9%) children (74.1% male; P=0.000, compared to females) and more frequently diagnosed in black children (6.8% of black children had ADHD diagnosis) than white (4%), Native American (2.7%), Hispanic (1.6%), or Asian (1.3%) children. In contrast to eastern Wisconsin and to Milwaukee County (a subset of the eastern Wisconsin study where black rates were identical to that of Dane County), black race rather than white race was predictive of ADHD in Dane County, while median household income, population density, and distance to nearest park were not associated. The range of ADHD within school district boundaries was 2.4%-7.1% (for N > 100/district). In the group of districts with >4% ADHD diagnosis, the increased rates were largely among whites.

Conclusion: ADHD diagnosis was much less common in this Dane County cohort than in eastern Wisconsin and was more common among blacks, but not predicted by other geo-demographic factors. Like eastern Wisconsin, ADHD diagnosis prevalence varied with apparent school district boundaries.

……

Research in Developmental Disabilities 33 (2012) 2028–2039

Contents lists available at SciVerse ScienceDirect

Research in Developmental Disabilities

Effects of hypermedia instruction on declarative, conditional and procedural knowledge in ADHD students

Rosa Angela Fabio [a,*], Alessandro Antonietti [b]

[a] Department of Cognitive Science, University of Messina, Italy
[b] Department of Psychology, Catholic University of Milan, Italy

ARTICLE INFO

Article history:
Received 1 February 2012
Received in revised form 24 April 2012
Accepted 24 April 2012
Available online 28 June 2012

Keywords:
Learning
Attention
ADHD
Learning problems
Multimedia
Hypertext

ABSTRACT

Two groups of students aged between 12 and 14 years—27 with attention deficit/hyperactivity disorder (ADHD) and 28 with both ADHD and learning problems—were compared to a sample of 29 typically developing students in terms of the acquisition and retention of declarative, conditional and procedural knowledge either in a hypermedia learning or in a traditional instructional setting. Hypermedia instruction produced better learning outcomes than traditional instruction did; the benefits concerned prevalently procedural knowledge and emerged mainly in the retention phase. Hypermedia instruction led ADHD students to reach achievement levels similar to those of typically developing students. Furthermore, hypermedia instruction contrasted the decay of knowledge from the acquisition to the retention phase in both clinical groups. On the basis of these findings, hypermedia instruction is proposed as an approach that may help ADHD learners to overcome attention deficits.

1. Introduction

Hypermedia tools are computer-based devices designed to promote learning in educational settings. In comparison to traditional educational instruments, hypermedia tools have the advantage of providing learners with concepts presented through a variety of symbols (written texts, oral narratives, pictures, animations, and sounds) (Mayer, 2005) and of offering learners control over the instructional process by allowing them to choose the preferred sequence along with access contents (Shin, Schallert, & Savenye, 1994). In fact hypermedia tools are characterised by two features: (1) images, photos, diagrams, motion pictures, sounds, and texts are simultaneously available to activate learner's verbal/auditory and visual channels at the same time (Mayer, 2003); (2) thanks to the networked structure, organization of information is similar to human associative memory (Granic & Lamey, 2000).

With reference to the first issue, i.e., the simultaneous activation of different perceptual-cognitive channels, it has been argued that information is processed mainly through two channels: one processes verbal information such as texts or discourses; the other processes non-verbal information such as visuals. Learning is more effective when information is processed through two channels rather than when it is processed through only one channel independent on the other (Paivio, 1986, 1991; Schnotz & Lowe, 2003). Recently Mayer (2001) tried to understand how learners integrate information

* Corresponding author at: Faculty of Psychological and Educational Science, University of Messina, Via Concezione 6/8, 98122 Messina, Italy. Tel.: +39 90 344831; fax: +39 90 344831.
E-mail address: rafabio@unime.it (R.A. Fabio).
URL: http://infinitipossibili.jimdo.com/

0891-4222/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ridd.2012.04.018

from verbal and visual channels. According to Mayer, the learner first considers the relevant aspects of information presented through the two channels and then selects relevant words from verbal information and relevant images from visual information. The chosen words and pictures are then organised in the working memory. Finally, connections are formed between verbal and visual representations.

Considering the second issue, according to Jonassen and Grabinger (1990) learning involves the reorganization of knowledge structures. These structures are arranged in networks of interrelated concepts. Such structured networks, which are mirrored in the content structure of a hypermedia tool, are composed of nodes and ordered relationships connecting them, so that several contents linked to each other can be activated rapidly. This allows learners to be flexible in accessing concepts (Andris, 1996; Chou, 2001; Douglas & Riding, 1993; Ford & Chen, 2000; Ford & Ford, 1992; Graff, 2003; Riding & Grimley, 1999). The non-linear way of presenting contents can produce advantages in comparison to traditional linear ways (Chou & Wang, 1999; Lin, Liu, & Yuan, 2001), favouring the acquisition of the overall picture of the contents (Calcaterra, Antonietti, & Underwood, 2005; Fiorina, Antonietti, Colombo, & Bartolomeo, 2007) and memory retention (Granic & Lamey, 2000), making the learning process easier, raising individual motivation and level of activity and decreasing anxiety (Ayersman & Minden, 1995; Hede, 2002; Lohr, Ross, & Morrison, 1995). However, Baylor (2001) found learning costs if students apply a linear navigation mode (proceeding as though one is reading a textbook) on hypermedia content as they become moderately disorientated (Muller-Kalthoff & Moller, 2003). Such disorientation did not occur when navigation took a non-linear format and students had access to all nodes of the hypermedia tool. As a result on an incidental learning task, the users performed better in the non-linear navigation mode than those in the linear mode.

The alleged benefits of hypermedia devices have been supported by several studies (e.g., Mayer, 2003, 2005; Najjar, 1998; Sweller, 1999; Van Merrienboer, 1997). Such benefits have been proven also for students showing learning problems (Hall, Hughes, & Filibert, 2000). As far as this issue is concerned, Maccini, Gagnon, and Hughes (2002) conducted a comprehensive review of the literature on technology-based practices addressed to secondary school students identified as learning disabled. Hypermedia tools appeared to be relevant instruments for educating these kinds of students. However, few studies investigated the relationships between the effectiveness of hypermedia instructional tools and attention deficit/hyperactivity disorder (ADHD) although there are several reasons to hypothesize that hypermedia instruments can play a role to overwhelm the difficulties that ADHD students encounter in learning.

ADHD is one of the most prevalent developmental disorders diagnosed in childhood and it is characterised by excessive activity, short attention span, and impulsivity (American Psychiatric Association, 2000). A substantial amount of literature exists documenting the cognitive and behavioural deficits of persons with ADHD (Pennington & Ozonoff, 1996; Rucklidge & Tannock, 2002). Much emphasis has been placed on the role of motivational factors in understanding the performance deficits of children with ADHD. The influential work of Douglas (1983) highlighted the association between ADHD and difficulty in sustaining effort and motivation, particularly in the face of tedious tasks and minimal reinforcement. Barkley (1997) also stressed motivational factors in his model of executive functioning in ADHD, with poor motivation conceptualised as stemming primarily from a behavioural inhibition deficit leading to disruptions in the executive function of self-regulation of affect, motivation, and arousal. An indirect support to the role of motivational factors was provided by Slusarek, Velling, Bunk, and Eggers (2001), who showed that ADHD children performed an attention task requiring inhibitory control as well as normally developing children when high incentives were provided. We can argue that hypermedia tools should increase motivation thanks to the attraction, the curiosity and the sense of control over the learning process that they produce in the users. This leads to predict that ADHD students may perform better in learning tasks when they are allowed to employ such instruments.

In a pioneering study Kleinman, Humphrey, and Lindsay (1981) reported that ADHD children using the computer increased, as compared to a pen-and-pencil condition, the time they spent in working on mathematical tasks and the number of solved problems. Further investigations supported the hypothesis that technological devices are beneficial for people with ADHD (Bender & Bender, 1996; Dailey & Rosemberg, 1994; Ford, Poe, & Cox, 1993; Xu, Reid, & Steckelberg, 2002). For instance, it was repeatedly showed that ADHD children are equally successful than no-ADHD individuals in playing videogames <!–(Farrace-Di Zinno et al., 2001; Houghton et al., 2004; Shaw, Grayson, & Lewis, 2005), even if it emerged that ADHD children exhibited an higher amount of response preparation (Lawrence et al., 2002). In school settings, computer-assisted instruction—which, however, is not necessarily hypermedia in its own nature—was proved to help ADHD persons to improve academic achievement (Mautone, DuPaul, & Jitendra, 2005; Ota & DuPaul, 2002), perhaps because of the fact that students are faced to clearly designed contents, well-structured learning units which are provided them according to planned sequences of increasing complexity, and thanks to the immediate feedback which is given (Burt & Ryan, 1997). Solomonidou, Garagouni-Areou, and Zafiropoulou (2004) analysed the effects of different types of information and communication technologies use on students with ADHD symptoms. The dependent variables in their study were the different categories of behaviour shown by children during the activities carried out with the computer, such as reading the text carefully, fidgeting while reading the text, not following instructions, avoiding tasks, being distracted by extraneous stimuli, and so forth. Results showed that children with ADHD symptoms paid more attention when they watched videos and pictures or listened to short narration items, but they showed great difficulty in reading long texts or watching long videos with no narrative structure. These findings suggest that technological devices, if appropriate, can have a positive effect on ADHD learners.

In the studies mentioned above the use of computer-supported instructional tools introduced a variety of disparate variables (different structure of the matter contents, higher level of interaction with the materials, longer time spent in using

the computer, general modification of the overall educational setting, and so on), which prevent us to understand the specific role played by the hypermedia features of such tools in facilitating learning in ADHD students. A more strict control of the instructional material, of the environmental conditions and of the task demand was exerted by Fabio, Antonietti, and Tiezzi (2003) on the experimental procedure; it was found that the performance of ADHD students was similar to that of normally achieving students when concepts were presented through text, sounds, and pictures simultaneously, whereas, when the same concepts were provided only in an auditory form, ADHD students' performance was lower than that of the control students. This finding is consistent with the results described by Lomas (2002), who involved elementary school children diagnosed with ADHD and with mild/moderate learning disabilities into a computer-assisted cognitive training and realised that ADHD children learned better when information was presented through multiple channels.

Since the review of the literature showed that ADHD can benefit from hypermedia tools in learning, an interesting question arises in asking at which level of knowledge they are helped by such tools. Anderson (1995) classified knowledge into three levels: declarative, conditional, and procedural. In Anderson's (1995) taxonomy, procedural knowledge depends upon conditional knowledge and conditional knowledge depends in turn on declarative knowledge. Anderson (1995) defined *declarative knowledge* as explicit knowledge that we can report and of which we are consciously aware. Three subtypes of declarative knowledge have been proposed: labels and names, facts and lists, and organised discourses (Smith & Ragan, 1993). Learning facts and names requires making a mental connection between elements. When the connection between elements is meaningful, it can more easily be learnt: facts and lists can be learned better when they are integrated into prior knowledge. Organised discourse learning occurs when reading a text; it should also be integrated into the existing knowledge structure. Declarative knowledge learning involves three activities: linking the new knowledge to existing knowledge, organizing acquired knowledge in a new way, and elaborating knowledge in order to make the new knowledge meaningful for learners. *Conditional knowledge* consists of if–then or condition–action statements. These statements describe the relationship between two or more concepts. "If" statements indicate conditions and "then" statements indicate actions. Conditional knowledge includes propositions, principles, laws, axioms, theories, and postulates. Smith and Ragan (1993) stated that conditional knowledge enables learners to predict what happens if one condition or action is changed. To acquire conditional knowledge, learners should first determine the variables or concepts involved in the situation and then decide the rules to be applied to the situation. Once known and unknown variables are identified, the effect of known variables on unknown variables should be determined. At the end of the condition–action sequence, learners should reach a conclusion about the situation. *Procedural knowledge* involves both declarative and conditional knowledge. According to Schunk (1996), procedural knowledge consists of concepts, rules, and algorithms. It concerns how to perform cognitive activities and it is often implicit. Procedural knowledge originates in problem solving activities in which a goal is broken down into sub-goals for which the problem solver possesses operators (Anderson, 1995). Smith and Ragan (1993) claimed that procedural rules consist of a series of steps initiated in response to a particular class of circumstances to reach a specific goal; such rules suggest learners which actions should be taken.

According to Mayer's (2001) theory of multimedia learning, we can expect that hypermedia tools produce benefits in all the three kinds of knowledge. Since identifying or creating relations seems to be the core process of declarative, conditional, and procedural knowledge, we are led to hypothesize that the simultaneous presentation of texts or narrations and pictures or animations may facilitate the understanding and the retention of the three kinds of knowledge because multimedia exposure has been proved to be especially beneficial when the goal is to learn the structure underlying concepts. In most studies carried out in the perspective proposed by Mayer (1999), the materials to be learned did not concern single, separate concepts, but interconnected sets of data and causal relations. In order to promote the acquisition of such type of materials, the concomitant presentation of textual and figural stimuli should help students in selecting the relevant elements, organizing them and integrating them into a whole representation. Even if Mayer never tested this implication of his theory, we can assume that such an effect should occur also in students with ADHD: in this case multimedia devices should be beneficial since the pictures or the movies help the learner to address his/her attention toward the critical elements (selective attention) and to inhibit the tendency to move the focus of attention toward other elements prematurely, namely, before the former ones have been adequately processed (sustained attention). Pictures also suggest how the selected elements are to be related one another to reach the overall understanding of the topic, so preventing ADHD students to "jump" mentally from an element to another in an unproductive way, that is, without finding the proper way to link them. In Mayer's perspective, a further theoretical support to the alleged advantages that multimedia tools might provide to ADHD learners consists in the fact that if, because of the susceptibility to distraction of ADHD individuals, information has not been caught or has not been adequately processed by a sensory channel, the other channel can supply to this.

Also the arguments supporting the strengthens of hypertexts which were mentioned above induce to expect positive effects of hypermedia instruments in the acquisition and retention of declarative as well as conditional and procedural knowledge. If linking new information to pre-existing concepts is important for the construction of each kind of knowledge, hypertexts should facilitate the elaboration of declarative, conditional, and procedural knowledge since they allow the learner to access new data just starting from his/her previous knowledge (which prompts him/her to look for concepts that can extend what is already known), reduce the gap between what is familiar and what is unfamiliar, overcome contradictions, inconsistencies and misunderstandings in the prior knowledge, to answer questions risen on the basis of the possessed information. Also in this case the benefits produced by hypertexts should be shared by ADHD learners. Firstly, once a section of the hypertext has been examined, student's attention is attracted toward the contents to be learned because

of the need of choosing what section is better to access to. The action of selecting the next section prevents him/her to let his/her mind to "wander" away from the task. Secondly, if motivation is important in supporting the attentional investment and it is lacking in ADHD students, the possibility to move toward a section which meets personal interest should enhance curiosity and the willing to pay attention to the new concepts which are provided.

The experiment reported here was designed to examine students with ADHD, students with ADHD and learning problems (LP), and typically developing students in terms of the acquisition and retention of declarative, conditional, and procedural knowledge in a hypermedia learning environment vs. a traditional instructional environment. More specifically, the first question addressed in the study was whether declarative, conditional, and procedural knowledge are better acquired and retained when provided by a hypermedia tool as opposed to traditional instruction. The second question was whether the hypermedia tools yield the same better learning outcomes—if any—both in the acquisition and in the retention phase. The third question was whether clinical groups differ from each other and from a typically developing group in knowledge assimilation according to the instructional setting to which they are assigned. Moreover whether possible differences among clinical groups and differences between each of them and the control group depend on the phase (acquisition vs. retention phase) in which learning outcomes are assessed. The answers to the first and second questions should allow us to understand better the beneficial effects produced by hypermedia tools on learning thanks to the identification of the precise level of knowledge and phase of the learning process where such effects might occur. The answers to the third question should make clearer the role played by hypermedia devices in facilitating learning in ADHD students, allowing us to go beyond the general suggestions provided by the investigations carried out previously.

2. Methods

2.1. Participants

The participants in this study were selected from a sample of 1223 students attending to public schools in Lombardy, a region of the Northern Italy. Students ranged in age from 12 to 14 years and were attending to either the 1st or 2nd grade of the secondary school (corresponding to the 6th and 7th grades of the primary school). A wide sample of schools which were in touch with the Catholic University of Milano, since they had been involved in previous on-the-job training courses addressed to teachers, were contacted and asked to collaborate to the investigation. The procedure described below was followed in all schools which decided to participate.

To select students with ADHD symptoms, two phases were followed.

2.1.1. First phase

The Italian adaptation of the American ADHD Rating Scale-IV: School Version (DuPaul, Power, Anastopoulos, & Reid, 1998) and the Italian adaptation of the Disruptive Behaviour Disorder Rating Scale (Pelham, 1993) were used. The development of both the original psychometric instruments was based on the DSM-IV criteria for ADHD (American Psychiatric Association, 2000). The Italian adaptation of the American ADHD Rating Scale-IV, called SDAI, was devised by Marzocchi and Cornoldi (2000). The Italian adaptation of the Disruptive Behaviour Disorder Rating Scale, called SCOD, was devised by Marzocchi et al. (2001). The use of these scales as a first screening is a well-known method to identify learners with ADHD symptoms (Ford et al., 1993).

SDAI includes two subscales, each constituted by 9 items: distractibility or inattentivity (I) and hyperactivity (H). Items are endorsed on a four-point scale: Never or rarely (0), Sometimes (1), Often (2) and Very often (3). The possible total score that an individual can reach on each of the subscales ranges from 0 to 27. The cut-off criterion for both subscales is 14. If an individual obtains a score exceeding the cut-off in the first subscale only, he/she is classified as belonging to the ADHD-I (inattentive) subgroup; if he/she exceeds the cut-off in the second subscale only, he/she belongs to the ADHD-H (hyperactive) subgroup; if he/she exceeds the cut-off in both the subscales, he/she is classified as ADHD-C (combined, namely, both inattentive and hyperactive).

SCOD is composed of 13 items. Eight items provide a disruptive behaviour disorder index and 5 items provide a LP (learning problems) index in both mathematical and linguistic areas. Items are scored on a four-point scale: Never or rarely (0), Sometimes (1), Often (2) and Very often (3). The possible total score that an individual can reach on the disruptive behaviour disorder subscale ranges from 0 to 24 and the cut-off criterion is 12. The possible total score that an individual can obtain on the LP subscale ranges from 0 to 15 and the cut-off score is 8.

The psychometric evidence supporting SDAI can be summarised as follows. Marzocchi and Cornoldi (2000) reported on month test–retest reliability of .89 for the inattentive and .95 for the hyperactivity subscales; SDAI internal reliability was .97 and .94, respectively, for the inattentive and hyperactivity subscales. Regards to SCOD, Marzocchi et al. (2001) reported a one-month test–retest reliability of .92 for the disruptive behaviour disorder and of .89 for the LP subscales. Internal reliability for the two subscales was, respectively, .88 and .86.

SDAI and SCOD scales were applied to all students enrolled in the schools which agreed to participate in the investigation. For each student, the teacher who played the role of tutor was asked to fill in SDAI and SCOD. Teacher were told that, if they were uncertain about how to endorse some items of the scales and/or were lacking of relevant information, they could involve one or more colleagues in filling in the scales so to reach a shared response.

2.1.2. Second phase

Students who exceeded the cut-off scores in one or both SDAI subscales (I and H) passed to the second phase for a clinical diagnosis carried out by a specialised psychologist during individual interviews. The psychologist conducted interviews to exclude ADHD-like symptoms as bipolar disorders (early onset bipolar disorder), Tourette's syndrome, childhood depression, oppositional defiant disorder, and so on. She also examined if the symptoms causing impairment were reported in two or more settings and the onset age of the disorder. She collected data from both parents and teachers. During the interviews the psychologist also administered WISC-R (Wechsler, 1991). The interviews were also aimed at getting information about school achievement from parents, teachers, and students themselves. After the individual clinical assessment 6 participants (2 who reached the cut-off criteria on SDAI and 4 who reached the cut-off criteria on both SDAI and SCOD) were excluded from the study because of the diagnosis of other disorders (oppositional defiant disorders).

The final sample included 27 students with ADHD, 28 students with both ADHD and LP and 29 normally achieving students as a control group (see below).

2.1.3. Students with ADHD

The ADHD group was composed by 18 students who, on the basis of SDAI scores, met ADHD-C criteria, 7 who met ADHD-I criteria and 2 who met ADHD-H criteria. The presence of other disorders was excluded because these students obtained normal SCOD and IQ scores and thanks to what emerged in the clinical interviews. No child had a history of brain damage, epilepsy, psychosis, or anxiety disorders.

2.1.4. Students with ADHD + LP

Students belonging to this group met criteria for ADHD and obtained normal SCOD scores, except for the LP subscale (where they exceeded the cut-off criteria), as well as normal IQ scores. Learning problems were confirmed by what emerged in the interviews through the responses given by parents, teachers, and students themselves. These three sources of information converged in supporting the notion that the students was an underachiever in almost all disciplines and in excluding that low learning outcomes were caused by reduced motivation, socio-cultural deprivation, linguistic difficulties due to immigration, emotional or relational disorders or problems.

2.1.5. Normally achieving students

The sample of the initial 1123 students—with the exclusion of (i) the students included in the clinical groups previously described, (ii) the students who obtained SDAI and SCOD scores out of the normal range but were not included in any clinical group, and (iii) the students diagnosed as affected by behavioural, emotional and/or relational problems by the psychologists of the schools—was the basis for the control group. A set of students was randomly extracted from such a sample. Their gender and age were considered in order to extract students that could constitute a group whose boys/girls ratio and whose mean age matched approximately the boys/girls ratios and the mean ages of the clinical groups.

The characteristics of ADHD, ADHD + LP and control students are summarised in Table 1.

As expected, the ADHD, ADHD + LP, and the control group differed significantly on the SDAI distractibility, $F(2, 81) = 21.60$, $p < .001$ and on SDAI hyperactivity subscales, $F(2, 81) = 18.11$, $p < .001$. Even though IQ mean scores—as measured by the WISC-R—of each experimental group were within the normal range, a one-way analysis of variance showed that IQ scores of ADHD and ADHD + LP students were significantly lower than the IQ scores of the control group, $F(2, 81) = 20.53$, $p < .01$. Therefore, in all analyses including a group factor IQ was added as a covariant factor.

Participants in each group (ADHD, ADHD + LP, control) were assigned either to the hypermedia ($N = 37$) or to the traditional instruction ($N = 37$) condition through a matched-pair technique.

Signed parental consent forms were requested and obtained for all participants.

Table 1
Characteristics of the three groups participating in the experiment.

Groups	Measures	Values
ADHD	No. of boys/girls	20/7
	Age (mean; SD in parentheses)	13.60 (1.80)
	IQ (mean; SD in parentheses)	96.00 (6.70)
	SDAI-distractibility (mean; SD in parentheses)	19.80 (2.45)
	SDAI-hyperactivity (mean; SD in parentheses)	15.40 (6.01)
ADHD + LD	No. of boys/girls	20/8
	Age (mean; SD in parentheses)	13.50 (1.80)
	IQ (mean; SD in parentheses)	91.20 (5.80)
	SDAI-distractibility (mean; SD in parentheses)	18.75 (2.55)
	SDAI-hyperactivity (mean; SD in parentheses)	9.90 (2.10)
Control	No. of boys/girls	20/9
	Age (mean; SD in parentheses)	13.70 (2.01)
	IQ (mean; SD in parentheses)	107.50 (6.95)
	SDAI-distractibility (mean; SD in parentheses)	1.00 (0.20)
	SDAI-hyperactivity (mean; SD in parentheses)	0.80 (0.32)

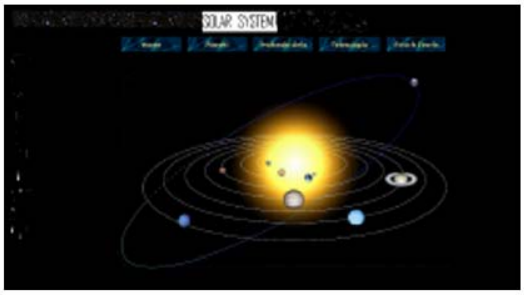


Fig. 1. An example of informational screen.

2.2. Instruments

2.2.1. Hypermedia learning tool (HLT)

The hypermedia instrument devised for this study concerned the origin of the solar system, the sun and a description of three planets. Concepts were arranged in order to be relevant to 1th to 2th secondary school grade students. The hypermedia tool could be navigated by using a Web browser. The material was developed through the hypertext markup language (HTML). An instructional system development process and a conceptual linking approach guided the development of the hypermedia tool, which included texts, sounds, pictures and graphics. When text was presented a narrative voice read always the text. The HLT It consisted of 60 screens: 5 screens were introductory, 1 was the main menu, 49 provided information and 5 were for practice. An example of informational screen is presented in Fig. 1. Designing the hypermedia learning material involved three phases: preparation, development and evaluation. The phases are described in the following sub-sections.

2.2.1.1. Phase 1: Preparation. a. Determining the users' characteristics. Learners' characteristics are one of the most important factors affecting the design of hypermedia learning material. If the learner has prior knowledge, information should be integrated into the existing mental structure and the learner should be induced to follow meaningful learning steps in the instructional tool. The users who participated in this study had no previous specific knowledge of the units selected for the study (their teachers were interviewed to assess this). Then, two subject matter experts (a university and a secondary school science teacher) were consulted about the participants' intellectual level. They agreed that the learning units selected for the study would be appropriate for 6th to 7th grade students.

b. Conducting content analysis. Content analysis was carried out and concepts, interrelated concepts and procedures were determined on the basis of the objectives of the selected units. Systematic relationships between the concepts were organised and a subject–matter experts evaluated the semantic relationships of the concepts thus determined. In light of this evaluation, the semantic relationships between the concepts were reorganised.

c. Determining the learning strategies. According to Schunk (1996), meaningful learning involves gaining ideas, concepts and principles and then integrating new knowledge into existing knowledge. Thus, general knowledge was provided first, followed by detailed and specific knowledge.

d. Identifying the knowledge organisation approaches that best suit the learning strategies. At this stage, the issues of knowledge organisation and linking nodes were managed. Hierarchical links were used: first, basic concepts were presented and then subordinate concepts related to the basic concepts were provided. In addition to hierarchical links, an elaboration approach was used to explain concepts from simple to complex levels (i.e., general to specific knowledge). Both approaches were consistent with the learning strategies used in this hypermedia tool.

2.2.1.2. Phase 2: Development. a. Concept mapping. To ascertain interrelations between concepts determined in content analysis, concept maps of the units were constructed. This was helpful to show each node and links between nodes.

b. Story boarding. Story boarding was the last step before the programming stage. It involved showing each navigation window on a page. Each window to be designed in this study was shown on a separate page. Active keys, the names of linked windows, links, texts, sounds, pictures and graphics were also shown on that page.

c. Programming. An HTML editor for programming was used to implement the designed hypermedia.

2.2.1.3. Phase 3: Evaluation. After the material was developed, it was given to an instructional design specialist, to a subject-area expert and to three subject-area teachers for evaluation. The material was revised and improved according to the feedbacks received from those experts.

2.2.2. Achievement test

A test was used to determine students' achievement on different types of knowledge (declarative, conditional and procedural) before the experiment, at the end of the acquisition phase, and one month after the experiment (retention). To

Table 2
Examples of the three types of knowledge.

Examples of declarative knowledge questions
• What is a supernova?
• When the solar system begun to exist, which was the shape of the nebula?
• Why Mars is red?
Examples of conditional knowledge questions
• If gas and cosmic dust continuously go around the sun, what will happen to solar nebula?
• If an astronaut reached Mars and opened a water container, what should happen to water?
• If Jupiter was bigger, what should happen?
Examples of procedural knowledge questions
• A man on Mars weights 25 kg; how much does he weight on the Earth?
• I know that in a Jupiter's band winds blow on west. In which direction do winds blow two bands later? In which direction do winds round five bands later?
• Two galaxies are 195,000,000,000 km far each other; how many light years are they far?

check the content validity of the test, a table of specifications was used to represent the learning objectives in the questions. Declarative knowledge questions focused on facts, names and lists involved "what" and "which" types of questions. Conditional knowledge questions focused on understanding a network of condition-action sequences and predicting what happens if one of the variables in the sequence changes within the context of if–then, condition–action or relationship statements. Procedural knowledge questions emphasised higher-level cognitive activity such as employing algorithms and rules or solving problems. Table 2 reports some examples of the questions.

The test was given to three subject-area teachers who assessed the questions in terms of the three knowledge levels as well as of the validity and relevance to the subject matter. Such an assessment helped us to revise some questions. The revised version of the test was given to 10 students (5 girls and 5 boys aged 12–14). Their first task was to assess item difficulty and clarity. Students were asked to score difficulty and clarity on a scale ranging from 1 (minimum) to 10 (maximum). The analysis of each item showed that one item was too easy and four items were too difficult; these items were therefore eliminated. Some of the items were revised to improve clarity. As a result, 39 questions (13 declarative, 13 conditional and 13 procedural) were included in the test. The test was presented in the form of a booklet, with the space to write the response under each question. A maximum time of 20 min was allowed to answer the questions. Protocols were scored by two independent judges. A set of criteria were devised to attribute either score 0 or 1 to each response. The reliability of such a scoring system was tested by asking both judges to score the same 5 randomly chosen protocols. The inter-rater agreement resulted to be very high (the same score was attributed by both judges to 194 out of 195 responses). Three total scores-corresponding to declarative, conditional and procedural knowledge-could be computed by summing up scores in the respective questions.

2.3. Procedure

At the beginning of the experiment, participants assigned to the hypermedia and traditional instruction conditions were asked to respond to some questions to check their prior knowledge about the topic to be studied. Three questions concerned declarative knowledge, 3 conditional knowledge, and 3 procedural knowledge. The questions were extracted from the achievement test previously described. No significant difference among the three sub-samples emerged by comparing scores in the declarative, conditional and procedural questions (a one-way ANOVA was carried out for each question: F values ranged from 0.54 to 1.63).

Then participants in the hypermedia condition were given an introductory session about the use of the hypermedia tool, whereas in the traditional instruction condition they were given a brief introduction concerning classroom activities to be carried out. In the hypermedia condition participants studied the content of the hypermedia tool in a computer laboratory for 30 min. Each student was equipped with a personal computer which allowed him/her to browse freely the hypermedia tool. Students received help from the teacher about how to browse the hypermedia tool only if they requested it. In the traditional instruction condition students received the same information provided to the other group (that is, the same statements) for the same amount of time by being exposed to oral explanation. To eliminate possible biases, the same teacher conducted the instructional activities in both conditions.

After having been presented with the concept to be learned, the achievement test was administered to all students in both conditions. One month after the learning experience, the same achievement test was given to participants of both conditions to measure the level of retention of the three types of knowledge. During the test, the participants in the hypermedia and traditional instruction conditions had no access to the learning materials. Testing was always carried out by the same person in both conditions. Table 3 summarises the design and the procedure of the study.

2.4. Statistical analyses

Data were analysed using SPSS 14.0 for Windows. The descriptive statistics of the dependent variables were examined. The dependent variables (the numbers of correct answers in the achievement test) were submitted to weighted multivariate

Table 3
Design of the experiment.

Condition	Base-line	Introduction	Treatment	Acquisition test (just after the teaching session)	Retention test (one month after the teaching session)
Hypermedia	Prior knowledge questions	How to use the hypermedia How classroom activities will be carried out	Hypermedia	Achievement test	Achievement test
Traditional	Prior knowledge questions		Traditional classroom instruction	Achievement test	Achievement test

and univariate analyses of variance with two between-subject factors – Condition (hypermedia learning environment vs. traditional instruction) and Group (ADHD vs. ADHD + LP vs. Control) – and two repeated measures – Phase (acquisition vs. retention) and type of knowledge (declarative vs. conditional vs. procedural). The alpha-level was set to .05 for all statistical tests. In case of significant effects, the effect size and the power of the test were reported. The effect sizes were computed and categorised according to Cohen (1988). The Greenhouse–Geisser adjustment for nonsphericity was applied to probability values for repeated measures. IQ was treated as a covariate. Omnibus tests were evaluated with two-tailed $\alpha = .05$. Planned pairwise comparisons were performed among all the three groups.

In a complex design like that of the present study, there is an opportunity to test many hypotheses of interest for numerous variables and the need to consider possible confounding factors. We employed the following strategy in order to minimise Type I error. For families of 3 pairwise tests, we used unadjusted a levels of .05, an approach that successfully maintains a levels for this number of comparisons (Myers & Well, 2003, p. 252). For families comprising more than 3 tests, we adjusted levels by the Bonferroni's correction. We reported nominal p levels and identified results as significant, marginal, or not significant.

3. Results

The first question addressed in this study was whether declarative, conditional, and procedural knowledge are better acquired and retained when provided by a hypermedia tool as opposed to traditional instruction. Table 4 reports means and standard deviations of declarative, conditional, and procedural knowledge scores in the groups under the two instructional conditions in each phase of the experiment.

With reference to the first question, the main effect of Condition and Type of knowledge were significant, respectively $F(1, 78) = 5.99$, $p < .05$, $\eta_p^2 = .07$ and $F(2, 156) = 26.51$, $p < .01$, $\eta_p^2 = .26$. Globally considered, knowledge assimilation was better in the hypermedia than in the traditional instruction setting. Furthermore, as expected, performances in the declarative knowledge questions were better than in the conditional and procedural questions: the first type of knowledge, in fact, is less demanding than the other two types in terms of cognitive processing. Worthily, we found a significant Condition × Type of knowledge interaction, $F(2, 156) = 6.49$, $p < .01$, $\eta_p^2 = .08$, indicating that, even though students performed better in all types of knowledge when assigned to the hypermedia condition, the differences between the two conditions were higher in procedural knowledge. Univariate comparisons of each type of knowledge were significant ($p < .01$) except for declarative knowledge.

The second question was whether the hypermedia tools yield the same better learning outcomes both in the acquisition and in the retention phase. The main effect of Phase was significant, $F(1, 78) = 17.77$, $p < .01$, $\eta_p^2 = .18$: as

Table 4
Means and standard deviations of declarative, conditional and procedural knowledge scores in the groups under the two instructional conditions in each phase of the experiment.

Groups	Hypermedia instruction				Traditional instruction			
	Acquisition		Retention		Acquisition		Retention	
	M	SD	*M*	SD	*M*	SD	*M*	SD
Declarative								
ADHD	11.35	4.98	10.80	4.76	8.56	3.05	5.10	3.22
ADHD + LD	7.90	5.56	7.66	3.99	10.90	4.11	6.32	3.56
Control	11.10	3.77	11.25	3.94	12.80	4.15	10.90	3.58
Conditional								
ADHD	8.10	5.29	8.00	3.18	7.00	2.70	4.90	5.12
ADHD + LD	6.60	3.01	6.44	2.21	6.01	2.90	3.30	2.68
Control	10.70	2.87	9.95	3.01	12.00	5.09	10.01	3.34
Procedural								
ADHD	8.98	4.33	9.80	3.48	7.22	3.12	3.70	2.27
ADHD + LD	5.43	3.96	6.12	3.84	6.45	3.57	3.10	2.18
Control	9.08	4.28	11.30	5.22	9.00	4.32	6.12	4.13

obvious, performances decreased in the retention phase. A significant Condition × Type of knowledge × Phase interaction emerged, $F(2, 156) = 5.97$, $p < .01$, $\eta_p^2 = .08$, supporting the notion that, even if students in the hypermedia condition outperformed students in the traditional instruction condition in both phases and in each type of knowledge, the superiority of the former condition emerged more clearly in the retention phase and concerned prevalently the conditional and procedural knowledge. More precisely, the highest advantage concerned procedural knowledge in the retention phase: in this case hypermedia instruction allowed learners even to improve the performance as compared to the acquisition phase.

The third question was whether clinical groups differed from each other and from the control group in knowledge assimilation according to the instructional setting to which they were assigned. There was a significant Condition × Group interaction, $F(2, 156) = 6.39$, $p < .01$, $\eta_p^2 = .08$, and a significant Condition × Group × Type of knowledge interaction, $F(4, 156) = 7.63$, $p < .01$, $\eta_p^2 = .17$. Even if, in general, all groups of students learned better in the hypermedia than in the traditional instruction condition, the differences between the two conditions were higher in the clinical groups. Furthermore, as far as declarative knowledge is concerned, only ADHD students benefited from hypermedia instruction. Hypermedia instruction improved conditional knowledge (approximately to a similar extent) only in the clinical groups. Procedural knowledge was highly increased by the hypermedia tool in the control and ADHD students (who obtained similar scores), but not in the ADHD + LP students who obtained a limited benefit.

The fourth question was whether differences between groups depended on the phase (acquisition vs. retention phase) in which learning outcomes were recorded. Differences between scores in the acquisition and retention phase by the clinical groups were lower in the hypermedia than in the traditional instruction condition.

If we take into account scores across all the three type of knowledge, we realise that hypermedia instruction (as compared to traditional instruction) greatly pulled up the performances of ADHD students to levels that were similar to those of the normally achieving students. This was not true for ADHD + LP students. Splitting the results with reference to groups, it was found that the main effect of Condition was significant in the ADHD group, $F(1, 26) = 4.26$, $p < .05$, but not in the ADHD + LP group, $F(1, 27) = 1.03$, $p = .22$.

4. Conclusions

The aim of the present study was twofold. First we were interested in assessing whether the benefits produced by hypermedia tools concern different kinds of knowledge to the same extent and occur in different stages of the learning process (first and second questions mentioned in Section 1). To answer these questions, the same instructional materials were implemented in a traditional instructional setting and in a hypermedia environment providing three types of knowledge (namely declarative, conditional, and procedural) and distinctive tests designed to evaluate each type of knowledge were administered to participants both immediately after the learning session (acquisition) and one month later (retention).

Second, we were interested in assessing whether benefits from hypermedia tools concern not only normally achieving students, but also those with ADHD and/or with ADHD and LP (third and fourth questions mentioned in Section 1). To achieve such a goal, the traditional and hypermedia instructional materials were presented both to typical developing students and to two clinical groups in which declarative, conditional, and procedural knowledge was tested for acquisition and retention.

As far as the first issue was concerned, results confirmed an expected result, namely, that performances in the retention test were worse than in the acquisition test. All the three types of knowledge showed a decay due to time. However, the hypermedia instrument significantly contrasted such a decay in comparison with the traditional instruction setting. Such a finding is consistent with Yildirim, Ozden, Yasar, and Aksu (2001) results. These authors made a comparison between a hypermedia learning environment and traditional instruction and reported that there were no significant short-term differences between the two conditions at the end of the treatment, whereas a month later students in the hypermedia learning environment showed they retained information better than did students in the traditional condition. The present study not only provided further evidence to support such a conclusion, but also has allowed us to maintain that long-term learning benefits yielded by hypermedia concern different types of knowledge, a fact not recognised in Yildirim et al.'s (2001) study.

The findings of the present experiment are consistent with the literature concerning hypermedia learning. As Jonassen (1991) stated, learning involves building new structures by assimilating environmental information, constructing new nodes and interrelating new nodes one another and with the existing ones. Learning thus requires forming links between existing knowledge and new knowledge to comprehend information. The hypermedia tool used in this study was designed on the basis of these principles so to enable students to build their knowledge structures effectively by forming links between their existing knowledge and new knowledge and by establishing a meaningful understanding of the concepts. These characteristics of the hypermedia learning environment helped students to retain knowledge in the long-term period. This is consistent also with the literature concerning the importance of using multiple sensory channels in learning (Clark & Paivio, 1991; Mayer, 2003). Moreover dual processing produces an additive effect because the learner creates more cognitive paths that can be followed to retrieve information (Bagui, 1998). Mayer (2001) suggested that information should be coded through different channels to help persons to retain knowledge more effectively. Dual coding reduces the cognitive load in one's memory (Mayer & Moreno, 1998), so that one can interpret the information by creating meaningful schema (Kalyuga,

Chandler, & Sweller, 2004; Tabbers, Martens, & Van Marrienboer, 2004). We developed hypermedia learning material for this study on the basis of the dual coding principle. Representation of information through multiple channels in the hypermedia learning environment appeared to be effective in contributing to the retention of all three types of knowledge tested in this study.

The second issue concerned the hypothesis that ADHD students performed better with hypermedia as opposed to traditional instruction. This hypothesis was confirmed. ADHD students exposed to the hypermedia learning environment outperformed the other clinical group both in the acquisition and retention phase with respect to all the three types of knowledge and they reached approximately the same levels of normally achieving participants both in the acquisition and retention phase. ADHD + LP students in the hypermedia condition failed to benefit to the same extent as ADHD participants did. It may be that deeper and wider structural deficits associated to LP impeded the beneficial effects of hypermedia instruction to emerge. Such effects might require a sufficient level of learning resources, which are lacking in students with LP, as a pre-condition. LP students might need more support in terms of training to facilitate their learning processes. It may be also that hypermedia instruction can produce a cognitive empowerment only in the input phase and do not in the elaboration phase. ADHD students need an empowerment of input processing thanks to visual presentation and increased motivation and this may be sufficient to improve learning outcome, but it seems to be necessary but not sufficient for LP students. Anyway, since the nature of the learning problems of students in this group is not clear, it is necessary to go over the boundaries of the present study to analyse better LP and also LD students; in future researches it may be useful to measure their level of cognitive resources, such as working memory.

In general, the hypermedia tool reduced learning differences in retention between the control group and the clinical groups as compared to what occurred with traditional instruction. The results of the present experiment suggest that ADHD students can benefit when information is presented through multiple channels and in a hypertext format. Hypermedia tools may have a positive effect on the retention of different types of knowledge. It may be due in part to the role of motivational factors and in part to the specific type of knowledge organisation and presentation. As Barkley (1997) argued, motivational factors are very important in executive functioning in ADHD. Hypermedia devices can rise motivational levels of ADHD students both because they introduce a change in the routine of school activities by varying the way in which concepts can be learned (novelty effect) and because they allow learners to access concepts according to personal preferences or interests (curiosity effect). Another possible explanation is based on the attention catching properties of the hypermedia tools. ADHD students, who usually encounter difficulties in keeping attention focused on the relevant information, benefit from a hypermedia presentation since it captures the learners attention or provides them with hints useful to allocate attention in the proper way.

Alternative interpretations are grounded on the intrinsic nature of the hypermedia instruments. When exposed to hypermedia tools, ADHD students receive information from multiple channels, so that if their attention is not adequately allocated to a channel, the other channel can "capture" and retain information which otherwise would be missed. In other words, multimedia stimulation increases the likelihood that relevant information is acquired. Students with ADHD might be helped by a hypermedia instrument also because it allows them to learn at their own pace (Solomonidou, Garagouni-Areou, & Zafiropoulou, 2004), so that they can allocate attention by following their personal rhythms. In this way each element to be learned receives an adequate amount of attention.

Further investigations are needed to clarify the precise reasons why hypermedia tools are beneficial for ADHD students. Nevertheless, it has been worthwhile assessing, in a systematic way and through the experiment here described, the kinds of knowledge and the phases of the learning process that can take advantage from hypermedia tools.

Acknowledgements

The authors thank Saverio Hernandez for collecting data.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. Washington: American Psychiatric Association.
Anderson, J. R. (1995). *Cognitive psychology and its implications* (4th ed.). New York: WH Freeman.
Andris, J. (1996). The relationship of indices of student navigational patterns in a hypermedia geology lab simulation to two measures of learning style. *Journal of Educational Multimedia and Hypermedia, 5*, 303–315.
Ayersman, D. J., & Minden, A. (1995). Individual differences, computers, and instruction. *Computers in Human Behavior, 11*, 371–390.
Bagui, S. (1998). Reasons for increased learning using multimedia. *Journal of Educational Multimedia and Hypermedia, 7*, 3–17.
Barkley, R. A. (1997). *ADHD and the nature of self-control*. New York: Guilford Press.
Baylor, A. L. (2001). Perceived disorientation and incidental learning in a web-based environment: Internal and external factors. *Journal of Educational Multimedia and Hypermedia, 10*, 227–251.
Bender, R., & Bender, W. (1996). *Computer-assisted instruction for students at risk for ADHD, mild disabilities or academic problems*. Boston, MA: Allyn and Bacon.
Burt, K. L., & Ryan, C. L. (1997). An investigation of the effects of medication and the use of computerized feedback in task performance of AD/HD children. *Issues in Special Education and Rehabilitation, 12*, 56–70.
Calcaterra, A., Antonietti, A., & Underwood, J. (2005). Stylistic differences in surfing hypermedia. *Computers and Education, 44*, 441–453.
Chou, H. W. (2001). Influences of cognitive style and training method on training effectiveness. *Computers and Education, 35*, 11–25.
Chou, H. W., & Wang, Y. F. (1999). Effects of learning style and training method on computer attitude and performance in World Wide Web page design training. *Journal of Educational Computing Research, 21*, 325–344.
Clark, J. M., & Paivio, A. (1991). Dual coding theory and education. *Educational Psychology Review, 37*, 250–263.
Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Dailey, E., & Rosemberg, M. (1994). ADD, computers and learning: Using computers to help children with ADD become efficient learners. *Attention, 1*, 8–16.
Douglas, G., & Riding, R. (1993). The effect of pupil cognitive style and position of prose passage title on recall. *Educational Psychology, 13*, 385–393.
Douglas, V. I. (1983). Attention and cognitive problems. In M. Rutter (Ed.), *Developmental neuropsychiatry* (pp. 280–329). New York: Guilford Press.
DuPaul, G., Power, T., Anastopoulos, A., & Reid, R. (1998). *ADHD rating scales-IV: Checklists, norms and clinical interpretation*. New York: Guilford Press.
Fabio, R. A., Antonietti, A., & Tiezzi, P. (2003). Decodifica dei messaggi uditivi e visivi nei soggetti con DDAI: Deficit selettivo o attenzione diffusa? [Decoding of auditory and visual stimuli in ADHD children: Selective deficit or spreading attention?]. *Studi di Psicologia dell'Educazione e della Formazione, 4*, 56–72.
Farrace-Di Zinno, A. M., Douglas, G., Houghton, S., Lawrence, V., West, J., & Whiting, K. (2001). Body movements of boys with Attention Deficit-Hyperactivity Disorder (ADHD) during computer video game play. *British Journal of Educational Technology, 32*, 607–618.
Fiorina, L., Antonietti, A., Colombo, B., & Bartolomeo, A. (2007). Thinking style, browsing primes and hypermedia navigation. *Computer and Education, 49*, 916–941.
Ford, M. J., Poe, V., & Cox, J. (1993). Attending behaviors of ADHD children in math and reading using various type of software. *Journal of Computing in Childhood Education, 4*, 183–196.
Ford, N., & Chen, S. Y. (2000). Individual differences, hypermedia navigation, and learning: An empirical study. *Journal of Educational Multimedia and Hypermedia, 9*, 281–312.
Ford, N., & Ford, R. (1992). Learning styles in an ideal computer-assisted learning environment. *British Journal of Educational Technology, 23*, 195–211.
Graff, M. (2003). Learning from web-based instructional systems and cognitive style. *British Journal of Educational Technology, 34*, 407–418.
Granic, I., & Lamey, A. V. (2000). The self-organization of the Internet and changing modes of thought. *New Ideas in Psychology, 18*, 93–107.
Hall, T. E., Hughes, C. A., & Filibert, M. (2000). Computer assisted instruction in reading for students with learning disabilities: A research synthesis. *Education and Treatment of Children, 23*, 173–193.
Hede, A. (2002). An integrated model of multimedia effects on learning. *Journal of Educational Multimedia and Hypermedia, 11*, 177–191.
Houghton, S., Milner, N., West, J., Douglas, G., Lawrence, V., Whiting, K., et al. (2004). Motor control and sequencing of boys with Attention-Deficit/Hyperactivity Disorder (ADHD) during computer game play. *British Journal of Educational Technology, 35*, 21–34.
Jonassen, D. H. (1991). Hypertext and instructional design. *Educational Technology Research and Development, 39*, 83–92.
Jonassen, D. H., & Grabinger, R. S. (1990). Problems and issues in designing hypertext/hypermedia for learning. In D. H. Jonassen & H. Mandl (Eds.), *Designing hypermedia for learning* (pp. 322–347). New York/Berlin/Heidelberg: Springer-Verlag.
Kalyuga, S., Chandler, P., & Sweller, J. (2004). When redundant on-screen text in multimedia technical instruction can interfere with learning. *Human Factors, 46*, 567–581.
Kleinman, G., Humphrey, M., & Lindsay, P. H. (1981). Microcomputers and hyperactive children. *Creative Computing, 7*, 93–94.
Lawrence, V., Houghton, S., Tannock, R., Douglas, G., Durkin, K., & Whiting, K. (2002). ADHD outside the laboratory: Boys' executive function performance on tasks on videogame play and on a visit to the zoo. *Journal of Abnormal Child Psychology, 30*, 447–462.
Lin, S. S. J., Liu, E. Z. F., & Yuan, S. M. (2001). Web-based peer assessment: Feedback for students with various thinking-styles. *Journal of Computer Assisted Learning, 17*, 420–432.
Lohr, L., Ross, S. M., & Morrison, G. R. (1995). Using a hypertext environment for teaching process writing: An evaluation study of three student conditions. *Educational Technology Research and Development, 43*, 33–51.
Lomas, K. M. (2002). Computer-assisted cognitive training with elementary school-age children diagnosed with attention deficit/hyperactivity disorder and mild/moderate comorbidity: A short term prospective study on attention, planning and behaviour. *Dissertation Abstracts International, Section B: The Sciences and Engineering, 63*(1-B), 535.
Maccini, P., Gagnon, J. C., & Hughes, C. A. (2002). Technology-based practices for secondary students with learning disabilities. *Learning Disability Quarterly, 25*, 247–262.
Marzocchi, G. M., & Cornoldi, C. (2000). Una scala di facile uso per la rilevazione dei comportamenti problematici dei bambini con Deficit di Attenzione e Iperattività [A scale to identify behavioural problems in ADHD children]]. *Psicologia Clinica dello Sviluppo, 4*, 43–62.
Marzocchi, G. M., Oosterlaan, J., De Meo, T., Di Pietro, M., PezzicaPizzica, S., Cavolina, P., et al. (2001). Disruptive Behaviour Disorder Rating Scale for teacher (Italian version). *Giornale di Neuropsichiatria dell'Età Evolutiva, 21*, 378–393.
Mautone, J. A., DuPaul, G. J., & Jitendra, A. K. (2005). The effect of computer-assisted instruction on the mathematics performance and classroom behavior of children with ADHD. *Journal of Attention Disorders, 9*, 301–312.
Mayer, R. E. (1999). Research-based principles for the design of instructional messages. *Document Design, 1*, 7–20.
Mayer, R. E. (2001). *Multimedia learning*. New York: Cambridge University Press.
Mayer, R. E. (2003). The promise of multimedia learning: Using the same instructional design methods across different media. *Journal of Educational Psychology, 83*, 484–490.
Mayer, R. E. (Ed.). (2005). *The Cambridge handbook of multimedia learning*. New York: Cambridge University Press.
Mayer, R. E., & Moreno, R. (1998). A split-attention effect in multimedia learning: Evidence for dual information processing systems In working memory. *Journal of Educational Psychology, 90*, 312–320.
Muller-Kalthoff, T., & Moller, J. (2003). The effects of graphical overviews, prior knowledge, and self-concept on hypertext disorientation and learning achievement. *Journal of Educational Multimedia and Hypermedia, 12*, 117–134.
Myers, J. L., & Well, A. D. (2003). *Research design and statistical analysis*. Lawrence Erlbaum: Mahwah, NJ.
Najjar, L. J. (1998). Principles of educational multimedia user interface design. *Human Factors, 40*, 311–323.
Ota, K. R., & DuPaul, G. J. (2002). Task engagement and mathematics performance in children with attention deficit hyperactivity disorder: Effects of supplemental computer instruction. *School Psychology Quarterly, 17*, 242–257.
Paivio, A. (1986). *Mental representations: A dual-coding approach*. New York: Oxford University Press.
Paivio, A. (1991). Dual coding theory: Retrospect and current status. *Canadian Journal of Psychology, 45*, 255–287.
Pelham, W. E. (1993). Pharmacotherapy for children with attention-deficit hyperactivity disorder. *School Psychology Review, 22*, 199–227.
Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal Child Psychology and Psychiatry, 37*, 51–87.
Riding, R. J., & Grimley, M. (1999). Cognitive style, gender and learning from multimedia materials in 11-year old children. *British Journal of Educational Technology, 30*, 43–56.
Rucklidge, J. J., & Tannock, R. (2002). Neuropsychological profiles of adolescents with ADHD: Effects of reading difficulties and gender. *Journal of Child Psychology and Psychiatry, 43*, 988–1003.
Schnotz, W., & Lowe, R. (2003). External and internal representations in multimedia learning. *Learning and Instruction, 13*, 117–123.
Schunk, D. H. (1996). *Learning theories* (2nd ed.). Englewood Cliffs, NJ: Prentice-Hall.
Shaw, R., Grayson, A., & Lewis, V. (2005). Inhibition, ADHD, and computer games: The inhibitory performance of children with ADHD on computerized tasks and games. *Journal of Attention Disorders, 8*, 160–168.
Shin, E. C., Schallert, D. L., & Savenye, W. C. (1994). Effects on learner control, advisement and prior knowledge on young student's learning in a hypertext environment. *Educational Technology Research and Development, 42*, 33–45.
Slusarek, M., Velling, S., Bunk, D., & Eggers, C. (2001). Motivation effects on inhibitory control in children with ADHD. *Journal of the American Academy of Child and Adolescence Psychiatry, 40*, 355–363.
Smith, P. L., & Ragan, T. J. (1993). *Instructional design*. New York: Macmillan.
Solomonidou, C., Garagouni-Areou, F., & Zafiropoulou, M. (2004). Information and communication technologies (ICT) and pupils with Attention Deficit Hyperactivity Disorder (ADHD) symptoms: Do the software and the instruction method affect their behavior? *Journal of Educational Multimedia and Hypermedia, 13*, 109–128.
Sweller, J. (1999). *Instructional design in technological areas*. Camberwell, Australia: ACER Press.
Tabbers, H. K., Martens, R. L., & Van Marrienboer, J. J. (2004). Multimedia instructions and cognitive load theory: Effects of modality and cueing. *British Journal of Educational Psychology, 74*, 71–81.

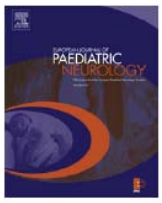
Van Merrienboer, J. J. G. (1997). *Training complex cognitive skills*. Englewood Cliffs, NJ: Educational Technology Press.
Wechsler, D. L. (1991). *Wechsler intelligence scale for children* (3rd ed.). San Antonio, TX: Psychological Corporation.
Xu, C., Reid, R., & Steckelberg, A. (2002). Technology applications for children with ADHD: Assessing the empirical support. *Education and Treatment of Children, 25*, 224–248.
Yildirim, Z., Ozden, M., Yasar, N., & Aksu, M. (2001). Comparison of hypermedia learning and traditional instruction on knowledge acquisition and retention. *Journal of Educational Research, 94*, 207–214.

ARTICLE IN PRESS

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2013) 1–8

ELSEVIER

Official Journal of the European Paediatric Neurology Society



Review article

Tourette Syndrome and comorbid ADHD: Current pharmacological treatment options

Renata Rizzo [a,*], *Mariangela Gulisano* [a], *Paola V. Calì* [a], *Paolo Curatolo* [b]

[a] *Section of Child Neuropsichiatry, Dipartimento di Scienze Mediche e Pediatriche, Catania University, Via Santa Sofia 78, 95123 Catania, Italy*
[b] *Section of Child Neuropsychiatry, Department of Neurosciences, University Tor Vergata, Via Montpellier 1, 00133 Rome, Italy*

ARTICLE INFO

Article history:
Received 10 September 2012
Received in revised form
30 December 2012
Accepted 26 January 2013

Keywords:
Tourette Syndrome
ADHD
Comorbidity
Pharmacological treatment
α-Agonist
Psychostimulants
Selective norepinephrine reuptake inhibitor

ABSTRACT

Background: Attention Deficit Hyperactivity Disorder (ADHD) is the most common comorbid condition encountered in people with tics and Tourette Syndrome (TS). The co-occurrence of TS and ADHD is associated with a higher psychopathological, social and academic impairment and the management may represent a challenge for the clinicians.
Aim: To review recent advances in management of patients with tic, Tourette Syndrome and comorbid Attention Deficit Hyperactivity Disorder.
Methods: We searched peer reviewed and original medical publications (PUBMED 1990–2012) and included randomized, double-blind, controlled trials related to pharmacological treatment for tic and TS used in children and adolescents with comorbid ADHD. "Tourette Syndrome" or "Tic" and "ADHD", were cross referenced with the words "pharmacological treatment", "α-agonist", "psychostimulants", "selective norepinephrine reuptake inhibitor", "antipsychotics".
Results: Three classes of drugs are currently used in the treatment of TS and comorbid ADHD: α-agonists (clonidine and guanfacine), stimulants (amphetamine enantiomers, methylphenidate enantiomers or slow release preparation), and selective norepinephrine reuptake inhibitor (atomoxetine). It has been recently suggested that in a few selected cases partial dopamine agonists (aripiprazole) could be useful.
Conclusion: Level A of evidence supported the use of noradrenergic agents (clonidine). Reuptake inhibitors (atomoxetine) and stimulants (methylphenidate) could be, also used for the treatment of TS and comorbid ADHD.

Taking into account the risk–benefit profile, clonidine could be used as the first line treatment. However only few studies meet rigorous quality criteria in terms of study design and methodology; most trials have low statistical power due to small sample size or short duration. Treatment should be "symptom targeted" and personalized for each patient.

Contents

* *Corresponding author.* Tel.: +39 3402647099; fax: +39 095495673.
E-mail address: rerizzo@unict.it (R. Rizzo).

1090-3798/$ – see front matter © 2013 European Paediatric Neurology Society. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejpn.2013.01.005

ARTICLE IN PRESS

2 EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2013) 1–8

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most common co-morbid condition encountered in people with tics and Tourette Syndrome (TS)[1]; it has been reported that 60%–80% of TS probands have comorbid ADHD.[2] About half of the individuals with chronic tics also meet diagnostic criteria for ADHD.[3] In referred tertiary clinical centers specialized on TS it has been reported that about half of the cases have comorbid ADHD, while 20% of children with ADHD presented comorbid tic disorder.

Furthermore, children with ADHD have an increased risk to develop comorbid tic disorders during their early school years. The Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA), and the Attention-Deficit Hyperactivity Disorder Observational Research in Europe (ADORE) studies reported the presence of tic disorder in 8–10% of ADHD patients.[4,5] Usually ADHD appears about 2–3 years before the tics, while in a smaller proportion of patients ADHD can be observed only after the tic onset; in addition, ADHD can continue into adolescence and adult life.

Comorbid ADHD can be accompanied by internalizing disorders, such as anxiety, as well as aggressive and oppositional disorders. Most studies suggest that ADHD is the main impairing factor on neuropsychological performance in comorbid children, while the presence of tics appears to have no or little influence on neuropsychological performance, particularly executive functioning.[6] Eddy et al. reported that high ADHD-symptom scores in TS were related to poorer QoL within the Self and Relationship domains.[7]

Rizzo et al. suggested that "pure" TS and "pure" ADHD differ in terms of behavioral and cognitive phenotypes while the combined disorder (i.e. TS + ADHD) appears somewhat to lie in between the two separate disorders from a behavioral point of view, but appears substantially closer to ADHD-only regarding behavioral and cognitive measures. TS + ADHD does not seem to be a more severe condition than ADHD alone.[8] TS and comorbid ADHD reflect a separate entity and not merely two-coexisting disorders. Banaschewski et al. suggested that some components of the etiological pathways of TS and comorbid ADHD may well be shared with the 'pure' conditions while others may be unique. It could be proposed that the comorbid condition would be a hybrid and combine the unique characteristics of both pure disorders. Suppression of tics may accentuate inattention in ADHD and attentional problems are correlated with the severity of tic, and inversely associated with the ability to suppress tics. In comorbid children, ADHD has been identified as more disruptive than TS but anxious and depressed symptoms were found to be equally or more strongly influenced by TD.[9]

The comorbidity between Tourette Syndrome and ADHD appear to have a complex pathogenesis and genetic factors can be implicated.[10] Genetic family study suggested that there may be two types of ADHD associated with TS. When ADHD precedes the appearance of tics, the conditions may be etiologically independent, but when ADHD follows the onset of tics they may be genetically related and ADHD may represent a variant expression of the underlying vulnerability genes for TS.[11] Abelson and colleagues (2006) identified a patient affected with TS and ADHD with a *de novo* chromosome 13 inversion, inv(13)(q31.1; q33.1.[12] More recently seven genes associated with TS were examined: DRD2, HRH3, MAOB, BDNF, SNAP25, SLC6A4, and SLC22A3 and it has been suggested that these genes have also been implicated in other disorders such as Attention Deficit Hyperactivity Disorder (ADHD), and Obsessive-Compulsive Disorder.[13]

Data on brain structure and neurochemistry are consistent with the notion that the two conditions may share similarities and differences. Hypofunction of catecholaminergic circuits, particularly those that project to the prefrontal cortex appear to be core features of ADHD,[14] whereas reduced volumes of the caudate nucleus, together with activation and hypertrophy of prefrontal regions seem to be core features of TS.[15,16] A significant loss of the normal globus pallidus asymmetry has been reported both in TS and ADHD patients.[17] Moreover, abnormal level of dopamine and glutamate have been reported in both conditions.[18] In details overactive dopamine transporter and alteration in phasic dopamine release could be responsible of tic and comorbid ADHD.[19]

The co-occurrence of TS and ADHD is in most cases associated with a higher psychopathological, social and academic impairment resulting from the negative impact of ADHD.[8,20] This co-occurrence causes clinical impairment, and the

ARTICLE IN PRESS
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2013) 1–8

treatment of tics and coexisting ADHD should be prioritized according to the impairment caused by each problem in order to treat the target symptoms.

The management of comorbid TS and ADHD may represent a challenge for the clinicians.

The present review will discuss clinical efficacy and safety parameters of pharmacological options treatment for tic disorders and comorbid ADHD in order to provide clinicians with an evidence-based rationale for the pharmacological treatment.

1.1. Search strategy

The information in this review is mainly based on peer review and original medical publications (PUBMED 1990 to June 2012). We included randomized, double-blind, controlled trials, open label related to pharmacological treatment for tic and TS used in children and adolescents with comorbid ADHD. The search term "Tourette Syndrome" or "Tic" and "ADHD", were cross referenced with the words "pharmacological treatment", and subsequently with "α-agonist", "psychostimulants", "selective norepinephrine reuptake inhibitor".

Selection criteria utilized included the statistical power of the studies defined as the probability of detecting a difference when it exists, and the relevance for the clinician. According to Bhardwaj et al.[21] a study that claims clinical relevance, defined as an intervention that has an effect of practical meaning, may lack sufficient statistical significance to make a meaningful statement. Statistical significance is defined as an interpretation of statistical data that indicates that an occurrence was probably the result of a causative factor and not simply a chance result. We have included studies with both clinical and statistical significance.

2. Therapeutic interventions

A comprehensive treatment program for TS and comorbid ADHD should include measures other than medicines such as cognitive-behavioral, psycho educational and psychosocial interventions.

In mild cases, psycho-education and reassurance for the patient and the family may be sufficient. Behavioural treatments such as Comprehensive Behavioural Intervention for Tics including Habit Reversal Training have been shown to be significantly better than other behavioural/psychological treatments and placebo.[22]

Psychological interventions, educational change, medication should be guided by a treatment plan drawn up for the individual including parental, child and child's school. Psychoeducation has the aim to improve the tolerance for symptoms and to support stress reduction.[23]

Children and adolescents with mild symptoms do not require drug treatment if their tics do not interfere with daily life or recreational activities.[24] Pharmacotherapy is not indicated for all children with TS and comorbid ADHD, and the decision to use any of the drug or combination of treatments must be based on a through assessment of the severity and impact of the child's symptoms.

2.1. Pharmacological treatment options

Currently, three classes of drugs are used in the treatment of TS and comorbid ADHD: alpha-agonists (clonidine [CLON] and guanfacine), stimulants (amphetamine enantiomers, methylphenidate [MPH] enantiomers or slow release preparation); selective norepinephrine reuptake inhibitor (atomoxetine). Recently a partial dopamine agonists (aripiprazole) resulted as an effective treatment for TS, in patients with mild ADHD symptoms. More studies in this field are needed.

Pharmacological treatment options for TS and comorbid ADHD are summarized in Table 1.

2.1.1. α 2-adrenoceptor agonists:

α-2 adrenergic receptor agonist activates presynaptic autoreceptors in the locus ceruleus, and reduces norepinephrine release and turnover. Recently it has been reported good efficacy in patients affected by tic and co-occurring ADHD.[25]

2.1.1.1. *Clonidine.* Clonidine has been used for nearly three decades in the treatment of TS, there are few controlled studies evaluating its effects on ADHD symptoms.[26] According to the American Academy of Neurology clonidine presented level A of evidence as effective treatment in children with TS and comorbid ADHD.[27,28] A randomized controlled study on 41 patients (age range 7–48 years) analyzed the safety and effectiveness of clonidine hydrochloride (3–5 μg/kg per day). Twenty-four subjects were randomly assigned to clonidine treatment and 23 to placebo. Forty subjects (21 given clonidine and 19 placebo) successfully completed the 12-week, double-blind clinical trial. Clinical ratings of tic severity improved for both groups. The magnitude of response was greater in the group receiving clonidine. Clinician-rated measures of motor tic severity, the degree to which the tics are "noticeable to others," motor tic counts from videotaped interviews, and parent-rated measures of impulsivity and hyperactivity were the most responsive to clonidine treatment. Adverse effects such as sedation, fatigue, faintness and/or dizziness, irritability were reported. They concluded that clonidine is more effective than placebo in patients with TS and ADHD; but due to the wide range of age this study compare non homogeneous patients causing lack of significance of the results.[27]

In a randomized controlled study comparing clonidine, MPH and placebo, clonidine appeared to be most helpful for impulsivity and hyperactivity; MPH for inattention. The authors conducted a multicenter, randomized, double-blind clinical trial in which 136 children with ADHD and a chronic tic disorder were randomly administered CLON alone, MPH alone, combined CLON + MPH, or placebo (2 × 2 factorial design). Each subject participated for 16 weeks (weeks 1–4 CLON/placebo dose titration, weeks 5–8 added MPH/placebo dose titration, weeks 9–16 maintenance therapy). The proportion of individuals reporting a worsening of tics as an adverse effect was similar in those treated with clonidine alone, MPH, or placebo. Compared with placebo, measured tic severity lessened in all the actively treated groups in the following order: clonidine + MPH, clonidine alone, MPH alone (Tourette Syndrome study group 2002).[19] The efficacy of clonidine increase if associated with methylphenidate.

Table 1 – Pharmacological treatment options for TS and comorbid ADHD.

Drug	Author (year)	N° of patients	Study duration	Study class	Age range (years)	Efficacy		Adverse effects
						TS	ADHD	
Clonidine	Leckman (1991)	41	12 weeks	I	7–48	+	+	Sedation and fatigue, faintness and/or dizziness, irritability.
Clonidine	Singer (1995)	37	6 weeks	II	7–13	–	–	Sedation
Clonidine/ Methylphenidate	Tourette's Syndrome Study Group. (2002)	136	16 weeks	I	7–14	+	+	Moderate to severe sedation
Guanfacine	Schaill (2001)	34	8 weeks	I	10.4 (mean age)	+	+/–	Transient sedation, insignificant decreases in blood pressure and pulse
Methylphenidate/ Dextroamphetamine	Castellanos (1997)	20	9 weeks	I	9.4 (mean age)	+/–	+	Loss of appetite, transient loss of weight and insomnia, increase of obsessive compulsive symptoms. At high dose vomiting.
Methylphenidate	Gadow (2007)	71	15 years	I	6–12	+/–	+	Sleep and appetite problems, headache, upset dizziness, modification of heart rate and diastolic blood pressure, weight loss
Atomoxetine	Spencer (2008)	117	18 weeks	II	7–17	+	+	Significant increases in mean pulse rate, nausea, decreased appetite, and decreased body weight.

TS: Tourette Syndrome.
ADHD: Attention Deficit Hyperactivity Disorder.
+: Strong evidence on efficacy.
–: No evidence on efficacy.
+/–: Little evidence of efficacy.
Study class according to AAN.

Sedation is commonly reported with clonidine treatment (28% reported moderate or severe sedation) there is no evidence of other adverse effects including cardiac toxicity.[28] As opposite Singer (2005)[29] in a double blind/placebo controlled protocol reported that clonidine did not alter ADHD or tic severity significantly on any measure with the exception of the "nervous/overactive" subscale of the Child Behavior Check List. He studied thirty-seven children with TS and ADHD between the ages 7–13 years. 34 (31 males, 3 females) completed the entire protocol in which each subject served as his or her own control and received, in a randomly assigned fashion, 6-week medication cycles with clonidine (0.05 mg four times daily), desipramine (25 mg four times daily), and placebo. Outcome measures for ADHD included Parent and Teacher Child Behavior Checklists (CBCL), continuous performance tests, and neuropsychologic tests of executive function. Sedation was reported as adverse effect of clonidine treatment. But these data are limited from the short duration of the study (6 weeks).

2.1.1.2. *Guanfacine.* Guanfacine was reported as an effective drug, type A of evidence, especially in the combined hyperactive/inattentive ADHD subgroups whereas it was less efficacious in the inattentive ADHD subtype.[30] A significant reduction of ADHD and tic symptoms has been reported in children and adolescents treated with guanfacine and only transient sedation as adverse effect.[31] Thirty-four medication-free subjects (31 boys and three girls with a mean age of 10.4 years) with ADHD, combined type, and a tic disorder were enrolled into the study. After 8 weeks of treatment, guanfacine was associated with a mean improvement of 37% in the total score on the teacher-rated ADHD Rating Scale, compared to 8% improvement for placebo. Nine of 17 subjects who received guanfacine were blindly rated on the Clinical Global Improvement scale as either much improved or very much improved, compared with none of 17 subjects who received placebo. The mean score on the parent-rated hyperactivity index improved by 27% in the guanfacine group and 21% in the placebo group, not a significant difference. On the Continuous Performance Test, commission errors decreased by 22% and omission errors by 17% in the guanfacine group, compared with increases of 29% in commission errors and of 31% in omission errors in the placebo group. Tic severity decreased by 31% in the guanfacine group, compared to 0% in the placebo group. One guanfacine subject with sedation withdrew at week 4. Guanfacine was associated with insignificant decreases in blood pressure and pulse.[31] As well as the Singer study on clonidine the main limitation of this double blind/placebo control study is the short duration (8 weeks).

2.1.2. *Stimulants*

2.1.2.1. *MPH.* Stimulants cause dopamine release, and there was a theoretical concern that these drugs could exacerbate tics. Well-designed controlled clinical trials have not indicated a deterioration of tics in persons treated with stimulants[32] nor induction of first tics by stimulant treatment even in children at risk.[33]

In the last decade several studies on short-term double blind (DB)/placebo control treatment of individuals with TS or tic and comorbid ADHD have been published. Strong evidence reported on the efficacy of methylphenidate in ADHD symptoms only little evidence reported on its efficacy on tics.[34,35] Castellanos et al. (1997) in a 9-week, placebo-controlled, DB crossover study compared methylphenidate,

ARTICLE IN PRESS
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2013) 1–8

and dextroamphetamine on tic severity in boys with ADHD and TS. Methylphenidate significantly decreased hyperactivity at all doses, as measured by day program teachers. Although there was no significant interaction between drug and dose indicating that additional improvements in hyperactivity were not observed for higher doses. Higher doses of methylphenidate (45 mg bis in die [b.i.d].) and dexamphetamine (22.5 mg b.i.d.) resulted in a significant reversible increases in tic severity. The AA reported: loss of appetite, transient loss of weight and insomnia, increase of obsessive compulsive symptoms and at high dose vomiting.[34] The main limitations were: the small sample size, moreover for clinical and ethical reasons the drug dosage were not randomized and four subject continued to assume a costant dose of haloperidol. Gadow et al. (2007) conducted a DB long-term observation study (1989–2004) to examine the safety and efficacy of immediate-release methylphenidate (MPH-IR) for the treatment of ADHD in 71 children (ages 6–12 years) with TS (96%) or chronic motor tic disorder (4%). The study sample included two cohorts of children; the initial group was recruited primarily to assess short-term immediate-release methylphenidate effects ($n = 39$ cohort 1 [Gadow et al., 1995])[36] which was followed by a naturalistic observation study through age (Gadow et al., 1999).[37] During the follow-up study, a second sample was recruited ($n = 32$, cohort 2). The two cohorts received placebo and three doses of methylphenidate (0.1, 0.3, and 0.5 mg/kg) twice daily for 2 weeks each. Treatment effects were assessed with an extensive battery of parent-, teacher-, child-, and physician-completed rating scales and laboratory tasks. MPH-IR effectively suppressed ADHD, oppositional defiant disorder, and peer aggression behaviors. There was no evidence that MPH-IR altered the overall severity of tic disorder or obsessive-compulsive disorder behaviors. Teacher ratings indicated the decrease of tic frequency and severity. In conclusion it appears to be a safe and effective short-term treatment for ADHD in the majority of children with chronic tic disorder. Sleep and appetite problems, headache, upset dizziness, modification of heart rate and diastolic blood pressure and weight loss were reported.[35]

Little evidence exists of the specific advantages or disadvantages of short-acting versus long-acting treatments in individuals with TS and comorbid ADHD. In general the extended release methylphenidate (MPH-ER) and MPH-IR have comparable treatment effects on measures of hyperactivity and inattention and normalized participant performance to control levels. In contrast, MPH-IR seems to have an advantage over MPH-ER in impulsivity treatments. These data suggest that it is crucial to assess the different domains of ADHD symptoms precisely over the course of a day to determine the optimal titration and stimulant formulation for a person with ADHD.[38]

With regards to TS and comorbid ADHD a recent open label study suggested that there is a clear tic-reduction effect, and not exacerbation, with a one-time dose of MPH compared to no medication in these children moreover youths with TS and ADHD appear to be able to suppress their tics with a behavioral reward comparable to youths with TS without ADHD.[39] The main limitations of this study are: the study design (open label) and the small sample size. Future research is needed to replicate those results with placebo control conditions and a substantially larger sample before drawing firm conclusions.

Short acting preparation should be used in the first instance and subsequently once-a day formulations regards to long acting treatment.

2.1.2.2. *Amphetamine*. Moreover even if dextroamphetamine has the same efficacy it is less tolerated than methylphenidate.[34]

Patients treated with stimulants frequently reported: sleep and appetite problems, headache, upset dizziness, modification of heart rate and diastolic blood pressure and loss of weight.[35]

2.1.3. *Selective norepinephrine reuptake inhibitor*

2.1.3.1. *Atomoxetine*. Atomoxetine is a non-stimulant drug used to treat ADHD[40] and acts as a presynaptic blocker of noradrenalin reuptake.[41] Level B of evidence is reported in patients affected by tic or TS and comorbid ADHD treated with atomoxetine.

A post hoc subgroup analysis (double blind/placebo control) focusing specifically on those patients with TS and comorbid ADHD [Spencer 2008 (placebo ($n = 56$) or atomoxetine (0.5–1.5 mg/kg/day, $n = 61$] showed that atomoxetine was effective in treating either the tic symptoms or ADHD in these patients. Significant increases in mean pulse rate, nausea, decreased appetite, and decreased body weight were reported.[42]

The very prominent role of the manufacturer (e.g. authorship) should be mentioned.

2.1.4. *Partial dopamine agonists*

Partial dopamine agonist acts as an antagonist of dopamine D2 receptors in hyperdopaminergic conditions and displays agonist properties under hypodopaminergic conditions.

Level C of evidence supported the use of aripiprazole in tic or TS and comorbid ADHD. A recent open label preliminary study, aripiprazole resulted an effective treatment for TS, but had moderate effects on co-occurring ADHD. The AA described the use of aripiprazole (10.0 ± 4.8 mg/day) in a consecutive group of 28 patients (mean age 12.1 ± 2.3 years, 26 males and 2 females) with a primary diagnosis of TS and comorbid ADHD, combined subtype.[43] Those interesting findings are limited because of the short duration of the study, the study design (open label not randomized).

3. Clinical recommendations

Any treatment plan for TS and comorbid ADHD must be based on a comprehensive diagnostic evaluation. Behavioural treatment should be recommended as an initial treatment option for patients with TS or tic and comorbid ADHD, especially if the symptoms are mild. Strong evidence report on the efficacy of habit reversal training compared to placebo or other psychological treatment.[22]

If pharmacotherapy is chosen for children with TS and comorbid ADHD, a number of effective treatment options are available, such as methylphenidate, alpha-2 agonists,

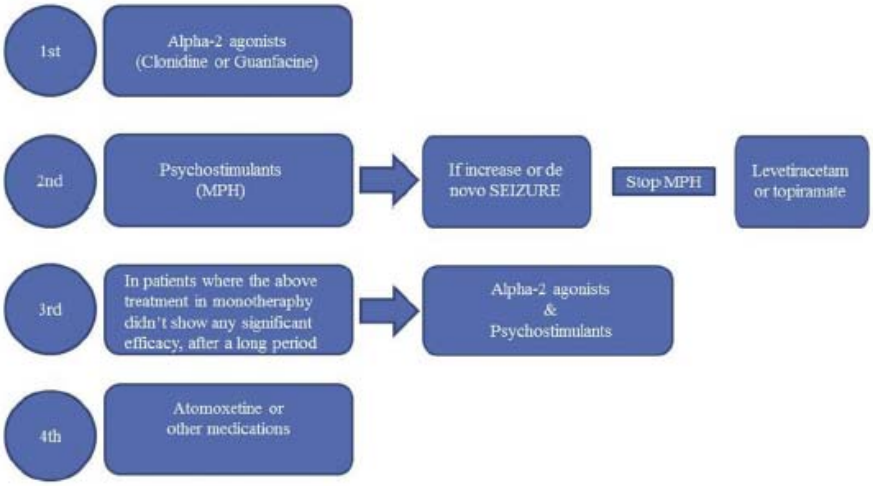


Fig. 1 – Therapeutic algorithm.

atomoxetine, and partial dopamine agonists choosing the correct first treatment is a major challenge for clinicians.[44]

It could be useful for the clinician, before starting any pharmacological treatment, to consider the most favorable efficacy versus adverse events ratio, to collect a detailed personal and family history and other risk factors for cardiac disease are likely to mediate risks such as obesity.

Moreover, pre-treatment checking and monitoring of pulse, blood pressure and ECG are recommended in all children with tics or TS and comorbid ADHD treated.[45,46] Detailed psychiatric history with special attention to emotional, behavioral changes is needed before prescription of any medication and during treatment families and caregivers should be given advice on the need to communicate to the doctor any observed change.[45]

Taking into account all the above parameters we propose the following therapeutic algorithm (Fig. 1).

Level A of evidence supported the efficacy and the safety of alpha-2 agonists that significantly improve both ADHD and tic symptoms, suggesting that these drugs (clonidine or guanfacine) can be considered as first choice treatment for tic, TS and ADHD.[47]

Stimulants should be the second choice of drugs given the quicker onset of action of any of these agents and may be particularly beneficial in children necessitating immediate improvement. Stimulants have level A of evidence on efficacy with regards to ADHD symptoms and little evidences of efficacy on tics. It is critical to document the type and severity of tics before starting treatment in order to establish a baseline against which to assess treatment associated changes. Clinicians should begin with a low dose of medication and titrate upwards. In addition, a short acting preparation should be used in the first instance and subsequently once-a day formulations, as there may be individual cases in which stimulants appear to exacerbate tics. In cases in which short-term dose reversal clearly indicates tic exacerbation, switching to another stimulant or a new drug class may be useful. However, because tics are naturally waxing and waning the "*cause and effect*" interpretation of drug effects and clinical implications could be difficult. A long-term observation of at least 3 months is sometimes required before a clinical decision can be made. It is medically appropriate to provide treatment with psychostimulants medication in patients with tics where the ADHD symptoms are significantly disturbing their quality of life.[48]

In patients with seizures, the frequency of seizures should be carefully monitored; if their seizures increases, or seizures develop *de novo*, the MPH should be discontinued. The relationship between TS, ADHD and epilepsy is not fully understood, an increased dopamine- and glutamate-mediated excitatory activity could explain the occurrence of the symptoms. Patients with a triple comorbidity could benefit from a treatment with an anti-epileptic drug, such as topiramate or levetiracetam.[49]

Extended release MPH allows clinician to optimize symptom control over the course of the day for an individual patient. Different patients appear to respond in different ways to extended release formulations. Comorbidity of TS and ADHD may reflect a common neurobiological substrate. Both TS and ADHD present dysfunction of the γ-aminobutyric acidergic system; positron emission tomography studies showed the decreased binding of GABA(A) receptors bilaterally in the ventral striatum, globus pallidus, thalamus, amygdala and right insula. In addition, the GABA(A) receptor binding was increased in the bilateral substantia nigra, left periaqueductal grey, right posterior cingulate cortex and bilateral cerebellum. These results are consistent with the longstanding hypothesis that circuits involving the basal ganglia and thalamus are disinhibited in Tourette Syndrome patients. In addition, the abnormalities in GABA(A) receptor binding in the insula and

cerebellum appear particularly noteworthy based upon recent evidence implicating these structures in the generation of tics.[50] Poor inhibitory control and volumetric reductions in fronto-striatal circuits appear to be core features of ADHD, whereas reduced volumes of the caudate nucleus together with activation and hypertrophy of prefrontal regions seem to be core features of TS.[51,52]

The third choice option, with A level of evidence, could be the association between stimulants and alpha-2 agonist (methylphenidate and clonidine in combination) that are far more effective for ADHD in children with comorbid tics than the single medications alone. This option should be considered in patients where the above treatments in monotherapy didn't show any significant efficacy after a long time period of illness.[28] If even a combined treatment brings no improvement of symptoms, a careful review of the diagnosis could be useful. Clinicians should avoid to start two medications simultaneously.[23]

Level B of evidence reported that atomoxetine can be effective in controlling tics and ADHD symptoms. It should be saved as last option because its important side effects and not widely documented experience in the setting of tics and TS.[53]

In consideration of the safe profile and the good efficacy on TS and ADHD symptoms aripiprazole could be considered as a good choice especially in young patients with mild ADHD symptoms, even if only level C of evidence is reported.[44]

In conclusion, treatment should be "symptom target", based on the severity of symptoms, the age of the patient, the duration of the illness and balancing the positive effects with the side effects.

Conflict of interests

None.

REFERENCES

1. Robertson MM, Eapen V, Cavanna AE. The international prevalence, epidemiology, and clinical phenomenology of Tourette syndrome: a cross cultural perspective. *J Psychosom Res* 2009;67:475–83.
2. Freeman RD, Fast DK, Burd L, et al. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. *Dev Med Child Neurol* 2000;42:436–47.
3. Freeman RD, Tourette Syndrome International Database Consortium. Tic disorders and ADHD: answers from a world-wide clinical dataset on Tourette syndrome. *Eur Child Adolesc Psychiatry* 2007;16:15–23.
4. Swanson J, Lerner M, March J, Gresham FM. Assessment and intervention for attention-deficit/hyperactivity disorder in the schools. Lessons from the MTA study. *Pediatr Clin North Am* 1999;46:993–1009.
5. Steinhausen HC, Nøvik TS, Baldursson G, et al. Co-existing psychiatric problems in ADHD in the ADORE cohort. *Eur Child Adolesc Psychiatry* 2006;1:I25–9.
6. Roessner V, Becker A, Banaschewski T, Rothenberger A. Executive functions in children with chronic tic disorders with/without ADHD—new insights. *Eur Child Adolesc Psychiatry* 2007;16(Suppl. 1):I/36–44.
7. Eddy CM, Cavanna AE, Gulisano M, et al. Clinical correlates of quality of life in Tourette syndrome. *Mov Disord* 2011;26:735–8.
8. Rizzo R, Curatolo P, Gulisano M, et al. Disentangling the effects of Tourette syndrome and attention deficit hyperactivity disorder on cognitive and behavioral phenotypes. *Brain Dev* 2007;29:413–20.
9. Banaschewski T, Neale BM, Rothenberger A, Roessner V. Comorbidity of tic disorders & ADHD: conceptual and methodological considerations. *Eur Child Adolesc Psychiatry* 2007;16(Suppl. 1):5–14.
10. Mathews CA, Grados MA. Familiality of Tourette syndrome, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder: heritability analysis in a large sib-pair sample. *J Am Acad Child Adolesc Psychiatry* 2011;50:46–54.
11. Pauls DL, Leckman JF, Cohen DJ. Familial relationship between Gilles de la Tourette's syndrome, attention deficit disorder, learning disabilities, speech disorders, and stuttering. *J Am Acad Child Adolesc Psychiatry* 1993;32:1044–50.
12. Abelson JF, Kwan KY, O'Roak BJ, et al. Sequence variants in SLITRK1 are associated with Tourette's syndrome. *Science* 2005;310:317–20.
13. Gunther J, Tian Y, Stamova B, et al. Catecholamine-related gene expression in blood correlates with tic severity in Tourette syndrome. *Psychiatry Res* 2012;30:593–601.
14. Cortese S. The neurobiology and genetics of Attention-Deficit/Hyperactivity Disorder (ADHD): what every clinician should know. *Eur J Paediatr Neurol* 2012;16:422–33.
15. Curatolo P, Paloscia C, D'Agati E, Moavero R, Pasini A. The neurobiology of attention deficit/hyperactivity disorder. *Eur J Paediatr Neurol* 2009;13:299–304.
16. Denckla MB. Attention-deficit hyperactivity disorder (ADHD) comorbidity: a case for "pure" Tourette syndrome? *J Child Neurol* 2006;21:701–3.
17. Kano Y, Ohta M, Nagai Y, Scahill L. Association between Tourette syndrome and comorbidities in Japan. *Brain Dev* 2010;32:201–7.
18. Hamilton LS, Levitt JG, O'Neill J, et al. Reduced white matter integrity in attention deficit hyperactivity disorder. *Neuroreport* 2008;19:1705–8.
19. Wong DF, Brasić JR, Singer HS, et al. Mechanisms of dopaminergic and serotonergic neurotransmission in Tourette syndrome: clues from an in vivo neurochemistry study with PET. *Neuropsychopharmacol* 2008;33:1239–51.
20. Gorman DA, Thompson N, Plessen KJ, et al. Psychosocial outcome and psychiatric comorbidity in older adolescents with Tourette syndrome: controlled study. *Br J Psychiatry* 2010;197:36–44.
21. Bhardwaj SS, Camacho F, Derrow A, Fleischer Jr AB, Feldman SR. Statistical significance and clinical relevance the importance of power in clinical trials in dermatology. *Arch Dermatol* 2004;140:1520–3.
22. Robertson MM. The Gilles de La tourette syndrome: the current status. *Arch Dis Child Educ Pract Ed* 2012 Oct;97(5):166–75.
23. Roessner V, Plessen KJ, Rothenberger A, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. *Eur Child Adolesc Psychiatry* 2011;20:173–96.
24. Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 2: tentative explanations for differing prevalence figures in GTS, including the possible effects of psychopathology, aetiology, cultural differences, and differing phenotypes. *J Psychosom Res* 2008;65:473–86.
25. Weisman H, Qureshi IA, Leckman JF, Scahill L, Bloch MH. Systematicreview: pharmacological treatment of ticdisorders – efficacy of antipsychotic and alpha-2adrenergicagonistagents. *Neurosci Biobehav Rev* 2012; 23 Oct;(12):00161–3. S0149-7634.

26. Robertson MM. Tourette syndrome, associated conditions and the complexities of treatment. *Brain* 2000;123:425–62.
27. Leckman JF, Hardin MT, Riddle MA, et al. Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1991;48:324–8.
28. Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology* 2002;58:527–36.
29. Singer HS, Brown J, Quaskey S, et al. The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. *Pediatrics* 1995;95:74–81.
30. Heal DJ, Smith SL, Findling RL. ADHD: current and future therapeutics. *Curr Top Behav Neurosci* 2012;9:361–90.
31. Scahill L, Chappell PB, Kim YS, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry* 2001;158:1067–74.
32. Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF. Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. *J Am Acad Child Adolesc Psychiatry* 2009;48:884–93.
33. Roessner V, Robatzek M, Knapp G, Banaschewski T, Rothenberger A. First-onset tics in patients with attention-deficit-hyperactivity disorder: impact of stimulants. *Dev Med Child Neurol* 2006;48:616–21.
34. Castellanos FX, Giedd JN, Elia J, et al. Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: effects of stimulant and dose. *J Am Acad Child Adolesc Psychiatry* 1997;36:589–96.
35. Gadow KD, Sverd J, Nolan EE, Sprafkin J, Schneider J. Immediate-release methylphenidate for ADHD in children with comorbid chronic multiple tic disorder. *J Am Acad Child Adolesc Psychiatry* 2007;46:840–8.
36. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Ezor SN. Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder. *Arch Gen Psychiatry* 1995;52:444–55.
37. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Grossman S. Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Arch Gen Psychiatry* 1999;56:330–6.
38. Günther T, Kahraman-Lanzerath B, Knospe EL, Herpertz-Dahlmann B, Konrad K. Modulation of attention-deficit/hyperactivity disorder symptoms by short- and long-actingmethylphenidate over the course of a day. *J Child Adolesc Psychopharmacol* 2012;22:131–8.
39. Lyon GJ, Samar SM, Conelea C, et al. Testing tic suppression: comparing the effects of dexmethylphenidate to No medication in children and adolescents with attention-deficit/hyperactivity disorder and Tourette's disorder. *J Child Adolesc Psychopharmacol* 2010;20:283–9.
40. Perwien AR, Kratochvil CJ, Faries DE, et al. Atomoxetine treatment in children and adolescents with attention-deficit hyperactivity disorder: what are the long-term health-related quality-of-lifeoutcomes? *J Child Adolesc Psychopharmacol* 2006;16:713–24.
41. Swanson CJ, Perry KW, Koch-Krueger S, et al. Effect of the attention deficit/hyperactivity disorder drug atomoxetine onextracellular concentrations of norepinephrine and dopamine in several brainregions of the rat. *Neuropharmacology* 2006;50:755–60.
42. Allen AJ, Kurlan RM, Gilbert DL, et al. Atomoxetine treatment in children and adolescents with ADHD and comorbidtic disorders. *Neurology* 2005;65:1941–9.
43. Spencer TJ, Sallee FR, Gilbert DL, et al. Atomoxetine treatment of ADHD in children with comorbid Tourette syndrome. *J Atten Disord* 2008;11:470–81.
44. Masi G, Gagliano A, Siracusano R, et al. Aripiprazole in children with Tourette's disorder and co-morbid attention-deficit/hyperactivity disorder: a 12-week, open-label, preliminary study. *JChild Adolesc Psychopharmacol* 2012;22:120–5.
45. Pringsheim T, Steeves T. Pharmacological treatment for Attention Deficit Hyperactivity Disorder (ADHD) in children with comorbid tic disorders. *Cochrane Database Syst Rev* 2011;13(4):CD007990.
46. Graham J, Banaschewski T, Buitelaar J, et al. European guidelines on managing adverse effects of medication for ADHD. *Eur Child Adolesc Psychiatry* 2011;20:17–37.
47. Gulisano M, Cali PV, Cavanna AE, et al. Cardiovascular safety of aripiprazole and pimozide in young patients with Tourette syndrome. *Neurol Sci* 2011;32:1213–7.
48. Du JC, Chiu TF, Lee KM, et al. Tourette syndrome in children: an updated review. *Pediatr Neonatol* 2010;51:255–64.
49. Erenberg G. The relationship between Tourette syndrome, attention deficit hyperactivity disorder, and stimulant medication: a critical review. *Semin Pediatr Neurol* 2005;12:217–21.
50. Rizzo R, Gulisano M, Cali PV, Curatolo P. ADHD and epilepsy in children with Tourette syndrome: a triple comorbidity? *Acta Paediatr* 2010;99:1894–6.
51. Lerner A, Bagic A, Simmons JM, et al. Widespread abnormality of the γ-aminobutyric acid-ergic system in Tourette syndrome. *Brain* 2012;135:1926–36.
52. Neuner I, Kupriyanova Y, Stöcker T, et al. White-matter abnormalities in Tourettesyndromeextendbeyondmotorpathways. *Neuroimage* 2010;51:1184–93.
53. Robertson MM. Attention deficit hyperactivity disorder, tics and Tourette's syndrome: the relationship and treatment implications. A commentary. *EurChild Adolesc Psychiatry* 2006;15:1–11.

ARTICLE IN PRESS

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2013) 1–8

ELSEVIER

Official Journal of the European Paediatric Neurology Society

Original article

Neurocognitive effects of methylphenidate on ADHD children with different DAT genotypes: A longitudinal open label trial

A. Pasini[a,*], L. Sinibaldi[b], C. Paloscia[a,f], S. Douzgou[c], M.B. Pitzianti[a], E. Romeo[d], P. Curatolo[a], A. Pizzuti[e]

[a] Division of Child Neuropsychiatry, Department of Neuroscience, University of Rome "Tor Vergata", Via Alberico 2 n.35, 00193 Rome, Italy
[b] Mendel Laboratory, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy
[c] Department of Genetics, Institute of Child Health, "Aghia Sophia" Children's Hospital, Athens, Greece
[d] Physiology Institute, Department of Neuroscience, University of Rome "Tor Vergata", Italy
[e] Department of Experimental Medicine and Pathology, University of Rome "La Sapienza", Italy
[f] Association for Therapy and Research in Developmental Age and Adults (Clinical Center ASTREA), Italy

ARTICLE INFO

Article history:
Received 21 May 2012
Received in revised form
10 November 2012
Accepted 19 February 2013

Keywords:
ADHD
Executive functions
Working memory
Methylphenidate
Dopamine transporter

ABSTRACT

The variable number of tandem repeat polymorphism in the 3'-untranslated region of the dopamine transporter gene (DAT) may influence the variability of the therapeutic response to methylphenidate (MPH) in Attention Deficit/Hyperactivity Disorder (ADHD). For this reason we evaluated the neuropsychological functioning after a prolonged period of MPH treatment and after a specific time from MPH suspension. Relationship between DAT VNTR genotypes and neurocognitive response to MPH was analyzed in a sample of 108 drug-naive ADHD patients. The performance of children with ADHD on measures of working memory, inhibition and planning was assessed at 4, 8 and 24 weeks and at 8 weeks after MPH withdrawal. Patients with 9/9 genotype evidenced an improvement in response inhibition and working memory only at 4 weeks of treatment, in planning at 24 weeks of therapy and after 8 weeks of MPH suspension. Patients with 9/10 showed an improvement in response inhibition at 4, 8 and 24 weeks of treatment, in planning at 24 weeks and after 8 weeks of MPH suspension. Patients with 10/10 evidenced an improvement in response inhibition and working memory at 4, 8 and 24 weeks of treatment and in planning at 4, 8 and 24 weeks of treatment and after 8 weeks of suspension. These results indicate that the 9/9 ADHD genotype has a different response at 24 weeks treatment with MPH. 10/10 DAT allele seems to be associated with an increased expression level of the dopamine transporter and seems to mediate the MPH treatment response in ADHD patients.

1. Introduction

The Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common, chronic, neuropsychiatric disorders in childhood and adolescence. The estimated prevalence in school-aged children is about 5%.[1] ADHD is characterized by in attention, hyperactivity, impulsive behavior and deficits in executive functions, including working memory, inhibitory

* Corresponding author. Tel.: +39 3356762428; fax: +39 0641400343.
E-mail address: pasini@uniroma2.it (A. Pasini).

1090-3798/$ – see front matter © 2013 European Paediatric Neurology Society. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejpn.2013.02.002

control, cognitive flexibility, verbal fluidity and planning ability.

Stimulant medication is still the main pharmacotherapy for ADHD, and methylphenidate (MPH) is the most commonly prescribed and studied drug.[2,3,4] Several studies have demonstrated the efficacy of MPH on the clinical symptoms of ADHD and on executive function deficits.[5,6,7,8,9] Using fMRI and the Multi-Source Interference Task, the activation and normalization of the cingulo-prefrontal-parietal neural network of ADHD drug-naive patients after 6 weeks of MPH administration were demonstrated[10] and a 12-week, placebo-controlled, double-blind, randomized, crossover trial found that MPH predominantly improves performance on recognition memory component tasks with modest executive demands.[11]

Nevertheless, the mechanisms that link the pharmacological actions of MPH to core neuropsychological processes over a long period of time are still unclear. Studies of chronic MPH administration allowed to explore the relationships among neuropsychological performance, response to medication and clinical status. To date, no studies have measured neuropsychological functioning after a specific period of MPH treatment withdrawal. Discontinuation of MPH treatment is common in the clinical practice of some countries (*AACAP Work Group on Quality Issues 2007; NICE 2006*). Suspension of the MPH prescription usually coincides with the schools closing for summer vacation. Moreover, some government drug-control agencies recently recommended to carry out studies on MPH treatment suspension.[12] Dopamine transporter gene (*SLC6A3 or DAT*) seems to play a crucial role in the susceptibility to ADHD as well as in treatment response variability to MPH in ADHD.[13,14,15] *DAT* encodes a protein controlling the dopamine (DA) concentration at synapse level through its reuptake. In particular, data from animal models, genetic studies and human neuroimaging studies suggest altered availability or function of *DAT* in ADHD.[16] Recent studies have shown a positive correlation between *DAT* availability in striatum and inattention in ADHD subjects and in healthy controls.[17] The positive association between *DAT* and inattention could reflect a lower and shorter DA signaling in subjects presenting a higher *DAT* concentration. The relationship between *DAT* availability in patients with ADHD and *DAT* gene variants is yet not completely clear. A variable number of tandem repeats (VNTR) in the *SLC6A3* 3′-untranslated region (3′UTR) is the most investigated polymorphism and it has been associated to differential gene expression. *DAT* 3′UTR VNTR has been associated with ADHD and other psychiatric disorders.[18,19,20,21,22] It presents two most common alleles: a 9-repeat (9R) and 10-repeat (10R) of a 40-base-pair (bp) sequence. In vitro studies suggested a significant effect of the VNTR on gene expression, but conflicting results exist regarding the effects of the 9R and 10R alleles.[23,24] Recent evidence showed higher striatal *DAT* concentration in subjects homozygous for the 10 allele,[25,26] but these data were not replicated in other studies.[27,28] Early results seem to indicate that non-responders to methylphenidate among ADHD patients have a low primary striatal *DAT* availability, whereas patients with better response to the drug show higher *DAT* concentration.

Finally, several lines of evidence suggest that *DAT* could be considered a predictor of MPH therapeutic response to. It has been shown that methylphenidate lowers *DAT* striatal availability very effectively in control subjects and in ADHD patients.[29] Different studies identified a better response to MPH in subjects with 10/10 and/or 9/10 genotypes compared to 9/9.[26,30] A meta-analysis showed a significant association between the 10R–10R genotype and low rates of MPH response, but the effect resulted to be small and still inconsistent.[31]

The aims of the present prospective study were: 1) to evaluate the effect of MPH on particular neurocognitive functions (working memory, inhibition and planning) after 4 and 8 weeks of treatment, after 24 weeks of treatment and 8 weeks after MPH withdrawal; 2) to determine whether there is a relationship between *DAT* 3′UTR VNTR genotypes and neurocognitive response to MPH.

2. Material and methods

2.1. Subjects

108 male, drug-naive patients admitted consecutively to the Child Neuropsychiatry Division of "Tor Vergata" Hospital and to an outpatients facility for child psychiatric patients were included in the present study. Participants were between 7 and 15 years of age ($M = 9.88$; $SD = 1.99$) and had a diagnosis ADHD according to DSM-IV-TR.

Inclusion criteria were: 1) male gender and DSM-IV-TR diagnosis of ADHD, combined type, confirmed by K-SADS-PL[32]; 2) no history of mental retardation, brain trauma or neurological diseases; 3) no physical impairment that prevented execution of the neuropsychological battery; 4) no comorbidities except for oppositive defiant disorder (ODD); 5) no previous exposure to other psychostimulants or psychopharmacological treatment; 6) agreement to participate in the study, with provision of informed consent from the parents, prior to inclusion.

Exclusion criteria were the following: 1) past or current history of tic symptoms, obsessive-compulsive disorders or other childhood mental disorders; 2) past or current neurological diseases; 3) co-morbidity of autistic spectrum disorders, language or learning disabilities; 4) refusal to participate in the study.

The sample of 108 subjects received all the same multimodal treatment according to Italian Guidelines on ADHD[33]: MPH, parent training and cognitive behavior therapy (CBT). Patients were divided into groups based on the *DAT* 3′UTR VNTR genotypes and compared with respect to the MPH treatment response.

2.2. Clinical assessment

2.2.1. Kiddies schedule for affective disorders and schizophrenia-present and lifetime version (K-SADS-PL)

K-SADS-PL was the clinical instrument to diagnose ADHD and to exclude other comorbid disorders. It is a semi-structured interview designed to evaluate the present and lifetime status of the 32 different psychiatric disorders included in the DSM-IV using objective diagnostic criteria.[32] K-SADS was administered to parents and children by a trained child psychiatrist.

ARTICLE IN PRESS
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2013) 1–8

2.2.2. ADHD rating scale-IV (ARS)

ARS is an 18-item scale used to assess ADHD severity according to the DSM-IV criteria. The scale includes 9 items regarding symptoms related to inattention and 9 items regarding symptoms related to hyperactivity and impulsivity.

2.2.3. Conners' parent rating scales revised, short version (CPRS-R:S)

CPRS-R:S is a 27-item scale used to evaluate ADHD severity and to monitor effects of treatment.[34] This instrument includes 4 subscales: oppositional, cognitive problems/inattention, hyperactivity and an ADHD index.

2.2.4. Children's Global Assessment Scale (C-GAS)

The Children's Global Assessment Scale (C-GAS)[35] is a reliable measure of overall severity of the disorder. This instrument has been used in order to obtain an independent measure of the children's general functioning at different times during treatment.

2.3. Neuropsychological tools

Executive Functioning (EF) was measured using the following tasks: Tower of London,[36,37] Continuous Performance Test II[38] and a working memory test using an n-Back paradigm (N-BWM).

2.3.1. Tower of London (ToL)

ToL[36,39] measures planning ability. The main dependent variable of this task is the average score, which is based on the number of attempts a child needs to solve the problems in the required number of steps. For each problem, scores range from zero (the problem was not solved after the third attempt) to three (the problem was solved at the first attempt). A second variable is the average decision time on the first attempt for each of the three levels of difficulty (time between presenting the problem and the moment when the child moves the first ball).

2.3.2. Continuous Performance Test II (CPT II)

CPT II[38] is a complex software used to measure attention, impulsivity/inhibition and vigilance. CPTII respondents are required to press the space bar or click the mouse whenever any letter other than the letter 'X' appears on the computer screen. The inter-stimulus intervals (ISIs) are 1, 2 and 4 s with a display time of 250 ms. The unique CPT paradigm is a test structure consisting of 6 blocks and 3 sub-blocks, each containing 20 trials (letter presentations). The presentation order of the different ISIs varies between blocks. The Reaction Time Inter-Stimulus Interval (RT-ISI) is used to assess inhibitory response.

2.3.3. N-Back working memory test

The N-Back Test is a measure of the working memory (WM). We developed a computerized WM test using the N-back paradigm. With this test it is possible to study visual-spatial WM. Subjects have to code the stored visual pattern position with respect to their temporal position and to change the temporal codes as new stimuli are presented.

During the test, subjects are required to monitor a sequence of 20 visual stimuli (locations) presented on a 15-inch computer screen. After an inter-stimulus delay, subjects are required to respond by selecting the stimulus presented *n* steps earlier in the sequence. The response is given by pressing one of three buttons corresponding to the left, center and right areas of the screen. To study visual-spatial WM, we used three different spatial locations (white squares). The squares were highlighted in a continuous sequence on the screen. In each of the 20 consecutive trials, one of the three locations presented was transiently selected by the software (1000 ms), changed from white to black and then back to white again, indicating the next position in the series to be remembered. Following a 3000 ms delay, the three white squares appear on the screen again for 3000 ms and the subject has to respond by pressing the button corresponding to the location highlighted one step back in the sequence (n-1). After 1000 ms, the next trial is presented.

2.4. MPH administration and treatment response

Short-acting MPH was administered at a mean dose of 0.5 mg/kg/day. MPH was taken at 8:30 A.M. and 1:00 P.M. The children were tested four times: before treatment (T0) and 90 min after their morning medication at 4, 8, and 24 weeks of treatment. All subjects performed the clinical and the neuropsychological battery described above. The last evaluation was made after 8 weeks of withdrawal. During the follow-up, nine children dropped out: 4 at 24 weeks and 5 who needed to continue treatment during summer. All parents underwent individual or group parent training specific for ADHD. All children attended a cognitive behavior treatment. During the summer break, treatments were suspended for both parents and children.

Genotyping

Genotyping of the *SLC6A3* (*DAT*) 3'UTR 40-bp VNTR polymorphism was determined using forward 5'-TGTGGTGTAGG GAACGGCCTGAG-3' and reverse 5'-CTTCCTGGAGGTCACGGC TCAAGG-3' primers. DNA fragment amplification by polymerase chain reaction (PCR) was performed as described elsewhere.[40] PCR products were separated by 4% agarose gel electrophoresis, visualized by ultraviolet transillumination and fragment sized by comparison with invitrogen 100 bp DNA ladder. In order to confirm the results obtained with agarose gel electrophoresis, genomic DNA fragments were PCR amplified using fluorescent labeled forward primer, resolved on an ABI Prism 3100 DNA sequencer (Applied Biosystems, Foster City, CA, USA) and analyzed with Genotyper software. Genotype classes were as follows: 54 patients with the 10/10 allele, 34 with the 9/10, and 11 with the 9/9 allele.

2.6. Statistical analysis

Statistical analysis was performed using the Repeated-Measures ANOVA Test. All statistical analyzes were carried out using the Statistical Package for Social Science 11.0 for windows. We compared the MPH treatment responses of the patients subdivided in groups based on the *DAT* VNTR genotype. A baseline comparison of the neurocognitive functions of the three genotype classes was performed using the one

way ANOVA: DAT 9/9 vs DAT 9/10; DAT 9/9 vs DAT 10/10; DAT 9/10 vs DAT 10/10.

3. Results

3.1. Baseline comparisons of neurocognitive performance among three DAT VNTR genotypes

A baseline comparison of the neurocognitive performances of the three DAT VNTR genotypes revealed no differences (see Table 1). In the Figs. 1–3 the trend of performance on neuropsychological tasks is represented as a function of MPH treatment weeks and DAT genotype (see Figs. 1–3).

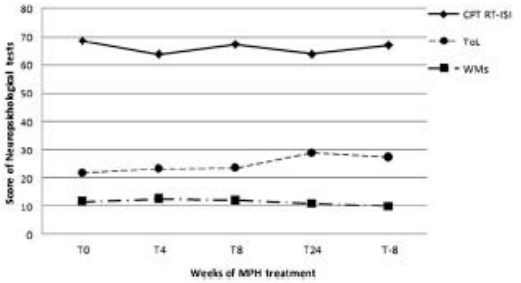


Fig. 1 – Effect of MPH on neuropsychological performance in ADHD patients with DAT 9/9 genotype.

3.2. Response inhibition (CPTII RT-ISI)

MPH produced an improvement of response inhibition at 4 weeks regardless of genotype: there was only an MPH time effect ($F = 28.917$; $p < 0.001$; observed power = 1.000) and not DAT effect, no difference was present among the three different genotype groups ($F = 2.067$; $p = 0.132$; observed power = 0.416) (see Table 2). MPH determined a better response inhibition at 8 ($F = 7.201$; $p = 0.001$; observed power = 0.927) and 24 weeks ($F = 5.892$; $p = 0.004$; observed power = 0.866) in patients with 9/10 and 10/10 genotype in comparison to 9/9 subjects (see Table 3). After 8 weeks of withdrawal all patients worsened. Their scores were similar to those obtained on performances without MPH ($F = 0.473$; $p = 0.625$; observed power = 0.125) and no differences were present among groups ($F = 2.173$; $p = 0.119$; observed power = 0.435). (see Tables 2 and 3).

3.3. Planning (ToL)

MPH produced a better planning performance at 4 ($F = 6.509$; $p = 0.002$; observed power = 0.899) and 8 weeks ($F = 6.384$; $p = 0.002$; observed power = 0.893) in children with 10/10 genotype compared to 9/9 and 9/10 subjects. At 24 weeks, improvement was in all ADHD participants ($F = 165.006$; $p < 0.001$; observed power = 1.000) without significant difference among three DAT genotypes ($F = 1.184$; $p = 0.311$; observed power = 0.254). After withdrawal of MPH, all subjects maintained the improvement ($F = 82.379$; $p < 0.001$; observed power = 1.000), regardless the genotypes ($F = 1.014$; $p = 0.367$; observed power = 0.222) (see Table 4).

3.4. Working memory

MPH produced an improvement of WM at 4 weeks regardless of genotype. There was only a time dependent MPH effect ($F = 26.913$; $p < 0.001$; observed power = 0.999) and not DAT effect ($F = 0.315$; $p = 0.731$; observed power = 0.099). At 8 weeks, only patients with 10/10 showed an improvement in WM evidenced by repeated ANOVA analyzes, using tests of within-subjects contrasts ($F = 28.532$; $p < 0.001$; observed power = 1.000) and test of between subjects effects ($F = 5.232$; $p = 0.007$; observed power = 0.821) (see Table 5). At 24 weeks, 10 allele homozygous children performed better than 9/9 ($p = 0.002$) and 9/10 subjects ($p = 0.002$) with respect to baseline tests ($F = 9.950$; $p < 0.001$; observed power = 0.982). After 8 weeks of withdrawal, children with 9/9 and 9/10 showed results comparable to their previous scores (i.e. those obtained prior to MPH treatment). Among the three DAT genotypes, only the 10 allele homozygotes shown an improvement after the treatment suspension ($F = 5.210$; $p = 0.007$; observed power = 0.819). (see Table 5).

Table 1 – Demographic and baseline data in three DAT polymorphisms and comparison of neurocognitive functions among three DAT genotypes using ANOVA Test.

Age, IQ and neurocognitive tests	DAT 10/10 N° = 54 Means and SD	DAT 9/10 N° = 34 Means and SD	DAT9/9 N° = 11 Means and SD	F and p value of ANOVA Test
Age (years)	9.79 ± 2.17	9.88 ± 1.62	10.36 ± 2.24	F = 0.363; p = 0.696
C-GAS	47.34 ± 8.21	48.28 ± 9.30	48.28 ± 7.26	F = 0.203; p = 0.817
FSIQ	96.64 ± 9.04	96.29 ± 10.65	94.63 ± 7.50	F = 0.120; p = 0.887
VIQ	97.31 ± 8.82	97.23 ± 11.89	95.72 ± 8.79	F = 0.265; p = 0.768
PIQ	94.18 ± 10.85	92.85 ± 9.23	92.27 ± 10.51	F = 2.294; p = 0.106
CPT-RTISI	64.35 ± 8.46	61.46 ± 10.93	68.51 ± 12.70	F = 0.666; p = 0.516
ToL	22.94 ± 4.86	21.94 ± 5.18	21.45 ± 4.80	F = 0.797; p = 0.434
SWM	10.72 ± 3.49	11.70 ± 2.89	11.54 ± 2.16	F = 1.093; p = 0.339

C-GAS: Children's Global Assessment Scale; FSIQ: Full Scale IQ; VIQ: Verbal IQ; PIQ: Performance IQ; CPT-RTISI: Continuous Performance Test Reaction Time Inter-Stimulus Interval; ToL: Tower of London; SWM: Spatial working memory.

ARTICLE IN PRESS
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2013) 1–8

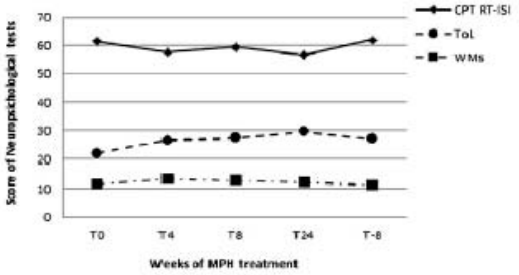


Fig. 2 – Effect of MPH on neuropsychological performance in ADHD patients with DAT 9/10 genotype.

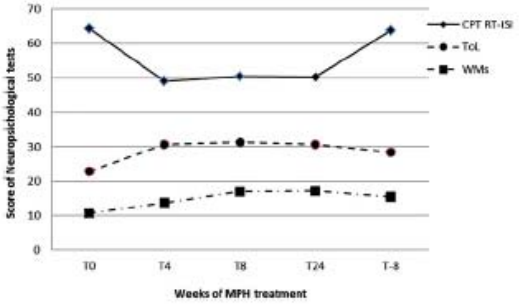


Fig. 3 – Effect of MPH on neuropsychological performance in ADHD patients with DAT 10/10 genotype.

3.5. *Global functioning (C-GAS)*

MPH produced a global improvement in children with 9/9 and 9/10 genotypes after 8 and 24 weeks. Vice versa, subjects with 10/10 showed improvement at 4, 8, and 24 weeks. After 8 weeks of withdrawal, improved global functioning was found in all children regardless of genotype.

4. Discussion

The acute effects of MPH in ADHD patients have been investigated in several studies. Nevertheless, even though ADHD patients are usually treated over a long period of time, only few studies considered the prolonged action of MPH. Our research has several limitations, such as the lack of ADHD female subjects, the small patients sample, and the little number of 9/9 subjects, due to the infrequency of this genotype in the general population. Nevertheless to our knowledge, this is the first study in which the neuropsychological effects of chronically administered MPH were evaluated in stimulant naïve ADHD subjects based on the DAT 3'UTR VNTR genotype. Furthermore, up to now no other investigation measured the neuropsychological effects following an 8-week MPH withdrawal period in ADHD patients. The study design allowed us to analyze the effects of MPH treatment suspension in ADHD patients, similar to what occurs in the clinical practice of some countries in which MPH is discontinued during summer holidays. Our Study has shown a partially restored cognitive functioning and a partially improved clinical status in ADHD children after 4, 8 and 24 weeks of MPH administration. After 4 weeks of MPH treatment, response inhibition and WM improved in ADHD patients, regardless of DAT genotype. Planning ability improved after 4 and 8 weeks of treatment only in DAT 10/10 subjects, while at 24 weeks it improved in all of the three groups. After 8 and 24 weeks of MPH administration, DAT 10/10 subjects have shown a statistically significant improvement in WM, compared with DAT 9/9 and DAT 9/10 subjects. At 8 and 24 weeks the inhibitory response improved in the 9/10 and 10/10 classes compared with the 9/9. After 8 weeks of MPH suspension, the planning ability was better than performance at baseline for all groups while the WM maintained a significant improvement only in 10/10 subjects. At the same time, after 8 weeks of drug suspension, inhibitory response measurements were not different from the baseline registered values for all of the three groups. These results might indicate that the 9/9 and partially 9/10 ADHD genotype has a different neurobiological response to long term treatment with MPH compared to the 10/10 genotype. DAT VNTR is considered to have functional significance since *in vitro* studies showed the 10-repeat allele to be associated with increased expression levels of the transporter[24,41] Recent studies reported that ADHD patients who did not respond to MPH therapy had low primary DAT availability, whereas patients responding well to MPH had high DAT density.[26,27,29,42] It has been postulated that some 10-repeats homozygous subjects might present increased DAT availability, which could explain the better MPH treatment response.[43] The possible association between 9/9 genotype and low availability of DAT might explain

Table 2 – Summary representation of ANOVA repeated measures results at different time of MPH administration: test of within-subjects contrasts and test between-subjects effects.

	T0-T4	T0-T8	T0-T24	T0-T8w
CPT-RTISI	(a) $F = 0.592$; $p = 0.555$	(a) $F = 23.576$; $p < 0.001$	(a) $F = 13.368$; $p < 0.001$	(a) $F = 0.473$; $p = 0.625$
	(b) $F = 2.067$; $p = 0.132$	(b) $F = 7.201$; $p = 0.001$	(b) $F = 5.892$; $p = 0.004$	(b) $F = 2.173$; $p = 0.119$
ToL	(a) $F = 9.543$; $p < 0.001$	(a) $F = 9.987$; $p < 0.001$	(a) $F = 0.012$: $p = 0.988$	(a) $F = 0.089$; $p = 0.915$
	(b) $F = 6.509$; $p = 0.002$	(b) $F = 6.384$; $p = 0.002$	(b) $F = 1.184$; $p = 0.311$	(b) $F = 1.014$; $p = 0.367$
SWM	(a) $F = 2.803$; $p = 0.066$	(a) $F = 28.532$; $p < 0.001$	(a) $F = 33.779$; $p < 0.001$	(a) $F = 25.331$; $p < 0.001$
	(b) $F = 0.315$; $p = 0.731$	(b) $F = 5.232$; $p = 0.007$	(b) $F = 9.950$; $p < 0.001$	(b) $F = 5.210$; $p = 0.007$

CPT-RTISI: Continuous Performance Test Reaction Time Inter-Stimulus Interval; ToL: Tower of London; SWM: Spatial working memory. (a) = Test of within-subjects contrasts and (b) = Test between-subjects effects.

Table 3 – Response inhibition and DAT genotypes. Pairwise comparisons of estimated marginal means using ANOVA repeated measures with adjustment for multiple comparisons (Bonferroni Test).

CPT-RTISI (weeks of MPH)	DAT genotypes	Mean differences	p Value
CPT-RTISI (T0-T4)	10/10 vs 9/10	2.079	p = 0.946
	9/9	−4.506	p = 0.453
	9/10 vs 9/9	−6.585	p = 0.139
CPT-RTISI (T0-T8)	10/10 vs 9/10	−3.061	p = 0.314
	9/9	−10.52	p = 0.001
	9/10 vs 9/9	−7.465	p = 0.040
CPT-RTISI (T0-T24)	10/10 vs 9/10	−1.737	p = 0.954
	9/9	−8.971	p = 0.003
	9/10 vs 9/9	−7.234	p = 0.029
CPT-RTISI (T0-T8w)	10/10 vs 9/10	2.380	p = 0.639
	9/9	−3.797	p = 0.601
	9/10 vs 9/9	−6.077	p = 0.138

CPT-RTISI: Continuous Performance Test Reaction Time Inter-Stimulus Interval.

Table 5 – Working memory and DAT genotypes. Pairwise comparisons of estimated marginal means using ANOVA repeated measures with adjustment for multiple comparisons (Bonferroni Test).

Working memory (weeks of MPH)	DAT genotypes	Mean differences	p Value
WM (T0-T4)	10/10 vs 9/10	−0.453	p = 1.000
	9/9	0.194	p = 1.000
	9/10 vs 9/9	0.647	p = 1.000
WM (T0-T8)	10/10 vs 9/10	1.531	p = 0.027
	9/9	2.107	p = 0.048
	9/10 vs 9/9	0.576	p = 1.000
WM (T0-T24)	10/10 vs 9/10	1.841	p = 0.002
	9/9	2.780	p = 0.002
	9/10 vs 9/9	0.939	p = 0.773
WM (T0-T8w)	10/10 vs 9/10	1.387	p = 0.032
	9/9	2.024	p = 0.041
	9/10 vs 9/9	0.638	p = 1.000

WM: Working memory.

the reduced response to long-term MPH treatment as seen in our set of patients. This hypothesis is supported by the recent evidence that MPH decreased DAT availability in normal subjects and in ADHD patients.[29] We also examined the hypothetical learning effect due to repeated neurocognitive testing. To date there is no scientific evidence of different learning effects depending on DAT genotype (even if the fact that there are no literature data does not exclude such effects per se). The results shown about the 9/9 and 9/10 subsets have to be confirmed in larger group of subjects even if this is complicated by the rare frequency of the 9/9 DAT genotype in the general population.[44,45,46] A critical point of our study was the 8-week observation period following suspension of MPH. During this time, we found the disappearance of improvement in the inhibition deficit in all subjects and the maintaining of improvement (difference from baseline) in planning ability and WM only in 10/10 patients. Recently, it was suggested that the DAT 10 allele might mediate neurocognitive deficits in ADHD.[47] The better neurocognitive response to MPH treatment of 10/10 and 9/10 patients on response inhibition compared to those with the 9/9 genotype seems to support the above-mentioned hypothesis. WM appears to be partially related to different neurobiological mechanisms since it improved after MPH treatment but did not return to pre-treatment levels after MPH suspension. Planning ability improvement does not appear to be related to DAT genotype since it improved in all of the three groups. The inhibitory control deficit, which is likely the most important executive function impaired in ADHD children and adolescents,[48,49,50] could be related to the 10 allele since it has been associated with the MPH influence on DAT density.[51,52] Our study suggests that ADHD response to MPH is influenced by different polymorphisms. Future studies should evaluate, combined effect of more genetic polymorphisms and environmental factors on psycho-stimulants response.

Table 4 – Planning ability and DAT genotypes. Pairwise comparisons of estimated marginal means using ANOVA repeated measures with adjustment for multiple comparisons (Bonferroni Test).

ToL (weeks of MPH)	DAT genotypes	Mean differences	p Value
ToL (T0-T4)	10/10 vs 9/10	2.453	p = 0.034
	9/9	4.442	p = 0.008
	9/10 vs 9/9	1.989	p = 0.568
ToL (T0-T8)	10/10 vs 9/10	2.492	p = 0.041
	9/9	4.639	p = 0.008
	9/10 vs 9/9	2.147	p = 0.524
ToL (T0-T24)	10/10 vs 9/10	1.052	p = 0.684
	9/9	1.605	p = 0.670
	9/10 vs 9/9	0.553	p = 1.000
ToL (T0-T8w)	10/10 vs 9/10	1.187	p = 0.361
	9/9	1.368	p = 1.000
	9/10 vs 9/9	0.180	p = 1.000

ToL: Tower of London.

Author contribution

Dr. Pasini and Dr. Paloscia had primary responsibility for protocol development and writing the manuscripit.

Dr. Pitzianti had responsibility for patient screening and outcome assessment.

Dr. Douzgou, Dr. Sinibaldi and Dr. Pizzuti performed the genetic analysis.

Dr. Romeo and Dr. Curatolo supervised the design and execution of study.

REFERENCES

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* 2007;164:942–8.

2. Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. *J Am Acad Child Adolesc Psychiatry* 1999;38:503–12.
3. Safer DJ, Malever M. Stimulant treatment in Maryland public schools. *Pediatrics* 2000;106:533–9.
4. Swanson J, Baler RD, Volkow ND. Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. *Neuropsychopharmacology* 2011;36:207–26.
5. Berman T, Douglas VI, Barr RG. Effects of methylphenidate on complex cognitive processing in attention-deficit hyperactivity disorder. *J Abnorm Psychol* 1999;108:90–105.
6. Scheres A, Oosterlaan J, Swanson J, Morein-Zamir S, Meiran N, Schut H, et al. The effect of methylphenidate on three forms of response inhibition in boys with AD/HD. *J Abnorm Child Psychol* 2003;31:105–20.
7. Shue KI, Douglas VI. Attention deficit hyperactivity disorder and the frontal lobe syndrome. *Brain Cogn* 1992;20:104–24.
8. Rubia K, Halari R, Cubillo A, Mohammad AM, Brammer M, Taylor E. Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naïve children with ADHD during a rewarded continuous performance task. *Neuropharmacology* 2009;57:640–52.
9. Sonuga-Barke EJ, Coghill D, DeBacker M, Swanson J. Measuring methylphenidate response in attention-deficit/hyperactvity disorder: how are laboratory classroom-based measures related to parent ratings? *J Child Adolesc Psychopharmacol* 2009;19:691–8.
10. Bush G, Spencer TJ, Holmes J, Shin LM, Valera EM, Seidman LJ, et al. Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Arch Gen Psychiatry* 2008;61:102–14.
11. Coghill DR, Rhodes SM, Matthews K. The neuropsychological effects of chronic methylphenidate on drug-naive boys with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2007;62:954–62.
12. EMEA. *Questions and answers on the review of medicines containing methylphenidate* 2008. Doc. Ref. EMEA/658285/2008.
13. Kooij JS, Boonstra AM, Vermeulen SH, Heister AG, Burger H, Buitelaar JK, Franke B. Response to methylphenidate in adults with ADHD is associated with a polymorphism in SLC6A3 (DAT1). *Am J Med Genet B Neuropsychiatr Genet* 2008;147B:201–8.
14. Roman T, Rohde LA, Hutz MH. Polymorphisms of the dopamine transporter gene: influence on response to methylphenidate in attention deficit-hyperactivity disorder. *Am J Pharmacogenomic* 2004;4:83–92.
15. Shang CY, Gau SS, Liu CM, Hwu HG. Association between the dopamine transporter gene and the inattentive subtype of attention deficit hyperactivity disorder in Taiwan. *Prog Neuropsychopharmacol Biol Psychiatry* 2010.. http://dx.doi.org/10.1016/j.pnpbp.
16. Mazei-Robison MS, Couch RS, Shelton RC, Stein MA, Blakely RD. Sequence variation in the human dopamine transporter gene in children with attention deficit hyperactivity disorder. *Neuropharmacology* Nov 2004;49(6):724–36.
17. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. Dopamine increases in striatum do not elicit craving in cocaine abusers unless they are coupled with cocaine cues. *Neuroimage* 2008 Feb 1;39(3):1266–73.
18. Faraone SV, Mick E. Molecular genetics of attention deficit hyperactivity disorder. *Psychiatr Clin North Am* 2010;33:159–80.
19. Franke B, Vasquez AA, Johansson S, Hoogman M, Romanos J, Boreatti-Hümmer A, et al. Multicenter analysis of the SLC6A3/DAT1 VNTR haplotype in persistent ADHD suggests differential involvement of the gene in childhood and persistent ADHD. *Neuropsychopharmacology* 2010;35:656–64.
20. Sáiz PA, García-Portilla MP, Arango C, Morales B, Arias B, Corcoran P, et al. Genetic polymorphisms in the dopamine-2 receptor (DRD2), dopamine-3 receptor (DRD3), and dopamine transporter (SLC6A3) genes in schizophrenia: data from an association study. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34:26–31.
21. van der Zwaluw CS, Engels RC, Buitelaar J, Verkes RJ, Franke B, Scholte RH. Polymorphisms in the dopamine transporter gene (SLC6A3/DAT1) and alcohol dependence in humans: a systematic review. *Pharmacogenomics* 2009;10:853–66.
22. Yang B, Chan RC, Jing J, Li T, Sham P, Chen RY. A meta-analysis of association studies between the 10-repeat allele of a VNTR polymorphism in the 3'-UTR of dopamine transporter gene and attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet* 2007;144B(4):541–50.
23. Greenwood TA, Kelsoe JR. Promoter and intronic variants affect the transcriptional regulation of the human dopamine transporter gene. *Genomics* 2003;82(5):511–20.
24. Mill J, Asherson P, Browes C, D'Souza U, Craig I. Expression of the dopamine transporter gene is regulated by the 3' UTR VNTR: evidence from brain and lymphocytes using quantitative RT-PCR. *Am J Med Genet* 2002;114:975–9.
25. Heinz A, Goldman D, Jones DW, Palmour R, Hommer D, Gorey JG, Lee KS, Linnoila M, Weinberger DR. Genotype influences in vivo dopamine transporter availability in human striatum. *Neuropsychopharmacology* 2000;22(2):133–9.
26. Cheon KA, Ryu YH, Kim JW, Cho DY. The homozygosity for 10-repeat allele at dopamine transporter gene and dopamine transporter density in Korean children with attention deficit hyperactivity disorder: relating to treatment response to methylphenidate. *Eur Neuropsychopharmacol* 2005;15:95–101.
27. Krause J, la Fougere C, Krause KH, Ackenheil M, Dresel SH. Influence of striatal dopamine transporter availability on the response to methylphenidate in adult patients with ADHD. *Eur Arch Psychiatry Clin Neurosci* 2005;255:428–31.
28. van de Giessen E, de Win MM, Tanck MW, van den Brink W, Baas F, Booij J. Striatal dopamine transporter availability associated with polymorphisms in the dopamine transporter gene SLC6A3. *J Nucl Med* 2009;50(1):45–52.
29. Krause J. SPECT and PET of the dopamine transporter in attention-deficit/hyperactivity disorder. *Expert Rev Neurother* 2008;8:611–25.
30. Stein MA, Waldman ID, Sarampote CS, Seymour KE, Robb AS, Conlon C, et al. Dopamine transporter genotype and methylphenidate dose response in children with ADHD. *Neuropsychopharmacology* 2005;30:1374–82.
31. Purper-Ouakil D, Wohl M, Orejarena S, Cortese S, Boni C, Asch M, et al. Pharmacogenetics of methylphenidate response in attention deficit/hyperactivity disorder: association with the dopamine transporter gene (SLC6A3). *Am J Med Genet B Neuropsychiatr Genet* 2008;147B:1425–30.
32. Kaufman J, Birmaher B, Brent D, Rao U, Ryan N. *Kiddie-sads-present and lifetime version*. The Department of Psychiatry, University of Pittsburgh School of Medicine; 1996.
33. Società Italiana di Neuropsichiatria Infantile (SINPIA). Zuddas A, e Masi G, editors. *Linee-guida per la diagnosi e la terapia farmacologica del Disturbo da Deficit Attentivo con Iperattività (ADHD) in età evolutiva* 2002.
34. Conners CK, Sitarenios G, Parker JD, Epstein JN. Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol* 1998;26:279–91.

35. Schaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry* 1983;40:1228–31.
36. Krikorian R, Bartok J, Gay N. Tower of London procedure: a standard method and developmental data. *J Clin Exp Neuropsychol* 1994;16(6):840–50.
37. Shallice T. Specific impairments of planning. *Philos Trans Royal Soc London B* 1982;298:199–209.
38. Conners CK. *Conners' continuous performance test*. Toronto: Multi-Health Systems; 1995.
39. Shallice T, et al. Specific impairments of planning. *Philos Trans R Soc Lond B Biol Sci* 1982.
40. Szekeres G, Kéri S, Juhász A, Rimanóczy A, Szendi I, Czimmer C, et al. Role of dopamine D3 receptor (DRD3) and dopamine transporter (DAT) polymorphism in cognitive dysfunctions and therapeutic response to atypical antipsychotics in patients with schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 2004;124B:1–5.
41. Fuke S, Suo S, Takahashi N, Koike H, Sasagawa N, Ishiura S. The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. *Pharmacogenomic J* 2001;1:152–6.
42. Vles JS, Feron FJ, Hendriksen JG, Jolles J, van Kroonenburgh MJ, Weber WE. Methylphenidate down-regulates the dopamine receptor and transporter system in children with attention deficit hyperkinetic disorder (ADHD). *Neuropaediatrics* 2003;34:77–80.
43. Kirley A, Lowe N, Hawi Z, Mullins C, Daly G, Waldman I, McCarron M, O'Donnell D, Fitzgerald M, Gill M. Association of the 480 bp DAT1 allele with methylphenidate response in a sample of Irish children with ADHD. *Am J Med Genet B Neuropsychiatr Genet* 2003;121B:50–4.
44. Kang AM, Palmatier MA, Kidd KK. Global variation of a 40-bp VNTR in the 3'-untranslated region of the dopamine transporter gene (SLC6A3). *Biol Psychiatry* 1999;46:151–60.
45. Mitchell RJ, Howlett S, Earl L, White NG, McComb J, Schanfield MS, et al. Distribution of the 3' VNTR polymorphism in the human dopamine transporter gene in world populations. *Hum Biol* 2000;72:295–304.
46. Santovito A, Cervella P, Selvaggi A, Caviglia GP, Burgarello C, Sella G, et al. DAT1 VNTR polymorphisms in a European and an African population: identification of a new allele. *Hum Biol* 2008;80:191–8.
47. Bellgrove MA, Hawi Z, Kirley A, Gill M, Robertson IH. Dissecting the attention deficit hyperactivity disorder (ADHD) phenotype: sustained attention, response variability and spatial attentional asymmetries in relation to dopamine transporter (DAT1) genotype. *Neuropsychologia* 2005;43:1847–57.
48. Alderson RM, Rapport MD, Kofler MJ. Attention-deficit/hyperactivity disorder and behavioral inhibition: a meta-analytic review of the stop-signal paradigm. *J Abnorm Child Psychol* 2007;35:745–58.
49. Bitsakou P, Psychogiou L, Thompson M, Sonuga-Barke EJ. Inhibitory deficits in attention deficit/hyperactivity disorder are independent of basic processing efficiency and IQ. *J Neural Transm* 2008;115:261–8.
50. Huizenga HM, van Bers BM, Plat J, van den Wildenberg WP, van der Molen MW. Task complexity enhances response inhibition deficits in childhood and adolescent attention deficit/hyperactivity disorder: a meta-regression analysis. *Biol Psychiatry* 2009;65:39–45.
51. Feron FJ, Hendriksen JG, van Kroonenburgh MJ, Blom-Coenjaerts C, Kessels AG, Jolles J, et al. Dopamine transporter in attention-deficit hyperactivity disorder normalizes after cessation of methylphenidate. *Paediatr Neurol* 2005;33:179–83.
52. Curatolo P, Paloscia C, D'Agati E, Moavero R, Pasini A. The neurobiology of attention deficit/hyperactivity disorder. *Eur J Paediatr Neurol* 2009;13(4):299–304.

ARTICLE IN PRESS
JNI-475678; No of Pages 4
Journal of Neuroimmunology xxx (2013) xxx–xxx
Contents lists available at SciVerse ScienceDirect
Journal of Neuroimmunology
journal homepage: www.elsevier.com/locate/jneuroim

Anti-Purkinje cell antibody as a biological marker in attention deficit/hyperactivity disorder: A pilot study

Francesca Passarelli [a,*], Renato Donfrancesco [b], Paola Nativio [a], Esterina Pascale [c], Michela Di Trani [d], Anna Maria Patti [e], Antonella Vulcano [e], Paolo Gozzo [a], Maria Pia Villa [f]

[a] Department of Molecular Medicine, University of Rome "Sapienza" Italy
[b] Neuropsychiatric Unit S. Pertini Hospital, Rome, Italy
[c] Department of Medico-Surgical Sciences and Biotechnologies, University of Rome "Sapienza" Italy
[d] Department of Clinical and Dynamic Psychology, University of Rome "Sapienza" Italy
[e] Department of Public Health and Infectious Diseases, University of Rome "Sapienza" Italy
[f] Paediatric Department S. Andrea Hospital, University of Rome "Sapienza" Italy

ARTICLE INFO

Article history:
Received 29 September 2011
Received in revised form 4 June 2012
Accepted 20 February 2013
Available online xxxx

Keywords:
ADHD
Anti-Yo antibodies
Purkinje cells
Immunofluorescence
Cerebellum

ABSTRACT

An autoimmune hypothesis has been suggested for several disorders in childhood. The aim of the study was to clarify the role of the cerebellum in ADHD and to evaluate the possible association between anti-Yo antibodies and ADHD. The presence/absence of antibodies was tested by indirect immunofluorescence assay on 30 combined subtype ADHD children, on 19 children with other psychiatric disorders (Oppositional-defiant and Conduct Disorders, Dyslexia) and 27 healthy controls.
Results showed a significant positive response to the anti-Yo antibody immunoreactivity in the Purkinje cells of the cerebellum of ADHD children, compared with the control group and the psychiatric non-ADHD children. This association points to an immune dysregulation and the involvement of the cerebellum in ADHD.

1. Introduction

It has been hypothesized that several childhood diseases are caused by autoimmune disorders. This hypothesis is supported by reports of significantly high anti-brain and, more specifically, anti-basal ganglia antibodies found in children with Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) (Murphy and Barkley, 1996; Pavone et al., 2004; Singer et al., 2004) or with Tourette's syndrome, as well as in patients with Sydenham's chorea, which is a manifestation of rheumatic fever following infection by group A β-hemolytic streptococci (GABHS) (Church et al., 2002, 2003).

The immune-mediated disorder hypothesis is further supported by the demonstration that the infusion of IgG of sera from patients with PANDAS induces oral stereotypies in rats (Taylor et al., 2002) and that antibodies from a patient with Sydenham's chorea reacted against neuronal antigens at the GABHS surface (Kirvan et al., 2003).

Attention-deficit/hyperactivity disorder (ADHD) is a serious psychiatric condition that causes marked behavioral and social impairment throughout a person's life. ADHD begins in childhood and may persist into adult life in a substantial subgroup of patients (Faraone and Biederman, 2005).

The precise etiology of ADHD is not fully understood. The majority of current theories focus on dysfunction in the prefrontal brain as well as in striatal and thalamic structures (i.e. fronto-striatothalamofrontal circuits). However, in structural imaging research, cerebellar abnormalities are among the most consistently reported findings in ADHD (Semrud-Clikeman et al., 2000; Ashtari et al., 2005).

Indeed, numerous volumetric studies have reported reduced cerebellar volumes and developmental alterations in the cerebellum in children with ADHD (Berquin et al., 1998; Castellanos and Acosta, 2002; Castellanos et al., 2002; Mackie et al., 2007).

Given it close relationship with the prefrontal cortex and basal ganglia, the cerebellum is thought to play an important role in cognition, particularly in verbal working memory, implicit learning, temporal information processing as well as in shifts in attention and emotional regulation (Schmahmann and Sherman, 1998; Ivry et al., 2002; Ito, 2008). Consequently, impaired cerebellar activity may result in cerebellum cognitive and affective syndrome (CCAS).

In view of the potential involvement of this brain structure in the onset of ADHD, we conducted a series of experiments aimed at elucidating the role played by the cerebellum in children affected by ADHD.

The aim of the study was to evaluate the possible role of anti-Yo antibodies as a marker of an immune response that is directed against

* Corresponding author at: Department of Molecular Medicine, University of Rome "Sapienza", viale dell'Università 30-00185 Rome Italy. Tel./fax: +39 06 49914528.
E-mail address: francesca.passarelli@uniroma1.it (F. Passarelli).

0165-5728/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jneuroim.2013.02.018

the cerebellum. Anti-Yo (PCA-1) neuronal antibodies represent some of the most commonly used markers employed in clinical practice for diagnosing paraneoplastic cerebellar degeneration (PCD). Such antibodies may also be found in ovarian cancer patients without PCD. Almost all paraneoplastic disorders are immune-mediated, thus hypothesizing an immune dysregulation (Darnell and Posner, 2003). If the association between anti-Yo antibodies and ADHD is validated, the subsequent step would be to find a causal relationship between ADHD and the presence of anti-cerebellum antibodies. Moreover, in order to evaluate the specific features of immune dysregulation in ADHD, we compared ADHD children with a control group without psychiatric disorders and with a group of children with other psychiatric disorders (Oppositional-defiant and Conduct Disorders, Dyslexia).

2. Material and methods

2.1. Subjects

We studied 30 consecutive drug-naïve Caucasian outpatients with ADHD (29 males and 1 female, mean age of 9.2 ± 2.3 years, age range of 6–17.5 years), diagnosed at the Clinic for Developmental Neurology and Psychiatry of the S. Pertini Hospital in Rome. All the ADHD subjects belonged to the combined subtype: we selected the combined subtype for the purposes of this pilot study so as to enroll the most serious cases of ADHD. Moreover, fifty percent of the ADHD children presented other psychiatric comorbidities, including Oppositional-defiant Disorder (ODD), Conduct Disorder (CD) and Dyslexia.

On the basis of the presence of comorbidities in the ADHD group, another group of children without ADHD psychiatric disorders were included in the study to be able to better define the specific features of immune dysregulation in this pathology: 19 children with a diagnosis of Oppositional-defiant or Conduct Disorders and Dyslexia (all males, mean age of 9.0 ± 2.8 years, age range of 6–15 years), were enrolled at the Clinic for Developmental Neurology and Psychiatry of the S. Pertini Hospital in Rome.

The control group was matched for sex and age and was composed of 27 healthy Caucasian sex and age-matched children (26 males and 1 female, 9.1 ± 1.8 years, age range 6–17 years), who were randomly recruited from a community-based survey and were attending two elementary and junior high schools from the same urban area of Rome.

Both the children and parents in the groups of patients with ADHD and other psychiatric disorders separately underwent a semi-structured psychiatric interview, i.e. the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), conducted by an experienced child psychiatrist (RD). All the children (i.e. the ADHD group, other psychiatric disorder group and control group) underwent an additional routine diagnostic assessment, based on the ADHD-Rating Scale (ADHD-RS) (DuPaul et al., 1998) adapted for the Italian population (Marzocchi and Cornoldi, 2000), which was filled out by the children's parents and school teachers.

The aim of this additional assessment was to confirm the diagnosis of ADHD according to the DSM-IV criteria in the children with ADHD and rule out the diagnosis in the children in both the other groups. On the basis of the Wechsler Intelligence Scale for Children-Revised (WISC-III) (Wechsler, 1991), all the children with an intelligence quotient (IQ) <70 were excluded.

All the children were assessed by means of a neurological evaluation: no evidence emerged of ataxia, encephalopathy or other neurological disorders. In accordance with the DSM-IV criteria, Dyslexia was assessed

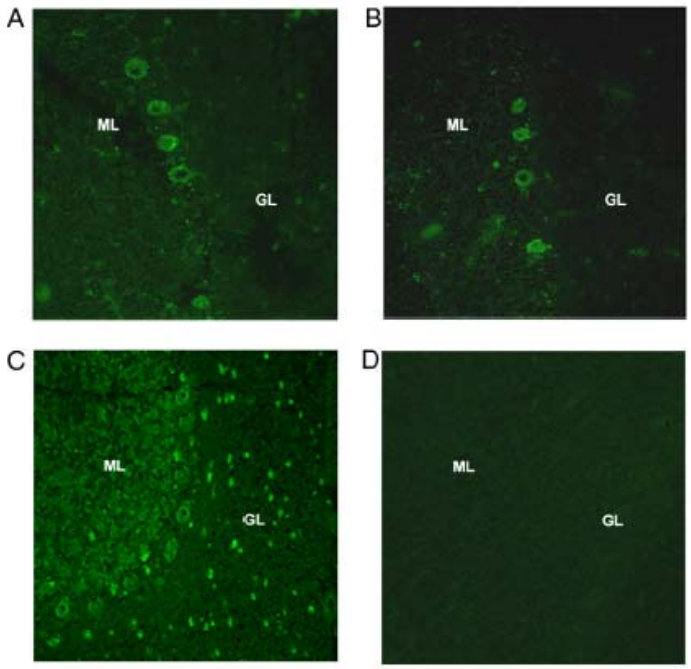


Fig. 1. Immunofluorescence reaction in ADHD patients. (A and B) Representative photomicrograph showing the positive immunofluorescence signal only for purkinje cells (anti-Yo antibodies) in ADHD children (left panel) and in neurological patient (right panel) 200X magnification. (C) Representative photomicrograph showing the positive immunofluorescence signal in the cerebellar neurons of ADHD patient (200×). The positive reaction shows staining of Purkinje cell cytoplasm and of granular neuronal nuclei (anti-Hu antibodies). (D) Representative photomicrograph showing the negative immunofluorescence reaction (200×). The reaction shows no staining neither of Purkinje cell cytoplasm nor in granular neuronal nuclei. ML, molecular layer; GL granular layer of cerebellum.

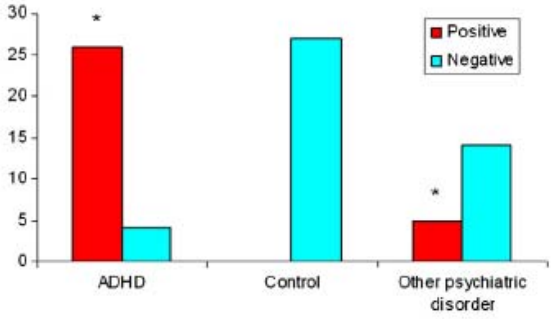


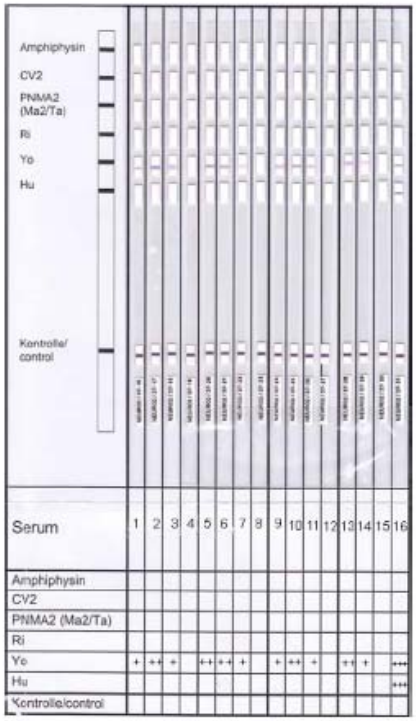
Fig. 2. Yo-positive antibodies in ADHD children. The columns shows the number of ADHD and other psychiatric disorder positive children (red column) to the anti-Yo antibodies compared to control (* = $p < 0.0001$ at Fisher's exact test). None of the children in the control group was positive. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

by means of the Italian "List of words" test (Job et al., 1995). The three groups of children were matched for social economic status as assessed according to the Hollingshead Scale (Hollingshead, 1957). The patients' medical history, neurological and physical examinations and an electroencephalogram during sleep were used to exclude any co-morbid medical and neurological condition.

Written informed consent was obtained from the parents of all the subjects enrolled in the study.

2.2. Immunohistochemistry and Western blot

Antibodies directed against Yo (PCA-1), were detected by indirect immunofluorescence assay (IFA). The method was performed on commercially available substrate of primate cerebellum and gut (Euroimmun Italia). The presence of specific antibodies was determined by their specific reactions to the cerebellar neurons (Purkinje, molecular or granular cells). The patients' sera were first diluted 1:10 in PBS-Tween and then incubated with the substrate provided in the presence of fluorescein-



Groups	n	EUROIMMUN Neuronal Antigens Profile EUROLINE	
		Yo Positive	Yo Negative
ADHD Children	30	26	4
Control Children	27	0	27
OCDD Children	19	5	14

Fig. 3. Western blot for the determination of neuronal autoantibodies in ADHD patients. A: representative line blots incubated with different patient sera. Control sera were lines 4, 8, 12 and 15. B: The intensity of the bands was automatically evaluated using the computer program EUROLINE Scan. The sensitivity of the test for Yo is 86% for ADHD children and 73% for children with other psychiatric disorders. See Materials and method.

labelled anti-human IgG conjugate in order to allow binding of the antibodies to the specific antigens of the substrate.

The positive reaction showed granular staining of the Purkinje cell cytoplasm (anti-Yo antibody) whereas the negative reaction did not evidence any staining. The immunofluorescence was visualized by means of a fluorescence microscope (LEICA, Leitz DMRB, Germany) at a magnification of 20× or higher.

Total of 163 patient sera ADHD, other psychiatric pathologies and control were assessed by using the EUROLINE neuronal antigen kit (Euroimmune, Italia) for western blot analysis. The kit consist in membrane chips with individual lines of purified, biochemically characterized antigens coated onto a separate membrane chip. The serum was diluted 1:100 in sample buffer provided. The intensity of the bands was automatically evaluated using the computer program EUROLINE Scan. The sensitivity of the test for Yo is reported in Fig. 3, B.

All the analyses were performed in double blind experiments, i.e. neither the subjects enrolled in the study nor the researchers involved knew whether each subject had been assigned to the control group or the experimental group.

2.3. Statistics

To assess nominal variables (sex, proportion of anti-Yo Ab positive/negative results) we used the Fisher's exact test, while to compare the age between the three groups (i.e. ADHD, other psychiatric disorders and control groups) we performed the Mann–Whitney *U* test. The significance was set at $p < 0.0001$. The alpha value for significance was 0.05.

3. Results

The three groups were matched for sex (p = n.s.) and age (p = n.s.). The results reported the presence of positive staining of the Purkinje cell, and thereby pointing to the presence of anti-Yo antibodies, while the presence of anti-Hu positive granular cell are occasionally noticed as shown in Fig. 1.

Twenty-six of 30 children in the ADHD group resulted positive for the anti-Yo antibody, whereas none of the children in the control group was positive. The difference between the two groups was significant ($p < 0.0001$). Only 5 children tested positive for the anti-Yo antibody in the group with no ADHD psychiatric disorders; this difference was significant when this group and the ADHD group were compared by means of the Fisher's exact test ($p < 0.0001$) (see Fig. 2).

4. Discussion

The present study demonstrates that combined subtype ADHD children display a significantly positive response to anti-Yo antibody immunoreactivity when compared to the control group. As none of the ADHD children were taking any drugs, we can exclude the effect of drug intake on the results.

To our knowledge, this is the first study to report the presence of an autoimmune marker in a subgroup of ADHD children.

The response we observed occurred above all in the Purkinje cells, a finding that is in agreement with structural imaging research, which has highlighted abnormalities in cerebellar topographic organization as one of the most consistent findings in ADHD. However, the putative functional topography of the cerebellar modulation of cognition and emotion remains unclear. Indeed, the discovery of a possible association between ADHD (combined subtype) and anti-Yo antibodies does not provide proof of a causal relationship and/or etiopathogenetic connection between ADHD and the anti-Yo antibody. Consequently, we may, for the time being, refer to the anti-Yo antibody merely as a possible marker of ADHD combined subtype.

In conclusion, our study points to a possible association between anti-Yo antibodies and ADHD (combined subtype). Further studies are warranted on a more representative group of subjects to investigate a possible association between anti-Yo antibodies and other ADHD subtypes and/or ADHD psychiatric comorbidities. Studies are also needed to assess the presence of the anti-Yo antibody in children with psychiatric disorders other than ADHD in order to determine whether anti-Yo antibodies are specific to ADHD as well as to shed light on a possible role of these antibodies in the pathogenesis of ADHD.

Acknowledgments

The authors give thanks to Dr B. Cecchini and Dr F. Valenti, Euroimmun Italia, for their generous support and contributions.

References

Ashtari, M., Kumra, S., Bhaskar, S.L., Clarke, T., Thaden, E., Cervellione, K.L., Rhinewine, J., Kane, J.M., Adesman, A., Milanaik, R., Maytal, J., Diamond, A., Szeszko, P., Ardekani, B.A., 2005. Attention-deficit/hyperactivity disorder: a preliminary diffusion tensor imaging study. Biol. Psychiatry 57, 448–455.

Berquin, P.C., Giedd, J.N., Jacobsen, L.K., Hamburger, S.D., Krain, A.L., Rapoport, J.L., Castellanos, F.X., 1998. Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. Neurology 50, 1087–1093.

Castellanos, F.X., Acosta, M.T., 2002. Syndrome of attention deficit with hyperactivity as the expression of an organic functional disorder. Rev. Neurol. 35, 1–11.

Castellanos, F.X., Lee, P.P., Sharp, W., Jeffries, N.O., Greenstein, D.K., Clasen, L.S., Blumenthal, J.D., James, R.S., Ebens, C.L., Walter, J.M., Zijdenbos, A., Evans, A.C., Giedd, J.N., Rapoport, J.L., 2002. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 288, 1740–1748.

Church, A.J., Cardoso, F., Dale, R.C., Lees, A.J., Thompson, E.J., Giovannoni, G., 2002. Anti-basal ganglia antibodies in acute and persistent Sydenham's chorea. Neurology 59, 227–231.

Church, A.J., Dale, R.C., Lees, A.J., Giovannoni, G., Robertson, M.M., 2003. Tourette's syndrome: a cross sectional study to examine the PANDAS hypothesis. J. Neurol. Neurosurg. Psychiatry 74, 602–607.

Darnell, R.B., Posner, J.B., 2003. Paraneoplastic syndromes involving the nervous system. N. Engl. J. Med. 349, 1543–1554.

DuPaul, G.J., Power, T.J., Anastopoulos, A.D., Reid, R., 1998. ADHD Rating Scale — IV. Guilford Publications, New York.

Faraone, S.V., Biederman, J., 2005. What is the prevalence of adult ADHD? Results of a population screen of 966 adults. J. Atten. Disord. 9, 384–391.

Hollingshead, A., 1957. Four Factor Index of Social Status. Yale University Department of Sociology, New Haven.

Ito, M., 2008. Control of mental activities by internal models in the cerebellum. Nat. Rev. Neurosci. 9, 304–313.

Ivry, R.B., Spencer, R.M., Zelaznik, H.N., Diedrichsen, J., 2002. The cerebellum and event timing. Ann. N. Y. Acad. Sci. 978, 302–317.

Job, R., Sartori, G., Tressoldi, P.E., 1995. Battery for the Evaluation of Dyslexia and Dysorthographia. Organizzazioni Speciali, Firenze, Italy.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version, (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatry 36, 980–988.

Kirvan, C.A., Swedo, S.E., Heuser, J.S., Cunningham, M.W., 2003. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. Nat. Med. 9, 914–920.

Mackie, S., Shaw, P., Lenroot, R., Pierson, R., Greenstein, D.K., Nugent, T.F., Sharp, W.S., Giedd, J.N., Rapoport, J.L., 2007. Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. Am. J. Psychiatry 164, 647–655.

Marzocchi, G.M., Cornoldi, C., 2000. Una scala di facile uso per la rilevazione dei comportamenti problematici dei bambini con deficit di attenzione e iperattività. Psicol. Clin. Svilupp. 4, 43–64.

Murphy, K., Barkley, R.A., 1996. Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. Compr. Psychiatry 37, 393–401.

Pavone, P., Bianchini, R., Parano, E., Incorpora, G., Rizzo, R., Mazzone, L., Trifiletti, R.R., 2004. Anti-brain antibodies in PANDAS versus uncomplicated streptococcal infection. Pediatr. Neurol. 30, 107–110.

Schmahmann, J.D., Sherman, J.C., 1998. The cerebellar cognitive affective syndrome. Brain 121, 561–579.

Semrud-Clikeman, M., Steingard, R.J., Filipek, P., Biederman, J., Bekken, K., Renshaw, P.F., 2000. Using MRI to examine brain-behavior relationships in males with attention deficit disorder with hyperactivity. J. Am. Acad. Child Adolesc. Psychiatry 39, 477–484.

Singer, H.S., Loiselle, C.R., Lee, O., Minzer, K., Swedo, S., Grus, F.H., 2004. Anti-basal ganglia antibodies in PANDAS. Mov. Disord. 19, 405–415.

Taylor, J.R., Morshed, S.A., Parveen, S., Mercadante, M.T., Scahill, L., Peterson, B.S., King, R.A., Leckman, J.F., Lombroso, P.J., 2002. An animal model of Tourette's syndrome. Am. J. Psychiatry 159, 657–660.

Wechsler, D., 1991. WISC-III. NCS Pearson Inc., USA.

ISCRIZIONI

Il corso si rivolge a psicologi, neuropsichiatri infantili e psicoterapeuti.
É previsto un numero massimo di 25 partecipanti.

Costi:
Il costo del corso è di **400 €**

Modalità di iscrizione:
L'iscrizione può essere effettuata all'indirizzo web:
http://www1.inpe.unipi.it/didattica/corsi/regform/

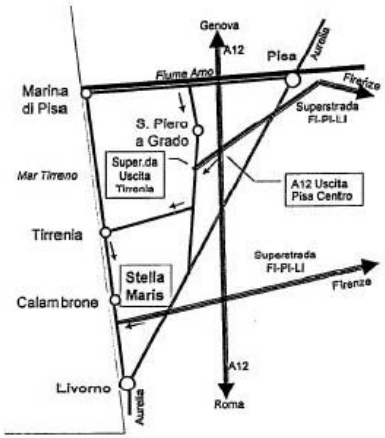
Venerdì 28 Giugno è prevista la **cena sociale** al costo aggiuntivo di 30€.
É obbligatoria la prenotazione.

Per le giornate del corso è stata inoltrata richiesta di accreditamento ECM per medici e psicologi

Per informazioni:
Dott. ssa Lisa Polidori
3477421640
lpolidori@inpe.unipi.it

COME SI RAGGIUNGE L'IRCCS STELLA MARIS

Dall'Autostrada A12 uscita Pisa Centro seguire indicazioni per Tirrenia, superata Tirrenia si arriva in località Calambrone.
Dalla superstrada FI–PI—LI:
- direzione Livorno fino all'ultima uscita, si prosegue verso Tirrenia
- direzione Pisa uscita San Piero a Grado-Tirrenia, seguire le indicazioni per Tirrenia e proseguire in direzione Livorno.



Sede del corso: Auditorium
IRCCS Fondazione Stella Maris
Viale del Tirreno, 341/A/B/C
56128 Calambrone (PI)

Fondazione Stella Maris - Pisa
per la Neuropsichiatria dell'Infanzia e dell'Adolescenza

SERVIZIO PER IL TRATTAMENTO DEI DISTURBI DEL COMPORTAMENTO

"Al di là delle nuvole"

28-29 Giugno 2013

Coping Power Program

Docente
Prof. J.Lochman
University of Alabama

COPING POWER PROGRAM

Il **Coping Power Program** è un programma multimodale per la gestione e il controllo della rabbia nei bambini dell'ultimo ciclo della scuola elementare e dei primi anni della scuola media.
L'intervento, basato sul modello sociocognitivo di Dodge, è rivolto sia ai bambini che ai loro genitori e si focalizza sia sui processi del contesto familiare che sui processi cognitivi dei bambini, cercando di promuovere migliori strategie di problem solving e migliori modalità di relazione con i pari.

***John E. Lochman** è Professore emerito di Psicologia Clinica presso l'Università dell' Alabama a Tuscaloosa e Professore aggiunto di Psichiatria e Scienze del Comportamento al Duke University Medical Center. E' il Direttore del Centro per la Prevenzione dei Problemi di Comportamento in età evolutiva dell'Università dell'Alabama. E' membro della commissione scientifica del Journal of Clinical Child and Adolescent Psychology, Behavior Therapy, Developmental Psychology, e il Journal of School Psychology, ed è il caporedattore del Journal of Abnormal Child Psychology.*

PROGRAMMA DEL CORSO:

Venerdi 28 Giugno:
9.00—13.00 e 14.00-18.00
Il Coping Power Program con i bambini.

La componente del Coping Power Program per i bambini è strutturata in 34 sessioni di gruppo che, utilizzando tecniche di matrice cognitivo-comportamentale, si prefiggono di potenziare:

- l'abilità ad intraprendere obiettivi a breve e a lungo termine,
- l'organizzazione e le abilità di studio,
- il riconoscimento e la modulazione della rabbia,
- il *perspective taking* ,
- il *problem-solving* in situazioni conflittuali,
- l'abilità a resistere alle pressioni dei pari,
- le abilità sociali e l'ingresso in gruppi sociali positivi.

Per tutta la durata del corso è prevista la traduzione consecutiva.

Per alcune parti del programma è prevista l'esemplificazione attraverso dei video di seduta in lingua italiana

Sabato 29 Giugno:
9.00—13.00 e 14.00-18.00
Il Coping Power Program con i genitori

La componente del Coping Power Program per i genitori è strutturata in 16 sessioni di gruppo con l'obiettivo di sviluppare e potenziare le abilità genitoriali relative a:

- gratificare e fornire attenzione positiva,
- stabilire regole chiare ed esprimere le aspettative sul comportamento del figlio,
- promuovere organizzazione e abilità di studio,
- utilizzare appropriate pratiche educative,
- modulare lo stress genitoriale,
- incrementare la comunicazione familiare ed il *problem-solving* in situazioni conflittuali,
- rinforzare le abilità di *problem-solving* che i bambini stanno acquisendo

RELATORI

Daniele Arisi
UONPIA, A.O. Ist. Ospedalieri di Cremona
Umberto Balottin
Neuropsichiatria Infantile, IRCCS Mondino, Univ. degli Studi di Pavia
Claudio Bissoli
UONPIA, IRCCS "Ca'Granda" Ospedale Maggiore Policlinico di Milano
Maurizio Bonati
IRCCS Ist. "Mario Negri" di Milano
Erika Buzzi
Scuola di Specialità, Univ. degli Studi di Milano
Mauro Camuffo
UONPIA, A.USL 9 di Grosseto
Daniela Candeloro
Scuola di Specialità Univ. Degli Studi di Pavia
Tristana Castrignanò
Scuola di Specialità, Univ. degli Studi di Varese
Antonio Clavenna
IRCCS Ist. "Mario Negri" di Milano
Stefano Conte
Neuropsichiatria Infantile, A.O. Ospedali Riuniti di Bergamo
Antonella Costantino
UONPIA, IRCCS "Ca' Granda" Osp. Maggiore Policlinico di Milano
Gianluca Daffi
UONPIA, A.O. Spedali Civili Presidio Ospedaliero dei Bambini di Brescia
Anna Didoni
UONPIA, IRCCS "Ca'Granda" Ospedale Maggiore Policlinico di Milano
Patrizia Di Noia
Genitore di Muggiò
Paola Effedri
UONPIA, A.O. Spedali Civili Presidio Ospedaliero dei Bambini di Brescia
Elena Filippini
UONPIA, A.O. Spedali Civili Presidio Ospedaliero dei Bambini di Brescia
Maria Teresa Foà
Scuola Primaria "Vinci", 1° Circolo, di Vimercate
Emiddio Fornaro
UONPIA, A.O. Ospedale Niguarda "Ca'Granda" di Milano
Andrea Gardini
Direttore Sanitario, A.O.Universitaria di Ferrara
Stefano Guerini
Scuola di Specialità, Univ. degli Studi di Brescia
Gian Marco Mazzocchi
Psicologia dello Sviluppo, Univ. degli Studi di Milano-Bicocca
Silvia Merati
UONPIA, A.O. Fatebenefratelli e Oftalmico di Milano
Corrado Meraviglia
UONPIA, A.O. Valtellina Valchiavenna di Sondrio
Paolo Moderato
Ist. Comunicazione Comportamento e Consumi, IULM di Milano
Massimo Molteni
IRCCS, Ist. Scientifico Eugenia Medea di Bosisio Parini
Luciano Montaldi
UONPIA, A.O. "G. Salvini" di Garbagnate Milanese
Paola Morosini
UONPIA, A.O. della Provincia di Lodi
Gaia Oldani
UONPIA, A.O. Fatebenefratelli e Oftalmico di Milano
Laura Reale
Scuola di Specialità, Univ. degli Studi di Milano; Ist. "Mario Negri" di Milano
Francesco Rinaldi
UONPIA, ASL Vallecamonica-Sebino
Ippolita Roncononi
Pediatra di Famiglia, ASL di Pavia
Monica Saccani
UONPIA, A.O. San Paolo, Univ. degli Studi di Milano
Roberto Segala
UONPIA, A.O. "Carlo Poma" di Mantova
Cristiano Termine
UONPIA, Ospedale di Circolo, Fondazione "Macchi" di Varese
Alessandra Tiberti
UONPIA A.O. Spedali Civili Presidio Ospedaliero dei Bambini di Brescia
Davide Villani
Neuropsichiatria Infantile, A.O. Provincia di Lecco
Antonio Vita
DSM, AO Spedali Civili di Brescia, Università di Brescia
Gian Vincenzo Zuccotti
Clin.Pediatrica, A.O.Ospedale Luigi Sacco, Univ. degli Studi di Milano

L'Istituto di Ricerche Farmacologiche "Mario Negri" si trova a Milano in zona Bovisa nelle vicinanze del Campus Politecnico (Ingegneria) e della Triennale Bovisa.
E' facilmente raggiungibile con il passante ferroviario, scendendo alle fermate di Bovisa (FNM) o Villapizzone (FS).
Se fermate a Bovisa ricordatevi di scendere le scale che si trovano sul lato destro della stazione.

Segreteria organizzativa:
Laboratorio per la Salute Materno Infantile
Dipartimento di Salute Pubblica
Istituto di Ricerche Farmacologiche
"Mario Negri" - IRCCS
Via Giuseppe La Masa, 19. Milano
Tel. 02 39014511 – fax 02 3550924
ADHD@marionegri.it

Neuropsichiatria Infantile - Polo Ospedaliero UONPIA
A. O. Spedali Civili di Brescia
P.le Spedali Civili, 1. Brescia
Tel. 030.3995722 - 030.3995723

La partecipazione è gratuita e prevede l'assegnazione dei crediti ECM.
L'iscrizione al Convegno è obbligatoria e deve essere effettuata entro il 15 maggio 2013 accedendo al link:
ADHD.marionegri.it

ADHD: per una condivisione dei percorsi diagnostico-terapeutici

Milano, 28-29 maggio 2013
Ore 9.00-18.00 - AULA A

Istituto di Ricerche Farmacologiche
"Mario Negri" – IRCCS
Via G. La Masa 19 - 20156 Milano

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

Azienda Ospedaliera SPEDALI CIVILI BRESCIA

Il Progetto: "Condivisione di percorsi diagnostico-terapeutici per l'ADHD in Lombardia" è stato in parte finanziato dalla Regione Lombardia e coinvolge 18 Centri di Riferimento per l'ADHD e il Laboratorio per la Salute Materno Infantile dell'Istituto di Ricerche Farmacologiche "Mario Negri".
Coordinatore del Progetto è la UONPIA degli Spedali Civili di Brescia

ADHD: PER UNA CONDIVISIONE DEI PERCORSI DIAGNOSTICO-TERAPEUTICI

Il disturbo da deficit di attenzione e iperattività (ADHD) è una delle più frequenti sindromi neuropsichiatriche infantili, sebbene la stima della prevalenza vari tra le nazioni.

La complessità della diagnosi necessita dell'uso di strumenti appropriati che consentano di valutare la presenza dei sintomi nei diversi contesti di vita del bambino. Così anche ogni terapia va adattata alle caratteristiche specifiche del bambino e del suo contesto di vita. L'effettiva scelta terapeutica è basata sulla valutazione di diversi fattori, tra cui la comorbilità, la situazione familiare e la collaborazione con la scuola. Il trattamento farmacologico rappresenta una delle scelte possibili che, comunque, va ad integrarsi agli altri interventi terapeutici che devono essere attivati. Tuttavia gli approcci diagnostici e terapeutici e assistenziali variano ampiamente tra i Centri di Riferimento.

Per meglio comprendere quali sono i determinanti significativi che caratterizzano i percorsi assistenziali per i pazienti con ADHD e per le loro famiglie, e contemporaneamente agire per migliorarne l'appropriatezza, a partire dal gennaio 2010 con il contributo della Regione Lombardia è stato attivato uno specifico progetto di NPIA per la creazione di una rete di Centri di Riferimento per l'ADHD con la finalità principale di definire e condividere pratiche basate sull'evidenza.

Le attività previste dal progetto sono organizzate in 3 sottoprogetti paralleli e sinergici:

- **Analisi dei percorsi esistenti in Lombardia per l'ADHD**
  La costruzione e l'aggiornamento continuo di un Registro regionale per l'ADHD consente di raccogliere informazioni approfondite relative a: dati anagrafici e anamnestici, percorsi di valutazione, diagnosi, interventi terapeutici sia non farmacologici che farmacologici.
- **Formazione e informazione**
  La formazione degli operatori sanitari e la sensibilizzazione della popolazione mira a diagnosi e interventi più tempestivi e appropriati.
- **Definizione di percorsi diagnostico-terapeutici condivisi**
  La condivisione di percorsi di riferimento comuni vuole garantire approcci e gestioni più omogenei da parte di tutti i Centri di Riferimento della Regione Lombardia.

PRIMA GIORNATA – 28 MAGGIO 2013

09.00 - 10.30

I BISOGNI PER IL PAZIENTE CON ADHD E PER LA SUA FAMIGLIA

Maurizio Bonati

La percezione del/la
- Genitore — *Patrizia Di Noia*
- Insegnante — *Maria Teresa Foà*
- Pediatra — *Ippolita Roncoroni*
- Psicologo — *Gian Marco Mazzocchi*
- Neuropsichiatra — *Paola Morosini*

10.30 - 11.00

Dal Registro regionale — *Anna Didoni*

LE CRITICITÀ NELL'APPROCCIO ALL'ADHD

Diagnosi categoriali o dimensionali? — *Massimo Molteni*

11.00 - 13.30

L'IMPIEGO CRITICO DEGLI STRUMENTI DIAGNOSTICI

Paolo Moderato

L'appropriatezza degli strumenti nei processi diagnostici — *Paolo Moderato*
L'osservazione clinica e la valutazione neuropsicologica — *Davide Villani*
Questionari e scale di valutazione — *Daniele Arisi*
qEEG e mapping cerebrale — *Luciano Montaldi*

14.30 - 15.30

Dal Registro regionale — *Paola Effedri, Elena Filippini*
Cosa mi porto a casa? — *Daniela Candeloro*

DISCUSSIONE

15.30 - 18.00

COMORBILITÀ

Gian Vincenzo Zuccotti

Comorbidità vs coesistenza e interazioni dei disturbi — *Gian Vincenzo Zuccotti*
Disturbi dell'apprendimento — *Emiddio Fornaro*
Disturbo oppositivo-provocatorio — *Monica Saccani*
I disturbi organici — *Roberto Segala*

Dal Registro regionale — *Cristiano Termine*
Cosa mi porto a casa? — *Stefano Guerini*

DISCUSSIONE

SECONDA GIORNATA – 29 MAGGIO 2013

09.00 - 13.00

TERAPIA

Andrea Gardini

Per una cura appropriata, sostenibile, equa, attenta alla persona e all'ambiente — *Andrea Gardini*
Interventi sul contesto
- Child traning — *Silvia Merati, Gaia Oldani*
- Parent training — *Claudio Bissoli*
- Teacher training — *Gianluca Daffi*

Approccio integrato psicodinamico — *Umberto Balottin*
L'uso razionale degli psicofarmaci — *Antonio Clavenna*

Dal Registro regionale — *Stefano Conte*
Cosa mi porto a casa? — *Erika Buzzi*

DISCUSSIONE

14.30 - 18.00

RISPOSTE ORGANIZZATIVE PER I BISOGNI

Antonella Costantino

Modelli organizzativi e Servizi di NPIA centrati sulla famiglia — *Antonella Costantino*
Le criticità per i servizi — *Francesco Rinaldi*
I percorsi di passaggio alla maggiore età
- Le evidenze — *Laura Reale*
- La pratica
  - Neuropsichiatria — *Mauro Camuffo*
  - Psichiatria — *Antonio Vita*

Dal Registro regionale — *Corrado Meraviglia*
Cosa mi porto a casa? — *Tristana Castrignanò*

DISCUSSIONE GENERALE

CONCLUSIONI E PROSPETTIVE

Alessandra Tiberti, Maurizio Bonati

Con il patrocinio della:

SINPIA
Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza

Per ricevere la newsletter iscriversi al seguente indirizzo:
http://crc.marionegri.it/bonati/adhdnews/subscribe.html

Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
Il Progetto è realizzato con il contributo, parziale, della Regione Lombardia
(in attuazione della D.G. sanità n. 3250 del 11/04/2011)
Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia"
"*Condivisione dei percorsi diagnostico-terapeutici per l'ADHD in Lombardia*".

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI
DIPARTIMENTO DI SALUTE PUBBLICA
Laboratorio per la Salute Materno Infantile
Via Giuseppe La Masa, 19 - 20156 Milano MI - Italia - www.marionegri.it
tel +39 02 39014.511 - fax +39 02 3550924 - mother_child@marionegri.i