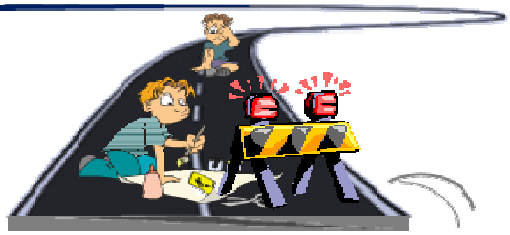
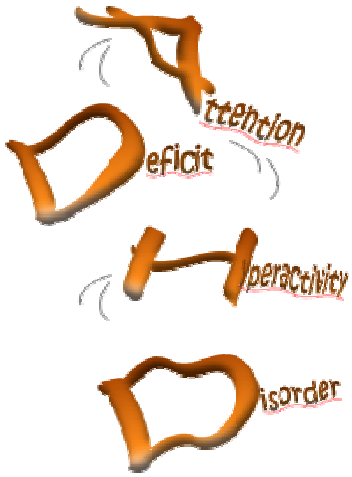
NEWSLETTER





INDICE:

MARIONEGRI
ISTITUTO DI RICERCHE FARMACOLOGICHE

BIBLIOGRAFIA ADHD DICEMBRE 2011

Chapter book 2012;61-91.
Attention-deficit/hyperactivity disorder.
Miller M, Hinshaw SP.
(from the chapter) This chapter discusses attention-deficit disorder in children and current interventions to address symptoms. Unlike the other disorders covered in this edition of Child and Adolescent Therapy: Cognitive-Behavioral Procedures, research on cognitive-behavioral treatments for youth with attention-deficit/hyperactivity disorder (ADHD) has been largely dormant in recent years. The main reason is that children and adolescents with ADHD have typically proved refractory to the types of treatment procedures categorized as "cognitive." Investigations of even the more behavioral treatments based on contingency management for which far better evidence regarding ADHD-related efficacy exists across the last two decades indicate the superiority of pharmacological treatments with respect to important domains of outcome, at least in the short term. So, for as heritable and neurobiologically based a condition as ADHD, are only medication treatments viable? This core question is one that we directly discuss in this chapter. At the outset, we provide the following categorical pronouncements about the state of the art of current intervention efficacy for ADHD, attempting to dispel several key myths regarding treatment for children and adolescents with this condition. As in previous editions of this volume, we review the existing behavioral and cognitive-behavioral treatment literature with respect to ADHD and provide exemplars of the kinds of self-management procedures that yielded initial evidence of promise, with the potential for extension and expansion in future applications. An overarching point for the entire chapter is that the more we learn about the impairments associated with attention deficits and hyperactivity as well as the neurological, neuropsychological, behavioral, familial, and social/interpersonal underpinnings of ADHD the more it becomes clear that (1) ADHD-related impairments are not limited to childhood; (2) the core deficits lead to lowered self-awareness of problems in functioning and, as a result, motivation to sustain change efforts is often low; and (3) the current arsenal of empirically supported pharmacological and behavioral treatments is still well below the threshold of providing clinically meaningful, lasting benefits for most children with this disorder. Thus, the ADHD treatment field has much to achieve, and innovative means both pharmacological and psychosocial of altering the disorganized, impulsive, dysregulated behavior related to this condition are strongly needed. As in the first three editions of this volume, we highlight two key facts. First, traditional contingency-based "behavioral" treatments include a number of cognitive elements; they are not exclusively behavioral in nature. Second, to be efficacious and effective for children with clinical levels of ADHD, cognitive procedures must include contingency management and other empirically supported behavioral strategies. Self-instructional training alone is not a viable treatment strategy for this population, as noted earlier and as detailed below. In essence, given the pressing need to develop, investigate, and disseminate effective psychosocial and multimodal treatments for the multiple problems and impairments related to ADHD, our goal is not to debate what is "behavioral" and what is "cognitive" but to focus on an integrated conception of cognitive-behavioral interventions as inclusive of incentive, motivation, affect, and integration of work in family and school contexts, as well as modification of cognitions.

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

Acta Psychologica. 2011 Nov;138:419-28.

LINKING IMPULSIVITY AND INHIBITORY CONTROL USING MANUAL AND OCULOMOTOR RESPONSE INHIBITION TASKS.

Roberts W, Fillmore MT, Milich R.

Separate cognitive processes govern the inhibitory control of manual and oculomotor movements. Despite this fundamental distinction, little is known about how these inhibitory control processes relate to more complex domains of behavioral functioning. This study sought to determine how these inhibitory control mechanisms relate to broadly defined domains of impulsive behavior. Thirty adults with attention-deficit/hyperactivity disorder (ADHD) and 28 comparison adults performed behavioral measures of inhibitory control and completed impulsivity inventories. Results suggest that oculomotor inhibitory control, but not manual inhibitory control, is related to specific domains of self-reported impulsivity. This finding was limited to the ADHD group; no significant relations between inhibitory control and impulsivity were found in comparison adults. These results highlight the heterogeneity of inhibitory control processes and their differential relations to different facets of impulsivity.

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Ann Neurol. 2011;70:S140-S141.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN EPILEPTIC CHILDREN WITH DEVELOPMENTAL DELAY.

Kim GH, Eun SH, Byeon JH.

Objective: It is known that the attention deficit hyperactivity disorder (ADHD) is more frequent in children with epilepsy than in the general pediatric population. The aim of this preliminary study was to investigate whether the prevalence of ADHD in epileptic children is higher even for people with well controlled epilepsy and without a significant developmental delay.

Methods: Epileptic children, aged 6 to12 years, who visited for 6 consecutive months were included in the study. Among them we included only those without significant developmental delay as well as being seizure -free for over 3 months. We utilized parent questionnaires based on DSMIV criteria to diagnose ADHD and Korean version of Child Behavior Checklist and Child Depression Inventory.

Results: We enrolled 56 patients (mean age, 9.662.3) including 27 boys and 29 girls. Twelve (21.4%) were diagnosed with ADHD (9 combined, 3 inattentive types; 6 boys, 6 girls). The number of ADHD patients vary by epilepsy types: childhood or juvenile absence epilepsy (42.8%, 3 of 7); cryptogenic focal epilepsy (20.8%, 5 of 24); generalized epilepsy (20.0%, 2 of 10); benign rolandic epilepsy (13.3%, 2 of 15).

Conclusions: The results indicate that the prevalence of ADHD can be higher even for children with well controlled epilepsy and without significant developmental delay. And the most predominant type of ADHD is the combined type, which is the same as in the general pediatric population.

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Behav Neurosci. 2011 Dec;125:979-87.

CONDITIONED INHIBITION IN A RODENT MODEL OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Green JT, Chess AC, Conquest CJ, et al.

A deficit in inhibition may underlie some of the symptoms of attention-deficit/hyperactivity disorder (ADHD), particularly impulsivity. However, the data on inhibitory deficits in children with ADHD are mixed. Moreover, there has been little characterization of inhibitory processes in animal models of ADHD. Pavlov's conditioned inhibition procedure allows a direct assessment of the inhibitory status of a stimulus via summation and retardation tests. Therefore, in the current study, we examined conditioned inhibition in spontaneously hypertensive rats (SHRs), the most well-validated animal model of ADHD. SHRs and Wistar rats were trained in a simultaneous feature-negative discrimination in eyeblink conditioning. Each session consisted of a mixture of 2 trial types: a tone paired with a periocular stimulation (A+) or a tone and light presented simultaneously without a periocular stimulation (XA). Both SHRs and Wistars were able to discriminate A+ from XA trials. In subsequent summation (X presented simultaneously with a different conditioned excitor, B) and retardation (X paired with the periocular stimulation) tests, the presence of inhibition to X was confirmed in both SHRs and Wistars: X reduced responding to B, and X was slow to develop excitation when paired with periocular stimulation. These results are the first to demonstrate Pavlovian conditioned inhibition in SHRs and to use summation and retardation tests to confirm X as a

conditioned inhibitor. The data indicate that conditioned inhibition is intact in SHRs; thus, inhibitory processes that do not require prefrontal cortex or cerebellum may be normal in this strain.

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Behavioural Pharmacology. 2011 Dec;22:794-804.

STRAIN DIFFERENCES IN SELF-ADMINISTRATION OF METHYLPHENIDATE AND SUCROSE PELLETS IN A RAT MODEL OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Marusich JA, McCuddy WT, Beckmann JS, et al.

Despite its abuse potential, methylphenidate (MPH) is widely prescribed for treatment of attention-deficit hyperactivity disorder (ADHD). The purpose of the present study was to examine MPH self-administration in a rat model of ADHD. Experiment 1 examined the acquisition of MPH self-administration and assessed the MPH dose effect curve in spontaneously hypertensive rats (SHR), an inbred rat model of ADHD, Wistar Kyotos (WKY), the progenitor strain for SHR, and Sprague Dawley (SD), an outbred control strain. Experiment 2 replicated Experiment 1, but replaced MPH infusions with sucrose pellets. Initial acquisition of MPH self-administration was greater in SHR and SD than WKY. However, with extended training using an incrementing fixed ratio schedule SHR and WKY did not differ in responding for MPH using the training dose (0.3 mg/kg/infusion) or other unit doses, except that SHR showed greater responding than WKY at 0.1 mg/kg/infusion. SHR also showed greater acquisition and maintenance of sucrose-reinforced responding compared with both WKY and SD. Greater initial acquisition of MPH self-administration in SHR than WKY may not be due to a strain-specific difference in sensitivity to the reinforcing effect of MPH.

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Child Neuropsychol. 2011 Nov;17:546-63.

COMPONENT ANALYSIS OF VERBAL VERSUS SPATIAL WORKING MEMORY TRAINING IN ADOLESCENTS WITH ADHD: A RANDOMIZED, CONTROLLED TRIAL.

Gibson BS, Gondoli DM, Johnson AC, et al.

Adaptive training of working memory (WM) using the Cogmed-RM intervention has recently shown some efficacy as an alternative treatment for ADHD, but this intervention may not be optimally designed. A recent component analysis of WM has suggested that maintenance in primary memory (PM) appears to be largely intact whereas recall from secondary memory (SM) appears to be deficient in ADHD relative to age-matched controls. However, extrapolating from basic research, there is reason to believe that Cogmed-RM may target the PM component more than the SM component; though training with spatial exercises may target the SM component more than training with verbal exercises. To investigate, participants diagnosed with ADHD were randomly assigned to either a verbal training condition (n=24) or a spatial training condition (n=23) using a randomized, controlled design, and both groups were instructed to complete at least 20 days of training. The PM and SM components of WM were assessed immediately before and after training using both verbal and spatial free recall tasks. The main findings showed that both versions of the intervention enhanced the maintenance of information in PM regardless of test modality, but not the recall of information from SM. Therefore, the component of WM that is improved by Cogmed-RM is not the same component of WM that is deficient in ADHD.

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Clin Neurophysiol. 2011 Dec;122:2390-99.

DIS-REGULATION OF RESPONSE INHIBITION IN ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): AN ERP STUDY.

Fisher T, Aharon-Peretz J, Pratt H.

Objective: To define the brain activity involved in impaired response inhibition of Attention Deficit Hyperactivity Disorder (ADHD) in adults.

Methods: Performance measures and brain activity of 14 adult ADHD subjects and 14 controls, matched for age, gender, and overall intelligence were compared in an auditory Go NoGo paradigm to tones. The

task required a button press (Go) to 80% and inhibition of response (NoGo) to 20% of the tones, according to the tones pitch.
Results: In NoGo trials ADHD subjects made significantly more commission errors compared to controls. ERPs of ADHD subjects showed smaller amplitudes of P3 (but not N2), and longer latencies of both N2 and P3. Source current density estimation revealed reduced activity in the right frontal dorsolateral cortex and in the posterior cingulate of the ADHD group. In addition, ADHD subjects showed an unexpected significantly enhanced response inhibition in Go trials, with excessive omission errors associated with significantly larger N2 amplitudes.
Conclusion: In ADHD the neural networks sub-serving response inhibition are impaired. Significance: ADHD is a general dis-regulation of behavioral inhibition, not limited to response inhibition.

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Eur Psychiatry. 2011 Nov;26:482-83.
HIGH FREQUENCY OF CHILDHOOD ADHD HISTORY IN WOMEN WITH FIBROMYALGIA.
Reyero F, Ponce G, Rodriguez-Jimenez R, et al.
Fibromyalgia and ADHD share some clinical features, and a reduced dopamine function has been proposed for both disorders. Here we found, in a large sample of fibromyalgia female patients, a higher frequency of childhood ADHD antecedent when compared with healthy women. Our data suggest that Fibromyalgia and ADHD have some common etiopathological mechanism.

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Exp Ther Med. 2010;1:701-05.
ASSOCIATION BETWEEN POLYMORPHISMS OF THE DBH AND DAT1 GENES AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN FROM JORDAN.
Gharaibeh MY, Batayneh S, Khabour OF, et al.
Attention deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders in children. In this study, the association between 10-repeats in the DAT1 gene and the (GT)n repeat in the DBH gene and ADHD was examined in children from Jordan. In addition, the levels of dopamine-(beta)-hydroxylase enzyme activity in the plasma of ADHD children were evaluated. Fifty children with ADHD and 50 age and gender-matched control subjects were recruited. The results showed significant differences between the ADHD group and controls with respect to the plasma levels of dopamine-(beta)-hydroxylase enzyme activity (25.4(plus or minus)2.3 vs. 84.7(plus or minus)5.0 (mu)mol/min; $p<0.01$). Moreover, the 10-repeat DAT1 gene and (GT)n DBH gene polymorphisms were significantly associated with ADHD development ($p<0.05$). In conclusion, the DBH and DAT1 genes appear to play a role in the development of ADHD in the Jordanian population.

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Exp Brain Res. 2011 Nov;215:45-52.
ABNORMAL AIR RIGHTING BEHAVIOUR IN THE SPONTANEOUSLY HYPERTENSIVE RAT MODEL OF ADHD.
Dommett EJ, Rostron CL.
The spontaneously hypertensive rat (SHR) is the most commonly used model of attention-deficit hyperactivity disorder (ADHD), displaying the main symptoms of the disorder which are responsive to psychostimulant treatments. Research to date has focused on behavioural tests investigating functioning of the striatum or prefrontal cortex in these rats. However, there is now evidence that the superior colliculus, a structure associated with head and eye movements, may also be dysfunctional in ADHD. Therefore, the aim of this study was to investigate whether the SHR demonstrated impairment in collicular-dependent behaviour. To this end, we examined air righting behaviour, which has previously been shown to be modulated in a height-dependent manner reliant on a functional superior colliculus. We assessed SHR, Wistar Kyotos and Wistars on static righting and air righting at 50 and 10 cm drop heights. There were no differences in static righting, indicating that there were no gross motor differences that would confound air

righting. Qualitative analysis of video footage of the righting did not reveal any changes previously associated with collicular damage, unique to the SHR. However, the SHR did show impairment in height-dependent modulation of righting in contrast to both control strains, such that the SHR failed to modulate righting latency according to drop height. This failure is indicative of collicular abnormality. Given that many rodent tests of attentional mechanisms involve head and eye orienting, which are heavily dependent on the colliculus, a collicular dysfunction has strong implications for the type of attentional task used in this strain.

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Journal of Abnormal Child Psychology: An official publication of the International Society for Research in Child and Adolescent Psychopathology. 2011 Nov;39:1111-23.

EXTERNAL VALIDATION OF BIFACTOR MODEL OF ADHD: EXPLAINING HETEROGENEITY IN PSYCHIATRIC COMORBIDITY, COGNITIVE CONTROL, AND PERSONALITY TRAIT PROFILES WITHIN DSM-IV ADHD.

Martel MM, Roberts B, Gremillion M, et al.

The current paper provides external validation of the bifactor model of ADHD by examining associations between ADHD latent factor/profile scores and external validation indices. 548 children (321 boys; 302 with ADHD), 6 to 18 years old, recruited from the community participated in a comprehensive diagnostic procedure. Mothers completed the Child Behavior Checklist, Early Adolescent Temperament Questionnaire, and California Q-Sort. Children completed the Stop and Trail-Making Task. Specific inattention was associated with depression/withdrawal, slower cognitive task performance, introversion, agreeableness, and high reactive control; specific hyperactivity-impulsivity was associated with rule-breaking/aggressive behavior, social problems, errors during set-shifting, extraversion, disagreeableness, and low reactive control. It is concluded that the bifactor model provides better explanation of heterogeneity within ADHD than DSM-IV ADHD symptom counts or subtypes.

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Journal of Abnormal Child Psychology: An official publication of the International Society for Research in Child and Adolescent Psychopathology. 2011 Nov;39:1085-98.

MUSIC AND VIDEO AS DISTRACTORS FOR BOYS WITH ADHD IN THE CLASSROOM: COMPARISON WITH CONTROLS, INDIVIDUAL DIFFERENCES, AND MEDICATION EFFECTS.

Pelham WE, Jr., Waschbusch DA, Hoza B, et al.

This study examined the effects of music and video on the classroom behavior and performance of boys with and without attention deficit hyperactivity disorder (ADHD) and examined the effects of 0.3 mg/kg methylphenidate (MPH). In one study, 41 boys with ADHD and 26 controls worked in the presence of no distractor, music, or video. Video produced significant distraction, particularly for the boys with ADHD, and MPH improved the performance of boys with ADHD across distractor conditions.There were individual differences in response to the music such that some boys were adversely affected and others benefited relative to no-distractor.In a second study, music and MPH were assessed in an additional 86 boys with ADHD to examine further the music results. In the presence or absence of music, MPH improved performance relative to placebo. Similar individual differences were found as in Experiment 1.

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J Abnorm Psychol. 2011 Nov;120:890-901.

DISENTANGLING THE ADULT ATTENTION-DEFICIT HYPERACTIVITY DISORDER ENDOPHENOTYPE: PARAMETRIC MEASUREMENT OF ATTENTION.

Finke K, Schwarzkopf W, MÃ¼ller U, et al.

Attention deficit hyperactivity disorder (ADHD) persists frequently into adulthood. The decomposition of endophenotypes by means of experimental neuro-cognitive assessment has the potential to improve diagnostic assessment, evaluation of treatment response, and disentanglement of genetic and environmental influences. We assessed four parameters of attentional capacity and selectivity derived from simple psychophysical tasks (verbal report of briefly presented letter displays) and based on a â€œtheory

of visual attention. These parameters are mathematically independent, quantitative measures, and previous studies have shown that they are highly sensitive for subtle attention deficits. Potential reductions of attentional capacity, that is, of perceptual processing speed and working memory storage capacity, were assessed with a whole report paradigm. Furthermore, possible pathologies of attentional selectivity, that is, selection of task-relevant information and bias in the spatial distribution of attention, were measured with a partial report paradigm. A group of 30 unmedicated adult ADHD patients and a group of 30 demographically matched healthy controls were tested. ADHD patients showed significant reductions of working memory storage capacity of a moderate to large effect size. Perceptual processing speed, task-based, and spatial selection were unaffected. The results imply a working memory deficit as an important source of behavioral impairments. The theory of visual attention parameter working memory storage capacity might constitute a quantifiable and testable endophenotype of ADHD.

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J Autism Dev Disord. 2011 Dec;41:1743-47.

BRIEF REPORT: PERFORMANCE PATTERN DIFFERENCES BETWEEN CHILDREN WITH AUTISM SPECTRUM DISORDERS AND ATTENTION DEFICIT-HYPERACTIVITY DISORDER ON MEASURES OF VERBAL INTELLIGENCE.

Zayat M, Kalb L, Wodka EL.

Performance patterns on verbal subtests from the WISC-IV were compared between a clinically-referred sample of children with either autism spectrum disorders (ASD) or attention deficit/hyperactivity disorder (ADHD). Children with ASD demonstrated a statistically significant stepwise pattern where performance on Similarities was best, followed by Vocabulary, then Comprehension. Although children with ASD and ADHD share multiple behavioral features, this pattern was not observed for those with ADHD. Greater deficits in social reasoning and verbal formulation for children with ASD (compared to ADHD) are hypothesized to account for this observed difference in their performance pattern. Clinical implications, including use of this identified pattern in combination with other symptoms suggestive of ASD in referral decision making are discussed.

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J Autism Dev Disord. 2011 Dec;41:1718-26.

DIFFERENTIAL DIAGNOSIS OF AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER BY MEANS OF INHIBITORY CONTROL AND THEORY OF MIND.

Buhler E, Bachmann C, Goyert H, et al.

Autism spectrum disorders (ASD) and attention deficit hyperactivity disorders (ADHD) are both associated with deficits in executive control and with problems in social contexts. This study analyses the variables inhibitory control and theory of mind (ToM), including a developmental aspect in the case of the latter, to differentiate between the disorders. Participants with an ASD (N=86), an ADHD (N=84) and with both disorders (N=52) in the age range of 5 22 years were compared. Results were differences in inhibitory control (ADHD<ASD) and in the ToM performance among younger (ASD<ADHD) but not among older children. We discuss whether common deficits in ToM differ in the developmental course.

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Journal of Clinical Child and Adolescent Psychology. 2011 Nov;40:837-47.

EXAMINING RELATIONSHIPS BETWEEN EXECUTIVE FUNCTIONING AND DELAY AVERSION IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Karalunas SL, Huang-Pollock CL.

Although motivation and cognition are often examined separately, recent theory suggests that a delay-averse motivational style may negatively impact development of executive functions (EFs), such as working memory (WM) and response inhibition (RI) for children with Attention Deficit Hyperactivity Disorder (ADHD; Sonuga-Barke, 2002). This model predicts that performance on delay aversion and EF tasks should be correlated for school-age children with ADHD. However, tests of these relationships remain sparse. Forty-

five children ages 8 to 12 with ADHD and 46 non-ADHD controls completed tasks measuring EFs and delay aversion. Children with ADHD had poorer WM and RI than non-ADHD controls, as well as nonsignificantly worse delay aversion. Consistent with previous research, RI was not related to delay aversion. However, delay aversion did predict WM scores for children with and without ADHD. Implications for the dual-pathway hypothesis and future research on cognitive and motivational processing in ADHD are discussed.

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J Consult Clin Psychol. 2011 Dec;79:784-95.

THE ROLE OF FAMILY EXPERIENCES AND ADHD IN THE EARLY DEVELOPMENT OF OPPOSITIONAL DEFIANT DISORDER.

Harvey EA, Metcalfe LA, Herbert SD, et al.

Objective: The present study examined the role of family experiences in the early development and maintenance of oppositional defiant disorder (ODD) symptoms in preschool-age children with behavior problems.

Method: Participants were 199 3-year-old children with behavior problems who took part in 4 annual child and family assessments.

Results: Children with behavior problems who were exposed to overreactive parenting practices, maternal depression, marital conflict, and lower family income tended to have more ODD symptoms 3 years later. Moreover, initial changes in paternal overreactivity and changes in maternal depression corresponded to initial changes in ODD symptoms. Children who met criteria for attention-deficit/hyperactivity disorder at 6 years of age were less likely to show improvement in ODD symptoms from 3 to 6 years of age, and they were more likely to have been exposed to negative parenting practices, marital conflict, and parental depression during the preschool years. Maternal depression and overreactivity mediated the relation between early hyperactivity and later ODD symptoms.

Conclusions: Results point to the importance of early family functioning in the development of ODD.

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Journal of Family Nursing. 2011 Nov;17:441-62.

CONTENDING AND ADAPTING EVERY DAY: NORWEGIAN PARENTS LIVED EXPERIENCE OF HAVING A CHILD WITH ADHD.

Moen ÃyL, Hall-Lord ML, Hedelin B.

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood disorders, and little attention has been paid to the parents and their experiences. The aim of this study was to gain a deeper understanding of the Norwegian parents lived experiences of having a child with an ADHD diagnosis. A descriptive design using phenomenological approach was chosen as the research method. Individual qualitative interviews with nine parents, who were members of the ADHD Association, were conducted. The interviews were analyzed according to Colaizzi method. The essential structure of the parents experiences was Contending and Adapting Every Day Windsurfing in unpredictable waters which was embedded in the interrelated main themes: Maintaining the Self and Parenthood, and Interacting With the Surrounding World. Being the parent of a child with ADHD is a demanding situation. Nurses need to address the needs of these parents and focus on the family unit.

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J Fam Pract. 2011;60:E1-E3.

MANAGING ADHD IN CHILDREN: ARE YOU DOING ENOUGH?

Withrow LM, Hash PAK, Holten KB.

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Journal of Family Psychology. 2011 Dec;25:873-84.

MECHANISMS UNDERLYING THE INFLUENCE OF DISRUPTIVE CHILD BEHAVIOR ON INTERPARENTAL COMMUNICATION.

Wymbs BT.

Prospective and experimental manipulations of child behavior have demonstrated that disruptive child behavior causes interparental discord. However, research has yet to test for mechanisms underlying this causal pathway. There is reason to suspect parent affect and parenting behavior explain child effects on interparental relations. To investigate this hypothesis, parent couples of 9- to 12-year-old boys and girls with attention-deficit/hyperactivity disorder (ADHD; n=51) and without ADHD (n=39) were randomly assigned to interact with a confederate child exhibiting disruptive or typical behavior. Parents rated their own affect, as well as the quality of their partner's parenting and communication, immediately following the interaction. Observers also coded the quality of parenting and communication behaviors parents exhibited during the interaction. Parents who interacted with disruptive confederates reported lower positive affect and higher negative affect than those who interacted with typical confederates. Parents were also noted by their partners and observers to parent disruptive confederates more negatively than typical confederates. Multilevel mediation models with observational coding and partner ratings both found that negative parenting explained the causal pathway between disruptive child behavior and negative communication. Exploratory analyses revealed that the strength of this pathway did not differ between parents of children with and without ADHD. Parent affect was not found to explain child effects on interparental communication. Though methodological issues limit the generalizability of these findings, results indicate that negative parenting may be one mechanism through which disruptive children cause interparental discord.

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J Paediatr Child Health. 2011.

PRACTITIONER CHARACTERISTICS AND THE TREATMENT OF CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Mitchell PB, Levy F, Hadzi-Pavlovic D, et al.

Aim: To investigate whether recent Australian practice conforms to the draft 2009 National Health and Medical Research Council (NHMRC) guidelines on the management of attention deficit hyperactivity disorder.

Methods: Data from the 2007 Special Review on Attention Deficit Hyperactivity Disorder in Children and Adolescents in New South Wales (NSW) were examined.

Results: Two hundred seven approved stimulant prescribers in NSW responded to a detailed survey on treatment practice (including 121 paediatricians and 67 psychiatrists). Overall, the practice identified in this survey of NSW approved stimulant prescribers was consistent with that recommended in the draft NHMRC guidelines. Paediatricians were more likely to inform families of developmental therapies. Most prescribers (67%) considered stimulants to be the first line of treatment for at least half of their patients. Psychiatrists were more likely to use stimulants as first-line treatments, while those recently qualified were less likely to prescribe. Half of the prescribers were willing to consider prescribing for children 4 years of age and younger. Paediatricians were more likely to consider prescribing to this age group, while those recently qualified were less likely. There were no significant differences in prescribing practice between child and adult psychiatrists. Most prescribers (67-97%) routinely monitored patients on stimulants for weight, height, blood pressure and academic progress. Psychiatrists were less likely to review these parameters than paediatricians, with this difference being largely due to adult psychiatrists.

Conclusions: There are significant differences in prescribing practice between paediatricians and psychiatrists. These variations may reflect differing training programs and patient populations, and merit close consideration in any review arising from the publication of the recent NHMRC guideline.

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Journal of Pineal Research: Molecular, Biological, Physiological and Clinical Aspects of Melatonin. 2011 Nov;51:394-99.

GENETIC VARIATIONS OF THE MELATONIN PATHWAY IN PATIENTS WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDERS.

Chaste P, Clement N, Botros HG, et al.

Melatonin is a powerful antioxidant and a synchronizer of many physiological processes. Alteration in melatonin signaling has been reported in a broad range of diseases, but little is known about the genetic variability of this pathway in humans. Here, we sequenced all the genes of the melatonin pathway AA-NAT, ASMT, MTNR1A, MTNR1B and GPR50 in 321 individuals from Sweden including 101 patients with attention-deficit/hyperactivity disorder (ADHD) and 220 controls from the general population. We could find several damaging mutations in patients with ADHD, but no significant enrichment compared with the general population. Among these variations, we found a splice site mutation in ASMT (IVS5+2T>C) and one stop mutation in MTNR1A (Y170X) detected exclusively in patients with ADHD for which biochemical analyses indicated that they abolish the activity of ASMT and MTNR1A. These genetic and functional results represent the first comprehensive ascertainment of melatonin signaling deficiency in ADHD.

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J Psychopathol Behav Assess. 2011 Dec;33:420-29.

WOMEN WITH CHILDHOOD ADHD: COMPARISONS BY DIAGNOSTIC GROUP AND GENDER.

Babinski DE, Pelham WE, Jr., Molina BSG, et al.

This study compared adult women with childhood ADHD to adult women without childhood ADHD and to adult men with childhood ADHD. The participants, all from a larger longitudinal study, included 30 women and 30 men (approximately age 23 to 24) with childhood ADHD, and 27 women without ADHD. Women with childhood ADHD were matched to comparison women on age, ethnicity, and parental education, and to men with childhood ADHD on age, ethnicity, and IQ. Self- and parent-reports of internalizing, interpersonal, academic, and job impairment, as well as substance use and delinquency indicated group differences on measures of self-esteem, interpersonal and vocational functioning, as well as substance use. Follow-up planned comparison tests revealed that almost all of these differences emerged by diagnostic status, and not by gender. This study adds to research on the negative adult outcomes of ADHD and demonstrates that the outcomes of men and women with childhood ADHD are relatively similar.

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J Psychopathol Behav Assess. 2011 Dec;33:430-37.

AN EVALUATION OF BEHAVIORAL APPROACH IN ADULTS WITH ADHD.

Mitchell JT, Robertson CD, Kimbrel NA, et al.

Motivational models emphasizing altered reinforcement sensitivity have been increasingly implicated in etiological accounts of attention-deficit/hyperactivity disorder (ADHD). Overactive behavioral approach tendencies are identified among these motivational models and are addressed within reinforcement sensitivity theory (RST). RST proposes that overactive behavioral approach is associated with over responsiveness to immediately reinforcing stimuli and results from an overactive appetitive motivational subsystem of the brainâ€"the behavioral approach system. The current study tested the hypothesis that behavioral approach would be higher in a clinical sample of adults diagnosed with ADHD relative to a control group. Experimental and self-report measures of behavioral approach were administered. Behavioral approach was higher in the ADHD group across both methods of assessment. Effect size estimates fell within the medium to large range. Implications for how these findings might be incorporated into future ADHD models are discussed.

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Journal of the History of the Behavioral Sciences. 2011;47:44-69.

THE END OF DRUGGING CHILDREN: TOWARD THE GENEALOGY OF THE ADHD SUBJECT.

Comstock EJ.

This genealogy of the ADHD subject will demonstrate that over the course of the twentieth century a new relation between power, knowledge, the body, and ethical practices of self-formation emerged around the ADHD-type in ways that are not captured by the received critical perspective. By examining the history of knowledge and practices surrounding the ADHD-type, this work will argue that the deviant subject that was located relative to external institutional moral/juridical values or standards is replaced over the course of the century by a new intelligibility of rational self-management. A further analysis of this emergent intelligibility attempts to advance the critical understanding of the increasingly prevalent ADHD phenomenon by showing how novel drug and brain imaging technologies work to link behaviors to identity, establishing new relations of power to the subject not captured by the received medicalization perspective. This work will be of interest to anybody interested in the relations among knowledge, drugs, power, and the ADHD subject.

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J Int Neuropsychol Soc. 2011 Nov;17:1167-68.

NEURODEVELOPMENTAL AND GENETIC DISORDERS: A BOOK REVIEW.

Phillips JM.

Reviews the book, "Handbook of Neurodevelopmental and Genetic Disorders in Children" edited by Sam Goldstein and Cecil R. Reynolds (see record 2010-24694-000). The book incorporates the latest scientific research and clinical practices as well as more focus on efficacious treatment interventions. In addition to the discussion of more common developmental, learning, and behavioral disorders, there are several additional strengths of this volume. Given the complexity of genetic disorders, this book is not ideal for parents but is certainly appropriate for the lay professional. The authors should be commended for bringing together a group of scholarly chapters from experts in their respective fields. Certainly, it is difficult to balance an emphasis on breadth versus depth when addressing the developmental disorders. The refreshing aspect of this book is its homage to more common childhood neurodevelopmental disorders including attention deficit hyperactivity disorder, learning disorders, and other behavioral and mood disorders. The handbook can be thought of as a stand-alone compendium highlighting the impact of genetics on neurodevelopment in children. In summary book is strongly recommended, particularly for pediatric specialists and neuropsychologists.

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J Int Neuropsychol Soc. 2011 Nov;17:1047-57.

COMPREHENSIVE EXAMINATION OF FRONTAL REGIONS IN BOYS AND GIRLS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Mahone EM, Ranta ME, Crocetti D, et al.

The current study examined regional frontal lobe volumes based on functionally relevant subdivisions in contemporaneously recruited samples of boys and girls with and without attention-deficit/hyperactivity disorder (ADHD). Forty-four boys (21 ADHD, 23 control) and 42 girls (21 ADHD, 21 control), ages 8 13 years, participated. Sulcal gyral landmarks were used to manually delimit functionally relevant regions within the frontal lobe: primary motor cortex, anterior cingulate, deep white matter, premotor regions [supplementary motor complex (SMC), frontal eye field, lateral premotor cortex (LPM)], and prefrontal cortex (PFC) regions [medial PFC, dorsolateral PFC (DLPFC), inferior PFC, lateral orbitofrontal cortex (OFC), and medial OFC]. Compared to sex-matched controls, boys and girls with ADHD showed reduced volumes (gray and white matter) in the left SMC. Conversely, girls (but not boys) with ADHD showed reduced gray matter volume in left LPM; while boys (but not girls) with ADHD showed reduced white matter volume in left medial PFC. Reduced left SMC gray matter volumes predicted increased go/no go commission rate in children with ADHD. Reduced left LPM gray matter volumes predicted increased go/no

go variability, but only among girls with ADHD. Results highlight different patterns of anomalous frontal lobe development among boys and girls with ADHD beyond that detected by measuring whole lobar volumes.

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Psychiatry Research: Neuroimaging. 2011 Nov;194:119-29.

NEURAL CORRELATES OF INHIBITORY CONTROL IN ADULT ATTENTION DEFICIT/HYPERACTIVITY DISORDER: EVIDENCE FROM THE MILWAUKEE LONGITUDINAL SAMPLE.

Mulligan RC, Knopik VS, Sweet LH, et al.

Only a few studies have investigated the neural substrate of response inhibition in adult attention deficit hyperactivity disorder (ADHD) using Stop-Signal and Go/No-Go tasks. Inconsistencies and methodological limitations in the existing literature have resulted in limited conclusions regarding underlying pathophysiology. We examined the neural basis of response inhibition in a group of adults diagnosed with ADHD in childhood and who continue to meet criteria for ADHD. Adults with ADHD (n=12) and controls (n=12) were recruited from an ongoing longitudinal study and were matched for age, IQ, and education. Individuals with comorbid conditions were excluded. Functional magnetic resonance imaging (fMRI) was used to identify and compare the brain activation patterns during correct trials of a response-inhibition task (Go/No-Go). Our results showed that the control group recruited a more extensive network of brain regions than the ADHD group during correct inhibition trials. Adults with ADHD showed reduced brain activation in the right frontal eye field, pre-supplementary motor area, left precentral gyrus, and the inferior parietal lobe bilaterally. During successful inhibition of an inappropriate response, adults with ADHD display reduced activation in frontoparietal networks previously implicated in working memory, goal-oriented attention, and response selection. This profile of brain activation may be specifically associated with ADHD in adulthood.

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Psychopharmacology. 2011 Nov;218:381-90.

METHYLPHENIDATE INCREASES CIGARETTE SMOKING IN PARTICIPANTS WITH ADHD.

Vansickel AR, Stoops WW, Glaser PEA, et al.

Rationale: Methylphenidate (Ritalin[sup]Â®[/sup]) is commonly prescribed for behavioral problems associated with attention deficit/hyperactivity disorder (ADHD). The results of previous studies suggest that methylphenidate increases cigarette smoking in participants without psychiatric diagnoses. Whether methylphenidate increases cigarette smoking in participants diagnosed with ADHD is unknown.

Objective: In this within-subjects, repeated measures experiment, the acute effects of a range of doses of methylphenidate (10, 20, and 40 mg) and placebo were assessed in nine cigarette smokers who were not attempting to quit and met diagnostic criteria for ADHD but no other Axis I psychiatric disorders other than nicotine dependence.

Methods: Each dose of methylphenidate was tested once while placebo was tested twice. One hour after ingesting drug, participants were allowed to smoke ad libitum for 4 h. Measures of smoking included total cigarettes smoked, total puffs, and carbon monoxide levels. Snacks and decaffeinated drinks were available ad libitum; caloric intake during the 4-h smoking session was calculated.

Results: Methylphenidate increased the total number of cigarettes smoked, total number of puffs, and carbon monoxide levels. Methylphenidate decreased the number of food items consumed and caloric intake.

Conclusions: The results of this experiment suggest that acutely administered methylphenidate increases cigarette smoking in participants with ADHD, which is concordant with findings from previous studies that tested healthy young adults. These data indicate that clinicians may need to consider non-stimulant options or counsel their patients before starting methylphenidate when managing ADHD-diagnosed individuals who smoke.

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Res Autism Spectr Disord. 2012 Jan;6:1-10.

EXPLOSIVE, OPPOSITIONAL, AND AGGRESSIVE BEHAVIOR IN CHILDREN WITH AUTISM COMPARED TO OTHER CLINICAL DISORDERS AND TYPICAL CHILDREN.

Mayes SD, Calhoun SL, Aggarwal R, et al.

Maternal ratings of explosiveness, opposition, and aggression were analyzed in 1609 children 6 16 years of age. Behavior problems were common in autism, ADHD-Combined type, and depression, whereas children with ADHD-Inattentive type, anxiety disorder, and acquired brain injury did not differ from typical controls. More than 40% of children with autism, ADHD-Combined type, and depression met criteria for oppositional-defiant disorder (ODD), and less than 15% did in the other groups. Male gender and low SES increased the risk of behavior problems, but correlations were small between behavior problems and age and IQ. Our findings have implications for new DSM-V diagnostic categories and criteria. The DSM-V needs to clarify whether or not an additional diagnosis of ODD should be made in children with autism who meet ODD criteria. The proposed DSM-V states that ADHD and temper dysregulation disorder with dysphoria not be diagnosed in autism, but does not mention ODD. Our study also suggests that diagnoses of temper dysregulation disorder with dysphoria and prepubertal bipolar disorder may be redundant to a diagnosis of ODD.

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Sleep Breathing. 2011;15:455-62.

APNEA-HYPOPNEA INDICES AND SNORING IN CHILDREN DIAGNOSED WITH ADHD: A MATCHED CASE-CONTROL STUDY.

Galland BC, Tripp EG, Gray A, et al.

Objectives: To measure apnea-hypopnea indices and snoring in children diagnosed with attention-deficit hyperactivity disorder (ADHD) in a case-control design. Additionally, the study design allowed us to investigate whether or not methylphenidate had any effect on breathing variables.

Methods: Twenty-eight children (22 boys) aged 6-12 years meeting diagnostic criteria for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV ADHD were studied together with matched controls. Two nights of polysomnography (PSG) were conducted that included recordings of snoring waveforms. A randomly assigned 48-h on-off medication protocol was used for ADHD children. Control children's recordings were matched for PSG night, but medication was not used. A low apnea-hypopnea index (AHI) threshold of >1event per hour was used to define sleep-disordered breathing (SDB) because of a clinical relevance in ADHD.

Results: Categorical analyses for paired binary data showed no significant differences between control and ADHD children for presence of an AHI >1 or snoring. Variables were extracted from a significantly shorter total sleep time (67 min) on the medication night in children with ADHD. Eight (28%) control and 11 (40%) ADHD children snored >60 dB some time during the night. Methylphenidate had no effect on central apneas, AHI, desaturation events, or any snoring data.

Conclusions: Our PSG findings show no strong link between ADHD and SDB although our findings could be limited by a small sample size. Findings from PSG studies in the literature argue both for and against an association between ADHD and SDB. Our results suggest medication is not a factor in the debate. (copyright) 2010 Springer-Verlag

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http://jama.ama-assn.org/content/306/24/2661.4.full?etoc

Health Agencies Update

EXPAND »

ADHD Care

Bridget M. Kuehn

KEYWORDS: attention deficit disorder with hyperactivity, child behavior, child psychiatry, child, preschool, methylphenidate, parents.

Programs that provide training in positive parenting techniques to help parents of preschoolers with attention–deficit/hyperactivity disorder (ADHD) manage their child's behavior are safe and effective, according to a new review. The article assesses the comparative effectiveness of ADHD interventions for young children.

In addition, the review, from the Agency for Healthcare Research and Quality, indicated that there is limited evidence supporting efficacy of medications in this age group and some evidence of risk.

The report found 8 high–quality studies supporting parental training programs as an ADHD intervention and no evidence of risks (http://tinyurl.com/ctmo3fn). Additionally, the review found only 1 high–quality study on the use of methylphenidate in the preschool population; this study found limited benefit of the drug and some evidence that children in this age group are more likely to experience adverse events, such as growth restriction.

Summary of Current Evidence

CADTH

October 2011

Guidelines and Recommendations for ADHD in Children and Adolescents

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions a thereby improve the quality of health care services.

The information in this report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this repor

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EXECUTIVE SUMMARY

Issue

Medications to treat attention-deficit/hyperactivity disorder (ADHD) in children and adolescents are available in short- and long-acting formulations. Short-acting formulations of methylphenidate (e.g., Ritalin) and dextroamphetamine (e.g., Dexedrine) are generally given two to three times daily.[1] They have been shown to be effective in reducing ADHD symptoms and provide dosing flexibility.[2-4] Compared with short-acting formulations, long-acting formulations are given less frequently, but are more expensive and are not covered in all insurance plans.[5] Recommendations about the use of long- or short-acting formulations are largely derived from expert opinion of best practices. Discourse on the use of long-acting formulations have centred on the following issues: compliance, social stigma, in-school dosing, and drug diversion.[6,7]

In 2010, publicly funded drug plans in Canada spent more than $35 million on long-acting formulations, which represented 77% of total expenditures on ADHD medications. As expenditures on ADHD medications continue to rise, health care decision-makers require evidence-based information on the issue of selecting the most appropriate formulation for treating ADHD in children and adolescents.

Objectives

The objective of this report was to summarize the current clinical evidence and findings of guidelines and recommendations. The report was also designed to explore the current utilization patterns and costs associated with the use of long- and short-acting ADHD medications.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make informed decisions.

Methods

Information provided is based on a review of eight Canadian and major international guidelines addressing long-acting and short-acting medications for ADHD in children and adolescents. In addition, drug payment information (i.e., administrative claims data) was obtained from IMS Brogan Inc.

Conclusions

Evidence-based recommendations support the use of stimulants as first-line therapy and the consideration of symptom profile in the use of long- or short-acting formulations when treating children and adolescents with severe ADHD.

The drug payment information presented in this summary report reveals substantial use of health care budgets to reimburse long-acting formulations. In 2010, expenditures on long-acting medications had exceeded $35 million (or 77% of total expenditures on ADHD medications) by public drug plans in Canada.

ABBREVIATIONS

AACAP	American Academy of Child & Adolescent Psychiatry
ADHD	attention-deficit/hyperactivity disorder
ADHD/HKD	attention-deficit and hyperkinetic disorders
AGREE	Appraisal of Guidelines for Research & Evaluation
AMP	amphetamines
CADDRA	Canadian ADHD Resource Alliance
CADTH	Canadian Agency for Drugs and Technologies in Health
CPP	clinical practice points
CPS	Canadian Paediatric Society
DEX	dextroamphetamine
DSM	Diagnostic and Statistical Manual of Mental Disorders
ER	extended release (also XR)
IR	immediate release
LA	long-acting
MPH	methylphenidate
MR	modified release
NCCMH	National Collaborating Centre for Mental Health
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NIHB	Non-Insured Health Benefits Program
RCT	randomized controlled trial
SA	short-acting
SIGN	Scottish Intercollegiate Guidelines Network
SR	sustained release
XR	extended release (also ER)

TABLE OF CONTENTS

1 INTRODUCTION

1.1 CONDITION

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder that affects approximately one in 20 children.[8] Core symptoms include inattention, hyperactivity, and impulsivity. Some children with ADHD show symptoms of inattention and are not hyperactive or impulsive. Others show symptoms of hyperactivity-impulsivity only. In most cases, however, symptoms of both inattention and hyperactivity-impulsivity are present. The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) identifies three subtypes of ADHD:

- ADHD, Combined Type
- ADHD, Predominantly Inattentive Type
- ADHD, Predominantly Hyperactive-Impulsive Type.

The core symptoms of ADHD will often persist throughout a person's lifetime, and approximately one-half to two-thirds of children with ADHD will continue to have significant problems as adults.[9] Management of ADHD may involve a combination of pharmacological treatments, behaviour modifications, lifestyle changes, and counselling.

1.2 PHARMACOLOGICAL TREATMENTS

Stimulants, including methylphenidate (MPH) and amphetamines (AMP) such as dextroamphetamine (DEX), have been used for more than 50 years to treat symptoms of ADHD and are considered the pharmacological treatment of choice.[10]

Medications to treat ADHD are available in short-acting (SA) and long-acting (LA) formulations. SA formulations of MPH (e.g., Ritalin) and DEX (e.g., Dexedrine) are generally given two to three times daily.[1] They have been shown to be effective in reducing ADHD symptoms and provide dosing flexibility.[2-4] Compared with SA formulations, LA formulations are given less frequently but are more expensive and are not covered in all insurance plans.[5] Recommendations to use LA or SA formulations have not been developed based on evidence. Discourse on the use of LA formulations has centred on the following issues: compliance, social stigma, in-school dosing, and drug diversion.[6,7]

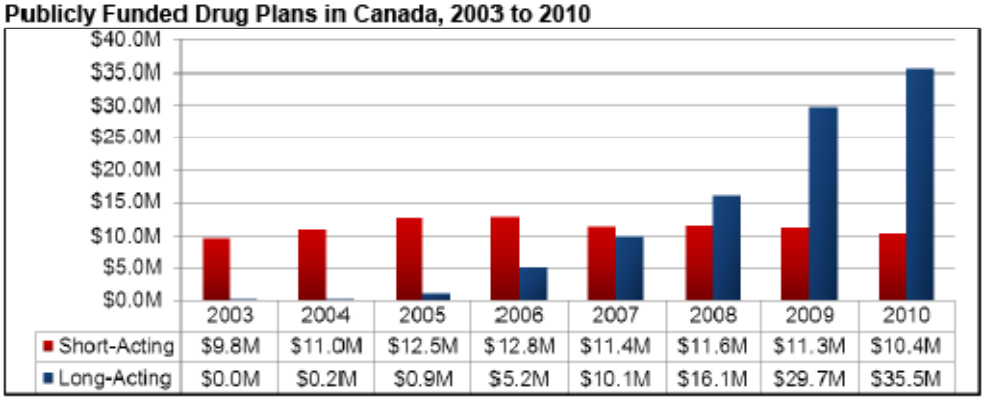
LA MPH stimulants include Concerta (extended-release MPH), generic extended-release MPH, and Biphentin (controlled-release MPH). LA AMP stimulants include Adderall XR (mixed salts AMP) and Vyvanse (lisdexamfetamine dimesylate). Strattera (atomoxetine) is a non-stimulant, LA medication indicated to treat ADHD. These medications are all indicated for the treatment of ADHD in patients aged six years and older.[1]

In various publications,[2-8,11] LA formulations are also referred to as extended release (ER or XR) or modified release (MR), while SA formulations are also referred to as immediate release (IR).

2 ISSUE

In 2010, publicly funded drug plans in Canada spent more than $35 million on LA formulations (see Figure 1), which represented 77% of total expenditures on ADHD medications (see Figure 2). As expenditures on ADHD medications continue to rise, health care decision-makers require evidence-based information on the issue of selecting the most appropriate formulation for treating ADHD in children and adolescents.

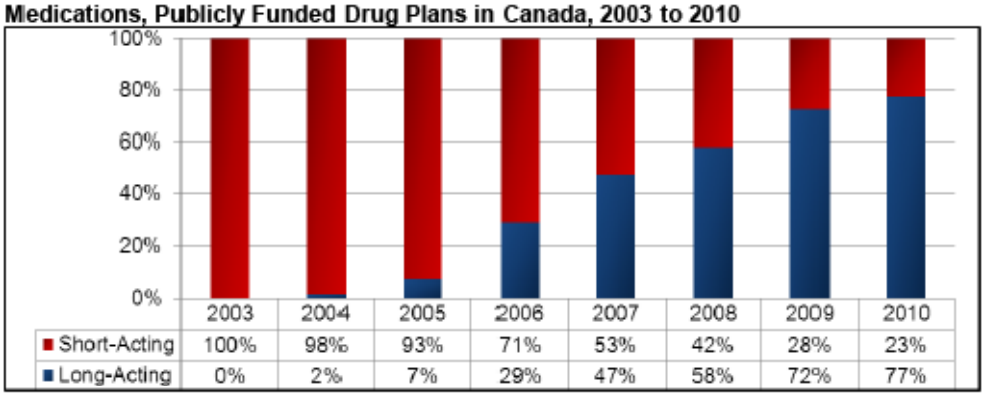
Figure 1: Expenditures ($) for Short-Acting and Long-Acting ADHD Medications, Publicly Funded Drug Plans in Canada, 2003 to 2010



	2003	2004	2005	2006	2007	2008	2009	2010
Short-Acting	$9.8M	$11.0M	$12.5M	$12.8M	$11.4M	$11.6M	$11.3M	$10.4M
Long-Acting	$0.0M	$0.2M	$0.9M	$5.2M	$10.1M	$16.1M	$29.7M	$35.5M

ADHD = attention-deficit/hyperactivity disorder; M = millions.
Figure 1 results were prepared using data from Brogan Inc., a unit of IMS, PharmaStat®, Public Drug Plan databases, 2003-2010, but the analyses, conclusions, opinions and statements expressed are those of CADTH and not of Brogan Inc., a unit of IMS.

Figure 2: Share of Expenditures (%) by Short-Acting versus Long-Acting ADHD Medications, Publicly Funded Drug Plans in Canada, 2003 to 2010



	2003	2004	2005	2006	2007	2008	2009	2010
Short-Acting	100%	98%	93%	71%	53%	42%	28%	23%
Long-Acting	0%	2%	7%	29%	47%	58%	72%	77%

ADHD = attention-deficit/hyperactivity disorder.
Figure 2 results were prepared using data from Brogan Inc., a unit of IMS, PharmaStat®, Public Drug Plan databases, 2003-2010, but the analyses, conclusions, opinions and statements expressed are those of CADTH and not of Brogan Inc., a unit of IMS.

3 OBJECTIVES

The objective of this report is to summarize the current clinical evidence and findings of guidelines and recommendations. The report was also designed to explore the current utilization patterns and costs associated with the use of LA and SA ADHD medications.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make informed decisions.

4 METHODS

4.1 Guidelines and Recommendations

A limited literature search was conducted on key resources including PubMed, ECRI, and Canadian and major international guidelines, as well as a focused Internet search. Methodological filters were applied to limit retrieval to guidelines. The search was also limited to English language documents published between January 1, 2006 and May 19, 2011.

Guidelines were included in the review if they were major national ADHD guidelines or produced by a recognized national organization and systematically developed. Relevant to the local environment, two Canadian guidelines were included.[5,8] The relevant population consisted of children and adolescents (aged ≤ 18 years). Guidelines were excluded if they were not systematically developed or were representative of a smaller jurisdiction (i.e., a US state), or a specific health care organization or health plan.

The Appraisal of Guidelines for Research & Evaluation (AGREE) instrument was used to evaluate the quality of the guidelines identified in the literature search.[12] Domains considered included scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability, and editorial independence. Numeric domain scores were not calculated. Instead, narrative assessment of each guideline is provided.

4.2 Economic Data

The following information refers to the economic data presented in Figures 1 and 2 of the Issues section of the report.

Aggregate-level data were obtained from IMS Brogan Inc. The IMS Brogan Inc. database is the largest source of drug payment information (i.e., administrative claims data) in Canada. IMS Brogan Inc. databases comply with federal and provincial privacy legislation.[13]

Aggregate-level data from public drug plans in Canada were available for nine of the 10 provinces (i.e., British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Québec, New Brunswick, Nova Scotia, and Newfoundland) and the Non-Insured Health Benefits (NIHB) Program. Aggregate-level data were not available for publicly funded programs in Prince Edward Island, Northwest Territories, Yukon Territory, and Nunavut Territory, because data from these programs are not provided to IMS Brogan Inc.

ADHD medications that were identified in the IMS Brogan Inc. database for publicly funded drug plans are presented in Table 1.

Table 1: Publicly Funded ADHD Medications in Canada (identified for the purpose of this report)

Brand Name	Available Strengths (mg)*	Average Cost ($)†
Long-Acting Formulations		
Adderall XR *(amphetamine mixed salts)*	5, 10, 15, 20, 25, 30	82.52
Biphentin *(methylphenidate HCl)*	10, 15, 20, 30, 40, 50, 60, 80	48.18
Concerta *(methylphenidate HCl)*	18, 27, 36, 54	73.58
Strattera *(atomoxetine)*	10, 18, 25,40, 60, 80, 100	93.17
Vyvanse *(lisdexamfetamine dimesylate)*	20, 30, 40, 50, 60	79.86
Short-Acting and Intermediate-Acting Formulations		
Adderall *(amphetamine mixed salts)*	20	N/A
Dexedrine *(dexamphetamine sulfate)*	5	50.44
Dexedrine Spansule *(dextroamphetamine sulphate)*	10, 15	46.08
Ritalin *(methylphenidate HCl)*	5, 10, 20	9.35
Ritalin SR *(methylphenidate HCl)*	20	14.54

Table 1 results were prepared using data from Brogan Inc., a unit of IMS, PharmaStat®, Public Drug Plan databases, 2003-2010, but the analyses, conclusions, opinions and statements expressed are those of CADTH and not of Brogan Inc., a unit of IMS.
* Strengths listed include available generic versions.
† Average cost (total cost divided by total claims) was calculated using 2010 data.

5 SUMMARY OF FINDINGS

5.1 Guidelines and Recommendations

Eight guidelines that addressed LA and SA medications for ADHD were identified. All guidelines were informed by evidence and include statements of consensus or best practice recommendations. The guidelines reviewed are found in Table 2.

Three national evidence-based guidelines were produced using rigorous scientific methods. These include guidelines by the Scottish Intercollegiate Guidelines Network (SIGN), the National Institute for Health and Clinical Excellence (NICE), and the Royal Australasian College of Physicians. Selected recommendations from these guidelines are found in Appendix 1.[2-4]

Table 2: Evidence-based Guidelines for ADHD

Organization	Year of Publication	Title of Publication
Major National Guidelines		
SIGN[2]	2009	*Management of Attention Deficit and Hyperkinetic Disorders in Children and Young People: A National Clinical Guideline*
NICE[3]	2009	*Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People and Adults*
Royal Australasian College of Physicians[4]	2009	*Australian Guidelines on Attention Deficit Hyperactivity Disorder*
Additional Guidelines		
CADDRA[5]	2011	*Canadian ADHD Practice Guidelines* (3rd Edition)
CPS (Feldman et al)[6]	2009	*Extended-release Medications for Children and Adolescents with Attention-Deficit Hyperactivity Disorder*
AACAP[11]	2007	*Practice Parameter for the Assessment and Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder*
AACAP (Gleason et al)[6]	2007	*Psychopharmacological Treatment for Very Young Children: Contexts and Guidelines*
European Society of Child and Adolescent Psychiatry (Banaschewski et al)[7]	2006	*Long-acting Medications for the Hyperkinetic Disorders: A Systematic Review and European Treatment Guideline*

AACAP = American Academy of Child & Adolescent Psychiatry; CADDRA = Canadian ADHD Resource Alliance; CPS = Canadian Paediatric Society; NICE = National Institute for Health and Clinical Excellence; SIGN = Scottish Intercollegiate Guidelines Network

SIGN (2009) National Clinical Guideline on ADHD

In 2009, SIGN published a national clinical guideline on the management of attention-deficit and hyperkinetic disorders (ADHD/HKD) in children and young people, which is an update of a 2001 guideline.[2] This clinical guideline was developed using a standard methodology based on a systematic review of the evidence. The complete guideline development methodology is found on the SIGN website.[14]

The overall aim of the guideline was to provide a framework for the evidence-based assessment and management of ADHD/HKD from which multidisciplinary and multi-agency approaches could be developed locally. The Guideline Development Group was multidisciplinary, including practising clinicians and patient or caregiver representatives. In addition, SIGN provided support for guideline development, literature review, and facilitation.

There was a clear link between recommendations and the supporting evidence. The recommendations were specific and easily identifiable, and levels of supporting evidence and grades of recommendations were stated. A number of independent expert referees reviewed the guideline. NHS Quality Improvement Scotland funded the guideline. All members of the guideline development group made declarations of interest.

Summary of recommendations from SIGN

Evidence-based:

a) SIGN recommends treatment of children with severe ADHD using stimulants as the first choice of medications. (Grade A.)
b) Atomoxetine is recommended in children where psychostimulant medication is not appropriate, not tolerated, or is ineffective. (Grade A.)

Grade A: at least one meta-analysis, systematic review, or good quality randomized controlled trial (RCT), and directly applicable to the target population

Consensus-based (good practice):

a) LA medications should be considered if there is a likelihood of diversion.
b) When selecting a formulation, clinicians should consider practical issues of convenience and applicability on an individual case basis.

Australian Guidelines on ADHD (2009)

Since November 2009, the Royal Australasian College of Physicians has provided access to draft Australian guidelines on ADHD.[4] This is an extensive guideline that includes recommendations and a discussion of the supporting evidence for all aspects of the diagnosis and treatment of ADHD. The guidelines are available in draft because a formal conflict of interest investigation into a researcher has not been completed in the United States.

In May 2011, the conflict of interest allegations had not been resolved, so the National Health and Medical Research Council (NHMRC) decided to convene a working party to develop clinical practice points (CPPs) to ensure up-to-date clinical advice on ADHD. The website noted that "the final CPPs will be provided to the Minister for Mental Health and Ageing for his consideration and possible public consultation, by the end of September 2011."[15]

In June 2011, the website stated, "while the work of this US-based researcher is referenced in the draft Guidelines, the researcher has not been involved in any way in the production of the Guidelines."[15] NHMRC guideline development processes were followed. The complete guideline development process was available as a separate appendix.[16] Steps included a literature review, stakeholder consultation, public consultation, email, and face-to-face meetings. As a result, until an update to the guidelines is ready, NHMRC will continue to provide access to the 2009 draft guidelines as an information resource.[15]

The aim of these guidelines was to support and inform the care of individuals with ADHD by providing a series of recommendations to guide assessment, management, and care. The guidelines apply to the care of preschoolers, children, adolescents, and adults with ADHD. They are intended to provide a framework based on the best available evidence that can be adapted to local needs and resources, and individual circumstances. The guideline development group included experts from key professional disciplines, including pediatrics, child and adolescent psychiatry, adult psychiatry, psychology, general practice, and education, as well as consumers

and caregivers. These guidelines addressed social and economic considerations in the treatment of ADHD, including the economic burden of ADHD and the cost-effectiveness of treatment.

The method for formulating the recommendations was clearly described. In the document, the research question, summary evidence statements (with level of evidence), and resulting recommendations were provided, followed by the research evidence. For areas of practice not addressed by current research, recommendations were developed based on the consensus opinion of the clinicians, educators, and consumers from the reference group. Funding for these guidelines was provided by the Australian Government's Department of Health and Ageing. Conflicts of interest were recorded for each member of the development group.

Summary of recommendations from the Australian guidelines

Evidence-based:

a) Where severe, impairing ADHD is present, treatment with stimulants (MPH or DEX) should be considered as a first-line pharmacological treatment. (Grade A.)
b) The choice of IR-MPH or ER-MPH depends on the symptom profile, as well as individual child and parent or caregiver preferences. (Grade A for children, grade B for adolescents.)
c) Atomoxetine should be considered for children and adolescents with severe ADHD who do not respond to or are intolerant of stimulant medication, or in whom stimulant medication is contraindicated. (Grade B.)

Grade A: Body of evidence can be trusted to guide practice.
Grade B: Body of evidence can be trusted to guide practice in most situations.

Consensus-based (best practice):

a) Not all people with ADHD require pharmacological management. Medications should only be used when symptoms are pervasive across settings and cause significant impairment in academic, social, or behavioural function.
b) IR forms should be the initial treatment, to titrate to the optimal dose, and they may be the preferred maintenance therapy for various reasons; for example, flexibility of dosing. If starting on IR stimulants, consideration should be given to changing to an ER form once the optimal dose has been established. This can help to avoid the stigma and inconvenience of taking medication at school.
c) Atomoxetine may be considered as the first-line medication if there is comorbid substance abuse, severe tic disorder, or anxiety disorder.

NICE (2009) Clinical Guideline on ADHD

In 2009, NICE published a clinical practice guideline on the diagnosis and management of ADHD in children, young people, and adults.[3] A technology appraisal on "methylphenidate, atomoxetine and dexamfetamine for the treatment of ADHD in children and adolescents" informed the recommendations on drug treatment.[17] The clinical practice guideline is high quality and was developed based on methods outlined in the NICE Guideline Manual.[18] Steps in developing this guideline included a literature review, stakeholder consultation, public consultation, and face-to-face meetings.

The aim of the NICE guideline was to advise on the treatment and management of ADHD. It is considered a patient-centred, evidence-based guideline and is relevant for children (older than three years), young people, and adults with ADHD. The guideline development group consisted of health care professionals, lay representatives, and technical experts. Consulted stakeholders included service users and caregivers, professional groups, and manufacturers. Health economic evidence was assessed and incorporated into the recommendations.

The guideline review process is available in a flow chart in the guideline (p. 47). The method for formulating the recommendations was clearly described. The guideline was developed over a series of meetings, in which clinical questions and clinical evidence were reviewed and assessed and recommendations formulated and reviewed. Recommendations were evidence based, where possible, and if evidence was not available, informal consensus methods were used. Recommendations were specific and easily identifiable and an extensive evidence review for each topic was provided. Various stakeholders reviewed the guideline extensively prior to publication. This guideline was commissioned by NICE and developed within the National Collaborating Centre for Mental Health (NCCMH). Conflicts of interest for each member of the Guideline Development Group were recorded.

An extensive review of the evidence for drug treatment of ADHD is provided. The quality of evidence for each drug or topic was rated. Following the evidence review is a summary and a list of recommendations. Individual recommendations were not assigned a level for the supporting evidence on which they were based or a strength of recommendation. Therefore, it is not clear to what extent each recommendation is based on evidence or expert opinion.

Summary of recommendations from NICE

a) Drug treatment is not indicated as the first-line treatment for all school-aged children and young people with ADHD. It should be reserved for those with severe symptoms and impairment. Where drug treatment is considered appropriate, MPH, atomoxetine, and DEX are recommended.

b) If there is a choice of more than one appropriate drug, the product with the lowest cost should be prescribed.

c) To improve adherence to drug treatment, simple drug regimens (for example, once-daily MR doses) are recommended for people with ADHD.

d) The decision regarding which product to use should be based on factors including:
   - specific issues regarding compliance; i.e., midday treatment dose at school
   - the potential for drug diversion and/or misuse
   - the preferences of the child or adolescent and/or his or her parent or guardian.

e) When prescribing MPH for the treatment of children or young people, MR preparations should be considered for the following reasons:
   - convenience
   - improving adherence
   - reducing stigma (does not need to take medication at school)
   - reducing problems schools have in storing and administering controlled drugs
   - their pharmacokinetic profiles.

f) Alternatively, IR preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels.

g) Consider atomoxetine if MPH has been tried and has been ineffective at the maximum tolerated dose, or if intolerant to low or moderate doses of MPH.

Additional ADHD Guidelines

Five additional ADHD guidelines were identified that included recommendations on LA versus SA drugs in children and adolescents. These guidelines varied with regard to their methodological quality. Recommendations on the use of LA versus SA drugs, along with relevant statements of evidence from each guideline, are found in Appendix 2.

In 2011, the Canadian ADHD Resource Alliance (CADDRA) published the third edition of its Canadian ADHD Practice Guidelines.[5] CADDRA is a national, independent, not-for-profit association with members from family practice, pediatrics, psychiatry, psychology, and other health professions. No objective or clinical question was specified for the guideline, but the authors included a list of core principles for the treatment of ADHD. The targeted users of the guideline are Canadian physicians who diagnose and treat ADHD, and the guideline applies to patients and their families living with ADHD.

Strengths of this guideline include the tools available for physicians and patients. Information, diagnostic instruments, forms, and scales that have been selected based on their validity, reliability and accessibility can be downloaded. These guidelines are considered an active document that will be revised online as new information comes available.

The major limitation is the lack of rigour used in the development of this guideline. For example, the methods used to search for evidence were not specified and no criteria were described for selecting the evidence. Specific recommendations were not identifiable and there was no link between recommendations and the supporting evidence. The authors state that evidence-based data were cited in the literature detailed in the reference section, and consensus-based statements were identified in the text. The introduction to the guideline states, "Consensus decisions have been made if there was no current evidence-based data available to deal with a specific clinical issue or where evidence-based data may have been impractical in the Canadian environment" (p. v).

CADDRA is an active advocacy group. Several statements were made in the document about the cost of many ER preparations, which are "beyond the reach" of many patients without extended health insurance: "CADDRA continues to advocate for a resolution of this problem at the government level" (p. 57). The Guidelines Committee "recommends that all medication approved for ADHD treatment should be accessible and covered by provincial drug plans" (p. 67). This advocacy, combined with a lack of supporting evidence for the group's recommendations, creates significant bias that threatens the validity of the recommendations.

Individual recommendations are not assigned a level for the supporting evidence on which they were based, or a strength of recommendation. Therefore, it is not clear to what extent each recommendation is based on evidence or expert opinion.

Recommendations

a) LA preparations, including Adderall XR, Biphentin, Concerta, Strattera, and Vyvanse, are recommended as first-line treatment of ADHD.
b) SA and intermediate-acting preparations are listed as second-line or adjunctive agents.

In 2009, the Canadian Paediatric Society published a statement on "extended-release medications for children and adolescents with attention-deficit disorder."[8] The objective of the statement was to critically appraise the evidence for the relative effectiveness of XR versus IR medications and to make recommendations for their appropriate use in the treatment of ADHD. The statement was targeted at physicians prescribing medication for ADHD.

Strengths included a clearly described scope and purpose. Stakeholder involvement included physicians but not patients or their families. Key recommendations were specific, unambiguous, and easily identifiable. The authors of the paper indicated that they had no conflicts of interest to declare. The major limitation is the lack of rigour of development. Clinical questions were not provided, and although the search strategy was detailed, the criteria for selecting the evidence and the methods for formulating the recommendations were not provided. The statement indicates that the quality of the studies was appraised, although the details of the appraisal of individual studies or systematic reviews were not provided. References were provided throughout the statement. There was no link between the recommendations and the supporting evidence and no levels of evidence were assigned. Therefore, it is not clear to what extent each recommendation is based on evidence or expert opinion.

This statement made the distinction between "efficacy" and "effectiveness," defining efficacy as how well a treatment works under tightly controlled study conditions, and effectiveness as how well a treatment works in a natural, real-world setting. The statement identified that cost is the major barrier to accessing XR preparations, and recommended that industry, private health insurance companies, and government work together to make these medications more accessible to all children with ADHD. No specific solutions were provided.

Recommendations

a) The authors acknowledge that the efficacy of IR and XR preparations are similar, as demonstrated through RCTs. Although not necessarily more efficacious than IR medication, the authors feel the XR preparations are more effective than IR and less likely to be diverted. Therefore, the authors recommend that XR preparations should be considered as first-line therapy.

In 2006, Banaschewski et al. published a supplement to European guidelines (2004) to provide recommendations about the use of LA medications for the hyperkinetic disorders.[7] The guideline was developed by a panel of experts from several European countries, including academic clinicians and clinical researchers. The author meetings were funded by several companies and authors' expenses were also paid. Potential conflicts of interests were declared.

The authors identified the clinical questions. The guideline states that a systematic review of published and unpublished trials was completed. Details of the search were not provided,

although it was stated that the authors used recent systematic reviews by NICE and SIGN to identify papers. They also referred to recent meta-analyses. In addition, the manufacturers were asked to submit information (published and unpublished). A "quantitative review of data" was also conducted, including the calculation of effect sizes using standard methodology. The criteria for selecting the evidence were not described. The methods for formulating the recommendations were not specified, although the method of guideline development was described as "iterative." Drafts of the paper were exchanged and discussed iteratively and all authors subscribed to the final document (and recommendations). There was a method for resolving disagreements, but in the end, all conclusions were unanimous. The paper included a narrative summary of each conclusion and a scientific examination of the data.

Strengths include the description of the guideline process and the clear presentation of the recommendations. Limitations include the lack of patient input. For each recommendation, there is a discussion of the supporting evidence and levels of evidence are assigned to certain, but not all, statements within the discussion.

Evidence statements

a) XR preparations are superior to placebo and some are equivalent to multiple doses of IR methylphenidate. (Grade A.)
b) LA stimulants have similar effect sizes than IR stimulants (level 1a), while effect sizes for non-stimulants (atomoxetine) are somewhat smaller.
c) SR medications may be less prone to abuse because they tend to have a slower rate of onset than IR. (Grade C.)
d) Key advantages of IR: lower cost and flexibility of dosages. (Consensus.)
e) Key advantages of LA: potential reduction of stigma at school, improved compliance, and possible reduced risk of misuse. (Consensus.)

Level 1a: the authors assigned a level of 1a; however, this does not match the grading systems described in the paper.
Grade A: at least one meta-analysis, systematic review, or good quality RCT, and directly applicable to the target population.
Grade C: well-conducted case control or cohort studies; directly applicable to target population.

Recommendations

a) LA preparations should be available and used.
b) They should not replace SA drugs (which will be the initial treatment for many children, for reasons of cost and flexibility of dosing). Individual clinical choice will determine the choice of formulation used.

The American Academy of Child & Adolescent Psychiatry (AACAP) published two guidelines on the treatment of ADHD. The *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder* was published in July 2007 and *Psychopharmacological Treatment for Very Young Children: Contexts and Guidelines* was published in December 2007.[6,11]

The objective of the practice parameter was to describe the assessment and treatment of children and adolescents with ADHD, based on the current scientific evidence and clinical consensus of experts in the field.[11] The Working Group consisted of academic clinicians and researchers. The parameter was targeted at clinicians who treat children and adolescents with ADHD. Clinical questions were not defined, although areas of discussion included clinical evaluation, comorbid conditions, research on the etiology, and interventions. The funding body for this Working Group and development of the practice parameter was not clear, although it was sponsored by the AACAP. Conflicts of interest for all members of the panel were recorded.

Details of the systematic literature search were provided, including databases searched from 1996 to 2006. In addition, bibliographies were reviewed and references were included from the previous version of the parameter. Articles were included if they "appeared to inform the field on the diagnosis and/or treatment of ADHD." Priority was given to recent authoritative reviews of literature and recent treatment studies within the previous two to three years. Treatment recommendations were based on empirical evidence and clinical consensus and were graded according to the strength of the underlying empirical and/or clinical support. The methods for formulating the recommendations were not described. The overall recommendations on best treatment practices were stated with a strength of underlying evidence, followed by a discussion of the supporting evidence. Specific recommendation statements about the use of LA agents were found within the text, and referenced. Individual references were not assigned a level of evidence and therefore it not clear to what extent each recommendation is based on evidence or expert opinion. Additional limitations included the lack of patient or family involvement.

Evidence statements

a) LA formulations are as efficacious as the IR forms and have been shown to be efficacious in adolescents as well as children (reference cited).
b) Advantages of LA: greater convenience for patient and family; enhanced confidentiality at school (no dose given at school); greater compliance (no references cited).
c) Disadvantages of LA: may have greater problematic effects on evening appetite and sleep (no references cited).
d) LA MPH may improve driving performance in adolescents relative to SA MPH (reference cited; RCT).
e) SA stimulants are often used as initial treatment in small children (< 16 kg) for whom there are no LA forms in sufficiently low dose (no references cited).

Although references were cited for some statements, the level of evidence was assigned for only one statement (see above statement (d)).

Recommendations (found within the body of the text)

a) Stimulants are recommended first-line treatment for ADHD. No specific formulation is recommended; it is the sole choice of the family and the clinician as to which agent should be used; each patient's treatment must be individualized.
b) Atomoxetine may be considered as the first-line agent for ADHD in individuals with an active substance abuse problem, comorbid anxiety, or tics.

The aim of the AACAP Working Group on Medication Treatment in Very Young Children was to develop best-practice algorithms for the use of psychopharmacological agents in preschool

children, based upon literature review, clinical experience, and expert consensus.[6] The Working Group included professionals with expertise in early childhood psychiatric disorders, psychopharmacology, pediatrics, psychology, and neurodevelopmental processes. The development of this algorithm was supported by a grant from the AACAP, which is the same organization that was responsible for editing and publishing the guideline. Conflicts of interest for all members of the panel were recorded. The target population of this guideline was preschool-aged children (three to six years). In Canada, ADHD medication is indicated in children aged six and older.

Systematic methods were used to search for evidence, and included a defined search period (1990 to 2007), a list of databases searched (limited to PubMed and PsycINFO), and defined search terms. Criteria for selecting the evidence were described as those publications that were "relevant," including evidence in preschool-aged children as well as the highest level of evidence in older children. Although specific methods for developing the algorithm were not described, input included a systematic literature review, survey responses from practising clinicians, and the research and clinical expertise of the Working Group.

Steps in the algorithm were specific and clearly identifiable. Each step of the algorithm was labelled with the level of supporting evidence and included different options for treatment. There was a discussion of the available evidence within the text of the document. Limitations included the lack of patient and/or family involvement. Clinical questions were not described.

Statements about the evidence

a) No data exist to support ER stimulants in preschoolers.
b) Clinical experience highlights the challenges of dosing three times a day.

Recommendations for preschoolers (steps of the algorithm)

a) First-line: MPH (level A); second-line: AMP (level C); third-line option: atomoxetine (level C); no formulations are specified.
b) ER formulations can be used to address compliance considerations. ER formulations limit dosing flexibility in the lowest dose ranges and therefore may be contraindicated in children whose optimal tolerated dose is lower than the ER dose.

Level A: well-controlled, randomized trials, large meta-analysis, or overwhelming clinical consensus.
Level B: empirical evidence, open trials, case series, or strong clinical consensus.
Level C: single case reports or no published reports, recommendation based on clinical and research experiences.

5.2 Limitations

Three national evidence-based guidelines were identified that were produced using rigorous scientific methods.[2-4] No major limitations were identified for the SIGN and Australia guidelines. Although the development process was rigorous in the NICE guideline, individual recommendations were not assigned a level for the supporting evidence on which it was based, or a strength of recommendation. Therefore, it is not clear to what extent each recommendation is based on evidence or expert opinion.

Five additional ADHD guidelines were identified that made recommendations for LA versus SA formulations.[5-8,11] These guidelines varied in their methodological quality. In general, guidelines were lacking in their rigour of development. In many cases, there was no link between recommendations and the supporting evidence. As there was no level of supporting evidence or grade provided for recommendations, it was not clear if they were based on evidence or expert opinion.

Vyvanse (lisdexamfetamine dimesylate) has been available in Canada since 2009.[19] It is not included in the guidelines reviewed, with the exception of the 2011 CADDRA guideline.

6 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Three national evidence-based guidelines were identified that were produced using rigorous scientific methods.[2-4] Five additional guidelines were identified that varied with regard to methodological quality.[5-8,11] All guidelines reviewed were informed by evidence and developed by consensus.

Evidence-based recommendations support the use of stimulants as first-line therapy when treating children and adolescents with severe ADHD. Atomoxetine is an LA non-stimulant treatment alternative that is generally considered a third-line treatment alternative after methylphenidate and amphetamine stimulants, except in the presence of certain comorbidities.

Evidence-based recommendations support the consideration of symptom profile in the use of LA or SA formulations. Discussions of evidence within the guidelines reviewed also state that LA formulations are as efficacious as SA, but not superior. Other recommendations about the use of LA or SA formulations are largely derived from expert opinion of best practice. Advantages of one formulation over another cannot be determined and guideline developers acknowledge the need for more research comparing LA and SA medications.

The drug payment information presented in this summary report reveals substantial use of health care budgets to reimburse LA formulations. In 2010, expenditures on LA formulations had exceeded $35 million (or 77% of total expenditures on ADHD medications) by public drug plans in Canada.

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APPENDIX 1: RECOMMENDATIONS FROM NATIONAL EVIDENCE-BASED GUIDELINES DEVELOPED USING RIGOROUS SCIENTIFIC METHODS

Organization	Recommendations
SIGN[2] (2009)	Overall recommendations (excerpts) • For school-aged children and young people with HKD (severe ADHD), medication is recommended (Grade A) • Psychostimulants are recommended as the first choice of medication for the core symptoms of ADHD/HKD in children (Grade A). IR versus ER • Use of MR formulations or ATX should be considered where there is likelihood of diversion (good practice point) • Clinicians should familiarize themselves with the release patterns of the different MPH formulations. It may be necessary to combine IR and MR preparations to provide medications cover throughout the day (good practice point) • When selecting a formulation, clinicians should consider practical issues of convenience and applicability on an individual case basis (good practice point). Place in therapy: ATX • ATX is recommended as treatment for the core symptoms of ADHD/HKD in children where psychostimulant medication is not appropriate, not tolerated, or is ineffective (Grade A). Grade A: at least one MA, SR, or good quality RCT, and directly applicable to the target population. Good practice point: recommended best practice based on the clinical experience of the guideline development group.
NICE[3] (2009)	Overall recommendations (excerpts) • Drug treatment is not indicated as the first-line treatment for all school-aged children and young people with ADHD. It should be reserved for those with severe symptoms and impairment. • Where drug treatment is considered appropriate, MPH, ATX, and DEX are recommended. • If there is a choice of more than one appropriate drug, the product with the lowest cost should be prescribed. • To improve adherence to drug treatment, simple drug regimens (e.g., once-daily MR doses) are recommended for people with ADHD. IR versus ER • The decision regarding which product to use should be based on factors including: o specific issues regarding compliance; i.e., midday treatment dose at school o the potential for drug diversion and/or misuse o the preferences of the child or adolescent and/or his or her parent or guardian. • When prescribing MPH for the treatment of children or young people, MR preparations should be considered for the following reasons: o convenience o improving adherence o reducing stigma (does not need to take medication at school) o reducing problems schools have in storing and administering controlled drugs o their pharmacokinetic profiles. • Alternatively, IR preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels. Place in therapy: ATX • Consider ATX if MPH has been tried and has been ineffective at the maximum tolerated dose, or if the child or young person is intolerant to low or moderate doses of MPH. No grades were provided for each recommendation. No link between the recommendation and supporting evidence was provided.

Organization	Recommendations
Royal Australasian College of Physicians[4] (2009)	Overall recommendations (excerpts) • Not all people with ADHD require pharmacological management (recommended best practice). • Medications should only be used when symptoms are pervasive across settings (e.g., school and home) and causing significant impairment in academic, social, or behavioural function, and after careful consideration of non-pharmacological approaches (recommended best practice). • Where severe, impairing ADHD is present, treatment with MPH or DEX should be considered as a first-line pharmacological treatment (grade A). IR versus ER • The choice of IR-MPH or ER-MPH depends on the symptom profile, as well as individual child and parent or caregiver preferences (grade A for children, grade B for adolescents). • IR forms should be the initial treatment, to titrate to the optimal dose, and they may be the preferred maintenance therapy for various reasons; for example, flexibility of dosing (recommended best practice). • If starting on IR stimulants, consideration should be given to changing to an ER form once the optimal dose has been established. This can help to avoid the stigma and inconvenience of taking medication at school (recommended best practice). • In some cases, the combined use of IR and ER forms is required. This should only be considered if there is inadequate symptom control with the ER form (recommended best practice). • ER forms of stimulants should not be routinely used in preschool-aged children (recommended best practice). Place in therapy: ATX • ATX should be considered for children and adolescents with severe ADHD who do not respond to or are intolerant of stimulant medication, or in whom stimulant medication is contraindicated (grade B). • ATX may be considered as the first-line medication if there is comorbid substance abuse, severe tic disorder, or anxiety disorder (recommended best practice). **Grade A:** Body of evidence can be trusted to guide practice. **Grade B:** Body of evidence can be trusted to guide practice in most situations. **Best practice points:** Recommended best practice based on clinical experience and expert opinion.

ADHD = attention-deficit/hyperactivity disorder; ATX = atomoxetine; DEX = dextroamphetamine / dexamphetamine; ER = extended release; HKD = hyperkinetic disorder; IR = immediate release; MA = meta-analysis; MPH = methylphenidate; MR = modified release; NICE = National Institute for Health and Clinical Excellence; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network; SR = systematic review.

APPENDIX 2: SUMMARY OF EVIDENCE AND RECOMMENDATIONS FROM GUIDELINES ON ADHD

Guideline	Relevant Statements about the Available Evidence	Relevant Recommendations on Long-acting versus Short-acting Drugs	Major Strengths/Limitations of Guideline
CADDRA[5] (2011)	• The evidence for treating ADHD is not discussed. The evidence comparing LA and SA agents is not discussed. • Central philosophy: treat each patient as a unique being; 13 principles for medication selection in the treatment of ADHD are provided (p. 55).	Medical treatment for uncomplicated ADHD for children and adolescents: • LA preparation, including Adderall XR, Biphentin, Concerta, Strattera, and Vyvanse are recommended as first-line • SA and intermediate-acting preparations are listed as second-line/adjunctive agents	Major limitation: rigour of development. No discussion of evidence supporting its practice guideline; no levels of evidence provided or strength of recommendations.
CPS: Statement[6] (2009)	• The authors acknowledge that the efficacy of IR and XR preparations are similar, as demonstrated through RCTs. • Although not necessarily more *efficacious* than IR medication, the authors feel the XR preparations are more *effective* than IR.	• When stimulant medications for ADHD are indicated, XR preparations should be considered as first-line therapy because these preparations are more *effective* and less likely to be diverted. • XR medications are more likely than IR medications to be used by the children and teenagers with ADHD for whom they have been prescribed.	Strength: identified scope and purpose and stakeholder involvement. Major limitation: rigour of development. No link between the recommendation and supporting evidence; no levels of evidence provided or strength of recommendations.
European: *Long-acting Medications for the Hyperkinetic Disorders*[7] (2006)	• XR preparations are superior to placebo and some are equivalent to multiple doses of IR MPH (grade A). • XR stimulants have similar effect sizes to IR stimulants (level 1a) while effect sizes for non-stimulants (ATX) are somewhat smaller. • SR medications may be less prone to abuse because they tend to have a slower rate of onset than IR (grade C). • Key advantages of IR: lower cost and flexibility of dosages (consensus). • Key advantages of LA: potential reduction of stigma at school, improved compliance, and possible reduced risk of misuse (consensus).	• LA preparations should be available and used. • They should not replace SA drugs (which will be the initial treatment for many children, for reasons of cost and flexibility of dosing). Individual clinical choice will determine the choice of formulation used.	Strength: clinical questions defined, as well as method of guideline development (iterative); link between supporting evidence and recommendation; levels of evidence are provided for some, but not all; statement of supporting evidence Limitations: recommendations are not assigned a level of evidence on which they are based.

Guideline	Relevant Statements about the Available Evidence	Relevant Recommendations on Long-acting versus Short-acting Drugs	Major Strengths/Limitations of Guideline
AACAP: Practice Parameter[11] (2007)	• LA formulations are as efficacious as the IR forms and have been shown to be efficacious in adolescents as well as children (reference cited). • Advantages of LA: greater convenience for patient and family; enhanced confidentiality at school (no dose given at school); greater compliance (no references cited). • Disadvantages of LA: may have greater problematic effects on evening appetite and sleep (no references cited). • LA MPH may improve driving performance in adolescents relative to SA MPH (reference cited; RCT). • SA stimulants often used as initial treatment in small children (≤ 16 kg) for whom there are no LA forms in sufficiently low dose (no references cited).	• Overall recommendation for treatment: The initial psychopharmacological treatment of ADHD should be a trial with an agent approved by the FDA for the treatment of ADHD (minimal standard). • Stimulants are recommended first line (references cited). • No specific formulation is recommended; it is the sole choice of the family and the clinician as to which agent should be used; each patient's treatment must be individualized. Place in therapy: ATX • May be considered as the first-line agent for ADHD in individuals with an active substance abuse problem, comorbid anxiety, or tics (references cited). • Preferred if the patient experiences severe side effects of stimulants, such as mood lability, tics (references cited).	Strength: major recommendations are easily identifiable, followed by a discussion of the relevant evidence. Limitation: rigour of development — methods for formulating the recommendations are not described.
AACAP: Treatment for the Very Young[6] (2007)	• No data exist to support ER stimulants in preschoolers. • Clinical experience highlights the challenges of dosing three times a day.	Steps of the algorithm: • First-line: MPH (level A) • Second-line: AMP (level C) • Third-line option: ATX (level C) No formulations are specified. ER formulations can be used to address compliance considerations. ER formulations limit dosing flexibility in the lowest dose ranges and therefore may be contraindicated in children whose optimal tolerated dose is lower than the ER dose. **Level A:** Well-controlled, randomized trials, large meta-analysis, or overwhelming clinical consensus. **Level B:** Empirical evidence, open trials, case series, or strong clinical consensus. **Level C:** Single case reports or no published reports, recommendation based on clinical and research experiences.	Strength: identified scope and purpose and stakeholder involvement; levels of evidence assigned to each step of the algorithm. Limitation: specific criteria for selecting evidence were not described.

AACAP = American Academy of Child and Adolescent Psychiatry; ADHD = attention-deficit/hyperactivity disorder; AMP = amphetamine; ATX = atomoxetine; CADDRA = Canadian ADHD Resource Alliance; DEX = dextroamphetamine / dexamphetamine; CPS = Canadian Paediatric Society; ER = extended release; FDA = Food and Drug Administration; IR = immediate release; LA = long-acting; MD = medical doctor; MPH = methylphenidate; RCT = randomized controlled trial; SA = short-acting; XR = extended release.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166667.htm

MedWatch The FDA Safety Information and Adverse Event Reporting Program

- Safety Information
- Safety Alerts for Human Medical Products
- 2012 Safety Alerts for Human Medical Products
- 2011 Safety Alerts for Human Medical Products
- 2010 Safety Alerts for Human Medical Products
- 2009 Safety Alerts for Human Medical Products
- 2008 Safety Alerts for Human Medical Products
- 2007 Safety Alerts for Human Medical Products
- 2006 Safety Alerts for Human Medical Products
- 2005 Safety Alerts for Human Medical Products
- 2004 Safety Alerts for Human Medical Products
- 2003 Safety Alerts for Human Medical Products
- 2002 Safety Alerts for Human Medical Products
- 2001 Safety Alerts for Human Medical Products
- 2000 Safety Alerts for Human Medical Products

Stimulant Medications used in Children with Attention-Deficit/Hyperactivity Disorder - Communication about an Ongoing Safety Review

Products involved include: Focalin, Focalin XR (dexmethylphenidate HCl); Dexedrine, Dexedrine Spansules, Dextroamphetamine ER, Dextrostat (dextroamphetamine sulfate); Vyvanse (lisdexamfetamine dimesylate); Desoxyn (methamphetamine); Concerta, Daytrana, Metadate CD, Metadate ER, Methylin, Methylin ER, Ritalin, Ritalin-LA, Ritalin-SR (methylphenidate); Adderall, Adderall XR (mixed salts amphetamine); Cylert (pemoline) and generics.

[UPDATED 12/12/2011] A large, recently-completed study, that included one study that evaluated heart attacks and sudden deaths in a sample of adults, and a second study that assessed strokes in these adults, has not shown an increased risk of serious adverse cardiovascular events in adults treated with ADHD medications. Patients should continue to use their medicine for the treatment of ADHD as prescribed by their healthcare professional.

Stimulant products and atomoxetine should generally not be used in patients with serious heart problems, or for whom an increase in blood pressure or heart rate would be problematic. Patients treated with ADHD medications should be periodically monitored for changes in heart rate or blood pressure.

[UPDATED 11/01/2011] FDA notified the public that a large, recently-completed study in children and young adults treated with medication for Attention-Deficit/Hyperactivity Disorder (ADHD) has not shown an association between use of certain ADHD medications and adverse cardiovascular events. FDA continues to recommend that healthcare professionals prescribe these medications according to the professional prescribing label. See the Data Summary of the FDA Drug Safety Communication for more information.

Audience: Pediatricians, Neuropsychiatric healthcare professionals

[Posted 06/15/2009] FDA notified healthcare professionals that it is providing its perspective on study data published in the American Journal of Psychiatry on the potential risks of stimulant medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children. This study, funded by the FDA and the National Institute of Mental Health (NIMH), compared the use of stimulant medications in 564 healthy children from across the United States who died suddenly to the use of stimulant medications in 564 children who died as passengers in a motor vehicle accident.The study authors concluded that there may be an association between the use of stimulant medications and sudden death in healthy children. Given the limitations of this study's methodology, the FDA is unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children. FDA believes that this study should not serve as a basis for parents to stop a child's stimulant medication. Parents should discuss concerns about the use of these medicines with the prescribing healthcare professional. Any child who develops cardiovascular symptoms (such as chest pain, shortness of breath or fainting) during stimulant medication treatment should immediately be seen by a doctor.

FDA is continuing its review of the strengths and limitations of this and other epidemiological studies that evaluate the risks of stimulant medications used to treat ADHD in children. FDA and the Agency for Healthcare Research and Quality are sponsoring a large epidemiological study that will provide further information about the potential risks associated with stimulant medication use in children. The data collection for this study will be complete later in 2009.

[11/01/2011 - Drug Safety Communication: Safety Review Update of Medications Used to Treat Attention-Deficit/Hyperactivity Disorder (ADHD) - FDA]

[06/15/2009 - Communication About An Ongoing Safety Review - FDA]
[06/15/2009 - News Release - FDA]
[06/15/2009 - Stimulant Medications Prescribing Information, Medication Guides - FDA]

Considerando il recente avvio del Registro regionale Lombardo per l'ADHD, il programmato avvio di altri registri regionali e di una nuova forma ridotta di registro Nazionale, la possibile autorizzazione all'immissione al commercio per alcune formulazioni a lento rilascio per il prossimo anno, e l'interesse suscitato dalle scorse edizioni, è in preparazione il

4° Workshop sull'ADHD

che si terrà a

Cagliari dall'8 al 10 Marzo 2012.

Quest'anno parteciperanno allo workshop anche alcuni colleghi europei che stimoleranno la discussione su argomenti controversi (p. es., comorbidità con Disturbi pervasivi dello sviluppo e/o ritardo mentale, neuro feedback come pratica terapeutica, efficacia degli interventi non farmacologici).

Come lo scorso anno lo workshop sarà articolato in Letture, Simposi, Dibattiti e Poster, cui si aggiungeranno i Seminari. I Seminari si svolgeranno in piccoli gruppi (25-30 partecipanti) e avranno due animatori (un italiano e uno straniero). I risultati di ciascun Seminario saranno riportati nella sessione plenaria per la discussione collettiva.

Alcuni dei temi saranno ulteriormente discussi nell'ambito della EUNETHYDIS *2nd International ADHD Conference* che si terrà a Barcellona il 23-25 Maggio.

Per maggiori informazioni: http://eunethydisconference.com/index.html

Alessandro Zuddas, Maurizio Bonati, Antonella Costantino, Gabriele Masi, Pietro Panei

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*".

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