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J. GORDON MILLICHAP, M.D., F.R.C.P., EDITOR

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ATTENTION DEFICIT DISORDERS

REDUCTION OF DRUG ABUSE IN ADOLESCENTS PREVIOUSLY TREATED WITH STIMULANTS FOR ADHD

The effects of early stimulant medication on subsequent risk for cigarette smoking and substance use disorders (SUDs) were evaluated in a 5-year, case-controlled, follow-up study of adolescent girls with ADHD at the Pediatric Psychopharmacology Program, Masachusetts General Hospital, Boston, MA, and Department of Psychiatry, New York State University, Syracuse, NY. Of 114 ADHD subjects (mean age 16.2 years; range 10 to 24 years at follow-up), 94 were treated with stimulants. No differences in age, rates of conduct disorder, ethnicity (95% white), socioeconomic status, parental history of SUDs, or severity of ADHD were identified at follow-up among those exposed or unexposed to stimulants. Subjects with ADHD receiving stimulants were more likely to have parents with a history of ADHD.

Stimulant-exposed adolescents with ADHD were 73% less likely to be diagnosed with SUD compared with those unexposed. Stimulant exposure provided a significant protective effect on development of any SUD and cigarette smoking (P=0.001), and this effect was maintained when controlling for conduct disorder. Furthermore, no increase in risk of class or severity of dependence was identified. Similarly, stimulant exposure had no significant effect on risk of alcohol abuse or alcohol dependence, and patients receiving prior therapy had a 72% lower risk and later onset of cigarette smoking. Age at onset or duration of stimulant therapy had no effect on risk of any SUD or cigarette smoking. In subjects who developed SUDs or started smoking, stimulant therapy had no effect on the duration of abuse. (Wilens TE, Adamson J, Monuteaux MC, et al. Effect of prior stimulant treatment for attention-deficit/hyperactivity disorder on subsequent risk for cigarette smoking and alcohol and drug use disorders in adolescents. **Arch Pediatr Adolesc Med** Oct 2008;162:916-921).

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(Respond: Timothy E Wilens MD, Pediatric Psychopharmacology Program, Masachusetts General Hospital, Harvard Medical School, 55 Parkman St, Yawkey 6A, Boston, MA 02114. E-mail: twilens@partners.org).

COMMENT. If we start stmulant treatment, will it increase the risk of drug abuse in my child with ADHD at a later age? This is a common concern and question of parents faced with the prospect of long-term therapy with stimulants for ADHD in a child of school age. Studies have demonstrated that ADHD is a risk for SUDs (Wilens TE et al. **J Nerv Ment Dis** 1997;185:475-482). Since stimulants are potential drugs of abuse, the assumption follows that they may increase the risk of cigarette smoking and SUDs when usd to treat ADHD. Opinions vary but most studies, including a meta-analysis, show no increase or even a protective effect against subsequent cigarette smoking or SUDs in adolescents and adults following early stimulant therapy for ADHD. (Wilens TE et al. **Pediatrics** 2003;111;179-185). The above group of investigators previously demonstrated a reduced risk for SUDs in adolescent boys who previously received stimulant therapy for ADHD (Biederman J, Wilens TE, et al. **Pediatrics** 1999;104:e20). The present study finds similar results in adolescent girls with ADHD who had received early stimulant treatment, even in those with comorbid conduct disorder. In addition to a reduction in risk of SUDs, cigarette smoking was also reduced, and risk of alcohol abuse or dependence was not increased. The results of this and similar studies should allay parental concerns about risk of later development of substance abuse in a child treated with stimulants for ADHD.

"Around the clock" or "intermittent" stimulant therapy: Pros and Cons. In the above study, "a life-time history of stimulant medication" was a criterion for selection of drug-exposed subjects. A continuous or intermittent dose regimen (with drug holidays) was not itemized. Opinions vary on the pros and cons of each method of treatment. Baron, David A, Temple University School of Medicine, at a recent Annual Chairs in Psychiatry Summit, favors "need to treat around the clock" "because the symptoms of the 'disease' are continuous." (**NeuroPsychiatry Review** Oct 2008;9(10): courtesy of Millichap, Martin G, Dept Health and Human Services, Waukesha, WI). Many would characterize ADHD as a 'syndrome' or 'symptom complex,' not a disease, and justification is tenuous for "around the clock" drug treatment, with its attendant adverse effects. Further studies are needed, comparing long-term effectiveness and toxicity of 'continuous' and 'intermittent' therapy of ADHD.

CARDIOVASCULAR RISK SCREENING BEFORE STARTING STIMULANTS FOR ADHD IN CANADIAN PRACTICE

Health Canada released a statement advising against stimulants in ADHD patients with cardiac disease in May 2006, after isolated reports of sudden death The impact of this advisory on 1) physicians' cardiovascular assessment of all children with ADHD before starting stimulant medications, and 2) on the treatment of children with potential or real cardiac disease was assessed by questionnaires mailed to noncardiologists and pediatric cardiologists in Canada from the Department of Pediatrics, IWK Health Centre, Dalhousie University, Halifax, Nova Scotia. Of a total of 2326 questionnaires distributed, 717 (31%) were returned. The proportion performing a full screen increased for both noncardiologists

(0.2% to 15.1%) and cardiologists (54.8% to 68.6%) after the advisory. The change in the use of a modified screen was 7.4% to 34.5% for noncardiologists and no increase for cardiologists (7.8% to 5.9%). The proportion of noncardiologists willing to prescribe stimulant medications in children with potential or actual cardiac issues showed a considerable decrease. These changes in practice following the advisory have occurred despite the lack of studies to address the actual cardiac risks of stimulant medications. Consensus recommendations are needed to determine whether screening before starting treatment is necessary and which children may be treated cautiously. (Conway J, Wong KK, O'Connell C, Warren AE. Cardiovascular risk screening before starting stimulant medications and prescribing practices of Canadian physicians: Impact of the Health Canada Advisory. **Pediatrics** October 2008;122:e828-e834). (Respond: Jennifer Conway MD. E-mail: jennifer.conway@iwk.nshealth.ca).

COMMENT. A full cardiac screen consists of all of the following: ask about a history of congenital heart disease, family history of sudden death, and family history of early coronary infarct, record the pulse and blood pressure, check for murmur, and obtain ECG. A modified screen differs only in that the ECG is performed selectively for children with abnormal exam.

In the US, the American Academy of Pediatrics, contrary to an American Heart Association statement advising pre-treatment ECG, considers routine ECG before starting stimulant therapy for ADHD to be unnecessary. Cardiac history and examination are recommended, and ECG and cardiac consultation, only if clinically indicated. (Perrin JM et al. **Pediatrics** 2008;122:451-453; **Ped Neur Briefs** Sept 2008;9:66).

SLEEP DISORDERS

OLFACTORY DYSFUNCTION AND HYPOCRETIN IN NARCOLEPSY

CSF orexin A (hypocretin-1) is decreased or absent in narcoleptic patients with cataplexy. Researchers at Christian-Albrechts University Kiel, Germany, analyzed olfactory sensation of 10 adult patients and 10 controls. Orexin-A was applied intranasally in 7 of the patients, and odor detection thresholds for 2-phenyl-ethyl alcohol were measured. Patients showed significantly lower scores for olfactory threshold, discrimination, and identification, separately, and for the total scores. In all patients, the odor detection olfactory threshold score increased after intranasal orexin A compared to placebo. Lack of CNS orexin is involved in the pathophysiological mechanism underlying olfactory dysfunction in narcolepsy. (Baier PC, Weinhold SL. Huth V, Gottwald B, Ferstl R, Hinze-Selch D. Olfactory dysfunction in patients with narcolepsy with cataplexy is restored by intranasal orexin-A (hypocretin-1). **Brain** Oct 2008;131:2734-2741). (Respond: Dr Paul Christian Baier, Department of Psychiatry and Psychotherapy, Christian-Albrechts University Kiel, Niemannsweg 147, 24105 Kiel, Germany).

COMMENT. Orexin A and B are neuropeptides synthesizd by neurons in and around the lateral hypothalamus and olfactory tract. Orexin is involved in sleep wake regulation. Olfactory dysfunction, an early predictor of Parkinsonism, is also a sign of narcolepsy with cataplexy. Correction of the associated orexin A defciency in the CSF by intranasal

administration will restore the olfactory sensation of patients with narcolepsy. The authors comment that orexin A intranasally is, theoretically, a promising treatment for narcolepsy and may be considered for future trial.

DIAGNOSIS AND MANAGEMENT OF NARCOLEPSY REVIEWED

Researchers at Duke University Medical Center, and Veterans Affairs Medical Center, Durham, NC, review the epidemiology, pathophysiology, diagnosis, and treatment of pediatric narcolepsy. Narcolepsy is a disorder of rapid eye movement (REM) sleep characterized by excessive daytime somnolence, associated with sleep paralysis, hypnagogic (when falling asleep) and hypnopompic (when awakening) hallucinations, and cataplexy. Prevalence is 0.05% in the US and Europe; 0.18% in Japan; and 0.002% in Israel; greater in males than females. Onset highest in second decade, with peaks at 14 yrs and 35 yrs. Etiology is unknown, possible neurodegenerative with autoimmune component. Patients with narcolepsy and cataplexy share the same HLA genotype. Predominantly sporadic, sometimes familial, only 25-31% concordance in twin studies. CSF levels of hypocretins less than 110 pg/ml are diagnostic of narcolepsy with cataplexy. Obesity with narcolepsy is associated with low 24 hr leptin levels, a hormone secreted by adipose tissue. Narcolepsy is idiopathic or secondary (symptomatic) and caused by hypothalamic tumors, head trauma, multiple sclerosis, vascular, and encephalitic disorders. In addition to the classic tetrad of narcolepsy symptoms, semi-purposeful, automatic behavior is common during the day, sometimes misdiagnosed as epilepsy, and frequent noctural awakenings. Obesity and obstructive sleep apnea frequently coexist. The interval between symptom-onset to diagnosis is about 10 years. Misdiagnosis is common in children with narcolepsy, leading to delay in treatment. The history combined with polysomnography and mean sleep latency (MSLT) <8 minutes are used in diagnosis in adults and in children older than 8 years. Two or more sleep onset REM sleep periods (SOREMP) in a MSLT within 15 min of sleep onset are consistent with narcolepsy. MRI is normal in idiopathic narcolepsy. Treatment includes lifestyle changes, brief naps, caffeine, reduced carbohydrates or Atkins diet, and pharmacotherapy (methylphenidate, amphetamines, and non-approved pediatric use of modafinil (Provigil), and sodium oxybate (Xyrem). Sodium oxybate is particularly effective in cataplexy in adults. Antidepressants have also been used to treat cataplexy and hypnogogic hallucinations in adults. (Peterson PC, Husain AM. Pediatric narcolepsy. **Brain Dev** Nov 2008;30:609-623). (Respond: A.M. Husain, E-mail: Aatif.husain@duke.edu)

COMMENT. A high index of suspicion is required in the diagnosis of narcolepsy. This review provides an excellent account of the diagnosis and treatment of narcolepsy. A sleep specialist reports the highest success rate for correct diagnosis among neurologists (55%), psychiatrists (11%), and pediatricians (0%). (Kryger MH et al. **Sleep** 2002;25:36-41).

From the Archives: Idiopathic narcolepsy: a disease sui generis. By Adie WI. **Brain** 1926;49:257-306 and The narcolepsies. By Kinnear Wilson SA. **Brain** 1928;51:63-109. Adie describes cases seen at Queen Square and misdiagnosed as epilepsy, and summarizes earlier reports by Gelineau (1880). Examples of patients are two soldiers courts-martialed for falling asleep on listening-post duty. Adie coins the term cataplexy associated with narcolepsy. He considers the etiology an endocrine-nervous disorder, a disease sui generis, a proposal

dismissed by his senior colleague, Kinnear Wilson, who regards narcolepsy as a syndrome with several different causes, traumatic, endocrine, epileptic, toxi-infective, circulatory, tumor, and idiopathic. Neither Adie nor Kinnear Wilson refers to hyposmia in their account of narcolepsy-cataplexy disorder, but they did locate the pathology in the floor of the third ventricle in symptomatic cases. (Compston A. **Brain** Oct 2008;131:2532-2535).

ELECTROENCEPHALOGRAPHY

PROGNOSTIC VALUE OF EEG IN ASPHYXIATED NEWBORNS TREATED WITH HYPOTHERMIA

Researchers at Children's Hospitals in Milan, Italy, determined the prognostic value of electroencephalographic patterns in 23 newborns with severe perinatal hypoxic-ischemic encephalopathy, treated with hypothermia. EEG monitoring was obtained within 48 hours after birth, and at follow-up at ages 1 week, 1 month, 3-6 months, and 1 year. EEG background activity was classified as follows: 1) inactive pattern; 2) severe low-voltage continuous pattern; 3) trace alternant-like, discontinuous pattern; and 4) monomorphic middle-voltage, continuous 30-100mcV activity, with poor spatial and sleep-state organization. Pattern 1 (inactive) in the first 48 hrs was associated with death or severe neurologic sequelae. Pattern 2 (low-voltage continuous) at age 1 week indicated a poor prognosis, and the persistence of EEG abnormalities in 67% patients at age 1 month was associated with a higher risk of neurologic sequelae. A normal EEG at age 1 month was associated with a favorable outcome at age 1 year. After 1 month of age, the EEG is less sensitive but more specific in prediction of outcome, due to the natural trend toward normalization with age. At age 1 year, 52% infants had normal neurologic examinations, 13% had minor sequelae, and 17% major sequelae; 17% had died within 1 month of age. (Mariani E, Scelsa B, Pogliani L, Introvini P, Lista G. Prognostic value of electroencephalograms in asphyxiated newborns treated with hypothermia. **Pediatr Neurol** Nov 2008;39:317-324). (Respond: Dr Scelsa, Department of Child Neurology, Vittori Buzzi Children's Hospital, Via Castelvetro 32, 20154 Milan, Italy. E-mail: b.scelsa@icp.mi.it).

COMMENT. These results confirm previous findings that background EEG abnormalities detected in newborns soon after hypoxic-ischemic encephalopathy are predictive of outcome, even in patients treated with hypothermia.

AMPLITUDE-INTEGRATED EEG IN THE NEWBORN

Th value of amplitude-integrated electroencephalography (aEEG) in the newborn is explored by researchers at Washington University, St Louis; Wilhelmina Children's Hospital, Utrecht, Netherlands; and Uppsala University Hospital, Sweden. The system was originally designed to monitor lower amplitude signals of 1 to 10 mcV and depressed cerebral activity in adults undergoing bypass surgery, as well as seizure activity. Meta-analysis has confirmed that the aEEG pattern in the first 6 hours of life of term newborns with hypoxic-ischemic encephalopathy is strongly predictive of outcome. Pattern-recognition may be more reliable than amplitude in the evaluation of aEEG. The electrode placement over parietal areas,

coinciding with vulnerable watershed areas of cortex, yields a high sensitivity (81%) for electrical seizure activity. Bedside aEEG monitoring "on-line" and around the clock is underway in the NICU to explore feasibility and impact on management of electrographic seizures. In contrast to a low sensitivity and high false-positive rate using electronic fetal heart monitoring, the early use of aEEG has a sensitivity of 85% to 91% for predicting neurodevelopmental outcome in term newborn infants with neonatal encephalopathy. aEEG is used to recruit patients for study of therapeutic hypothermia, and clinically to evaluate the newborn by complementing the neurologic examination, conventional EEG, and neuroimaging, not in isolation. (Shah DK, de Vries LS, Hellstrom-Westas L, Toet MC, Inder TE. Amplitude-integrated electroencephalography in the newborn: a valuable tool. **Pediatrics** Oct 2008;122:863-865). (Respond: Divyen K Shah MB ChB, Washington University, Department of Pediatrics, 8th Floor, NW Tower, 1 Children's Place, St Louis, MO 63110. E-mail: shah-d@kids.wustl.edu).

COMMENT. Analsis of clinical data at 18 months in a study of head cooling for neonatal encephalopathy found that infants with greater amplitude-integrated EEG, lower birth weight, absence of seizures, and higher Apgar score had significantly better outcomes. Gender and gestational age were not significantly associated with outcome. (Wyatt JS et al. **Pediatrics** 2007;119:912-921; **Ped Neur Briefs** June 2007;21:48).

EEG IN SPECIFIC LANGUAGE IMPAIRMENT

The value of routine wake electroencephalography in children with specific language impairment was reviewed retrospectively in 111 children examined over a 10-year interval at Montreal Children's Hospital, Quebec, Çanada. Children with known central nervous system disorders were excluded. Sleep-deprived EEG was not performed. The wake EEG was abnormal in 35 (31.5%) children, including 7 (6.3%) with epileptiform activity, and higher than that in 'normal' children (3.54%). (NS. P=0.12). The epileptiform activity was active in 3 patients. Three (2.7%) had excessive paroxysmal activity (PA) with hyperventilation, and 3 (2.7%) had excessive PA with photic stimulation. Female gender had a small association with abnormal EEG. Two patients with epileptiform EEGs received anticonvulsant medication on parental request; subsequent EEGs but not the speech were improved. Soft neurologic signs, macrocephaly, or microcephaly were present in 21 (18.9%) children, ADHD in 15 (13.5%), and comorbid learning difficulties in 14 (12.6%). (Venkateswaran S, Shevell M. The case against routine electroencephalography in specific language impairment. **Pediatrics** Oct 2008;122:e911-e916). (Respond: Michael Shevell MDCM, FRCP(C), E-mail: Michael.shevell@muhc.mcgill.ca).

COMMENT. Wake EEG is of uncertain value in the routine diagnostic evaluation of children with specific language impairment. Definitive recommendations await further investigation with both wake and sleep EEG. A previous prospective study including both wake and sleep EEG demonstrated abnormalities in almost half of the patients (14 of 32) with developmental dysphasia, and epileptic activity in 30 of the 32 in overnight recordings. (Echenne B et al. **Brain Dev** 1992;14:216-225). Patients with receptive dysphasia were at highest risk for abnormal EEG. (Tuchman R et al. **Pediatrics** 1991;88:1219-1225).

SEIZURE DISORDERS

PROPHYLACTIC PHENOBARBITAL AFTER RESOLUTION OF NEONATAL SEIZURES

The degree of practice variation in continuance of phenobarbital treatment despite resolution of neonatal seizures was evaluated by national survey conducted at the University of Rochester Medical Center, New York. Surveys mailed to 609 randomly selected child neurologists and 579 neonatologists were completed by 20.7% and 23.1%, respectively. Practices varied widely, with little difference in response frequencies between child neurologists and neonatologists. For child neurologists, prophylactic phenobarbital was always used in 5%, sometimes used in 72%, rarely in 19%, and never in 3%. Responses of neonatologists were similar. Duration of treatment was <1 month in 8%, 1-3 months in 45%, 3-6 months in 37%, none longer than 6 months. Drug levels were monitored routinely by 34%, and only when indicated by 57%. Physicians were more likely to respond yes to continuation of treatment for a given scenario than would be predicted by their overall responses to questions. Since the survey of practices 15 years ago, physicians are reporting less frequent and shorter phenobarbital treatment after resolution of neonatal seizures. (Guillet R, Kwon JM. Prophylactic phenobarbital administration after resolution of neonatal seizures: survey of current practice. **Pediatrics** Oct 2008;122:731-735). (Respond: Ronnie Guillet MD, PhD. E-mail: Ronnie_guillet@urmc.rochester.edu).

COMMENT. The relatively low response to this survey and surveys in general is explained by the length and complexity of questions, and the increasing number of similar requests. Possible late cognitive effects of long-term phenobarbital in the infant are one reason to limit duration of prophylactic treatment. A randomized trial is needed to determine benefits and adverse effects of continued therapy after discharge from the NICU.

PREVENTION OF STATUS EPILEPTICUS IN DRAVET SYNDROME: NATIONWIDE SURVEY IN JAPAN

Child neurologists and epileptologists at various university centers in Japan were surveyed by questionnaire to identify the most effective strategies for management of and prophylaxis against status epilepticus (SE) in children with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome), especially when associated with fever. Data from 109 patients were analyzed (51 males, 58 females; mean age 10.7 years +/- 6.53; range 1-37 years). Ten had no SE and were excluded. Anticonvulsants with excellent efficacy against SE occurrence were potassium bromide (41.7%), zonisamide (13.5%), clobazam (10%), valproate (8%), phenobarbital (6.7%), and phenytoin (2.6%). Clonazepam and carbamazepine were ineffective. Diazepam suppository was most frequently used against SE triggered by fever, but was effective in only 2.4% cases. Intravenous medications most effective in terminating ongoing SE were barbiturates (75-100%), midazolam (68.8%), diazepam (54.3%), lidocaine (21.4%), and phenytoin (15.4%). (Tanabe T, Awaya Y, Matsuishi T, et al. Management of and prophylaxis against status epilepticus in children with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome) – A nationwide

questionnaire survey in Japan. **Brain Dev** Nov 2008;30:629-635). (Respond: T Tanabe. E-mail: tanabemapa@pop01.odn.ne.jp).

COMMENT. The use of bromides for treatment of SMEI and their significantly higher efficacy than that of valproic acid and zonisamide are interesting and surprising observations. Bromides were first introduced for the treatment of epilepsy in 1853 (Locock C. **Lancet** May 23, 1857;527). After phenobarbital became available in 1912 and phenytoin in 1937, the use of bromides was largely discontinued. The administration of bromides is not as simple as that of newer anticonvulsant drugs. Its effectiveness depends on a lowered intake of sodium chloride in the diet. The onset of action is delayed for 2 to 3 weeks, and high blood levels are maintained for 1 to 2 weeks after bromides are discontinued. Unlike other anticonvulsants, an abrupt withdrawal of bromides is unlikely to precipitate status epilepticus.

Bromides are usually administered in liquid or tablet forms of sodium bromide or as triple bromide elixir, containing 400 mg each of sodium, potassium and ammonium bromide per 5ml. (Livingston S et al. **Amer J Dis Child** 1953;86:717-720)(Goodman LS, Gilman A. **The Pharmacological Basis of Therapeutics.** New York. Macmillan, 1955;156-163). Suggested starting and maintenance doses of bromides are as follows: For children under 3 years old, 160 mg 2x daily (maximum 320 mg 3x daily); 3 to 6 years old, 320 mg 2x daily (maximum 640 mg 3x daily). (Livingston S. **Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence.** Springfield, IL. Charles C Thomas, 1972;198, 268-274). A satisfactory blood level of bromides is generally 20 to 25 mEq/L (160 to 200 mg%). Drowsiness and cutaneous reactions are the most troublesome side effects. Administration of extra sodium chloride and fluids usually alleviates drowsiness. Acneiform rashes are a frequent occurrence in adolescents and adults, but are uncommon in infants and young children. Granulomatous lesions (bromoderma) will occur occasionally, taking months to disappear after bromide withdrawal.

Epileptic syndromes with high rates of status epilepticus, in addition to SMEI, include Panayiotopoulos syndrome and symptomatic occipital lobe epilepsy secondary to neonatal hypoglycemia (Okanishi T et al. **Brain Dev** Nov 2008;30:624-628).

RISK OF EPILEPSY IN OFFSPRING EXPOSED TO PREECLAMPSIA OR ECLAMPSIA

Researchers at the University of Aarhus, Denmark, and at centers in China and US, conducted a population-based study of singletons born in Denmark (1978-2004) with information on preeclampsia and epilepsy obtained from the Danish National Hospital Register. They identified 2.9% of children exposed to preeclampsia, and 0.04% to eclampsia during prenatal life. The incidence of epilepsy at 27-year follow-up was increased following exposure to either preeclampsia or eclampsia in children born after 37 weeks of gestation. Children born preterm showed no association between preeclampsia and epilepsy. In contrast, the incidence rate ratios were 1.29 for children born at term and 5.03 for children born postterm. (Wu CS, Sun Y, Vestergaard M, et al. Preeclampsia and risk for epilepsy in offspring. **Pediatrics** Nov 2008;122:1072-1078). (Respond: Chun Sen Wu MD, E-mail: cw@soci.au.dk).