Head Trauma Precedes Confusional Migraine

BY BETSY BATES Los Angeles Bureau

LOS ANGELES — Acute confusional migraines in children and adolescents are most common in young boys and are often associated with head trauma, Dr. A. David Rothner reported at the annual scientific meeting of the American Headache Society.

A review of 90 cases-22 from the Cleveland Clinic and 68 from a literature review-portrayed clear patterns of symptoms that may appear alarming to pediatricians and emergency department physicians. Confusion lasted from 10 minutes to 2 days, with the majority of patients remaining confused for 4 hours or less, but 25 (28%) were confused for 5-8 hours.

Not all children described headache, but some were so confused they were unable to communicate information about their symptoms. All were disoriented, 72 had amnesia, 63 had speech impairment, 49 had agitation, 49 had emesis, 36 had visual disturbances, and 33 had somnolence.

Notably, 74 children had a family history of migraine, and 52 had a personal history of migraine.

Acute confusional migraines were recurrent in more than a third of patients.

Boys aged 5-12 years, followed by boys aged 13-17 years, were most often affected. Proximal head trauma, often very mild, was present in more than a third of cases.

BRIEF SUMMARY: Consult the full prescribing information for complete product information. Daytrana™ (methylohenidate transfermal system) CII Rx Only

BritEr Summan . Unionate transfermal system) Daytrana™ (methylphenidate transfermal system) INDICATION AND USAGE Attention Deficit Hyperactivity Disorder (ADHD): Daytrana™ (methylphenidate transfermal system) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD): and is available in 10, 15, 20, and 30 mg dosing strengths. The efficacy of Daytrana™ was established in two controlled clinical traits in children with ADHD. Special Diagnosis considerations: Special Disorder (ADHD): and is syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-V-TR° characteristics. Meed for Comprehensive Treatment Program: Daytrana™ is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Brug treatment may not be indicated for all children with this syndrome. Stimulanis are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psycholosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the hybrican's assessment of the childred versions alone are insufficient. The effectiveness of Daytrana™ for long-term use, i.e., for more than 7 weeks, has not been systematicand the child's symptoms.

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CONTRAINDICATIONS Aquation: Daytrana™ is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these

ptoms. resensitivity to Methylphenidate: Daytrana™ is contraindicated in patients known to be hypersensitive to hylphenidate or other components of the product (polyester/ethylene vinyl acetate laminate film backing, acrylic adhesive, ne adhesive, and fluoropolymer-coated polyester). recoma: Daytrana™ is contraindicated in patients with gluacoma. Daytrana™ is contraindicated in patients with gluacoma.

EAC I (UNS). ase Inhibitors: Daytrana™ is contraindicated during treatment with monoamine oxidase inhibitors, and also o f 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises

WARNINGS Serious Cardiovascular Events Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart hythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Addust Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs. *Hypertension and Other Cardiovascular Conditions*

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Sufe: datuum is nuclease an exercise e.g., those with pre-existing fivpertension, heart failure, recent myocardiai imarcuon, or ventricular arrhythmia. Assessing Cardiovascular Status in Patients Being Treated With Stimulant Medications Assessing Cardiovascular arrhythmia. Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful his-tory (including assessment for a family history of suden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggests uch disease (e.g., electro-cardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation. **Contact Sensitization**: Use of DaytranaTM any lead to contact sensitization. DaytranaTM should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of DaytranaTM and is not by itself an indication of sensitization indications and the suspected if erythema is accompanied by evelopment of an allergic contact dermatitis, may develop systemic sensitization or ther systemic reactions if meritybenicitae-containing products are taken via other routes, e.g., orally. Manifestation should be disconstrued by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if meritybenicate-containing products are taken via other routes, e.g., orally. Manifestations development sensitization may include a lare-up of previous dermatilis or of prior positives, e.g., orally. Manifestations development sensitization to daystemic reactions and meritybenic develop systemic reactions and meritybenic development development. *Beviense* which development development of an allergic contact dermatitis, may develop systemic sensitization to adveranaTM as evidence

ieralized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, rhea, or vomiting. ients who develop contact sensitization to Daytrana[™] and require oral treatment with methylophenidate should be ated on oral medication under close medical supervision. It is possible that some patients sensitized to methylphenidate exposure to Daytrana[™] may not be able to take methylphenidate in any form. tudy designed to provoke skin sensitization revealed a signal for Daytrana[™] to be an irritant and also a contact sensitizer, s tudy involved an induction phase consisting of continuous exposure to the same skin site for 3 weeks, neek rest period, and then challenge/rechalenge, Under conditions of the study Daytrana[™] was more irritating than both the cake patch control and the negative control (saline). Of 133 subjects who participated in the challenge phase of the situziation study, at least 18 (13.5%) were contirmed to have been sensitized to Daytrana[™] was aced on the results of the situziation study, at least 18 (13.5%) were contirmed to have been sensitized to Daytrana[™] was aced on the results of the lilenge and/or rechallenge phases of the study. ng Daytrana[™] as prescribed, alternating application sites on the hip, no cases of contact sensitization were reported. were, since patients were not specifically assessed for sensitization in the clinical effectiveness studies, it is unknown what true incidence of sensitization is when Daytrana[™] is used as directed. *chalatic Adverse Events scienting Psychosis* ministration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-ministration of simulants.

Imp Psychocis ation of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-sychotic disorder.

existing psycholic disorder. **Bipplar Illness** Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of con-cern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder, such screening should include a detailed psychiatric history, including a family history of sucide, bipolar disorder, and depression. **Emergence of New Psycholic or Manic Symptoms**. Teratment emergent psycholic or manic Symptoms, e.g., hallucinations, delusional thinking, or mania in children and adoles-cents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with verts out of 3.482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stim-ulant-treated patients compared to 0 in placebo-treated patients. **Adventssion**

(4) patients with events out of year exposure of the patients. Aggression Aggression Aggression and the postmarketing experience of some medications indicated for the treatment of ADHD, Athough there is no sys-tematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility. Long Term Suppression of Borwh: Caretal for 10 for 3 days per week through the year) have a temporary slowing in growth rate (or average, a total of about 2 m less growth in height and 2 / the gless growth in weight over 3 years), subgress that consistently medicated children (i.e., treatment for 7 days per week through the year) have a temporary slowing in growth rate (or average, a total of about 2 m less growth in height and 2 / the gless growth in weight over 3 years), without evidence of growth rate of using a temporary slowing in growth caretal dual of an evel patient who and patients who and y likely have west instructions begin to weight as expected may meed to have their treatment interrupted. Surgers: There is some clinical evidence that stimulants may lower the convolive threshold in patients with prior history of sizures, in patients with prior EEG abnormalities in absence of sizures, the drug should be discontinued. Visual Disturbance:: Difficulties wi

Idence should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can ded tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes specially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that follow-up. pression may occur av require follow-up

may require follow-up. PRECAUTIONS PRECAUTIONS PRECAUTIONS Precautions and the state of the

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. Human pharmacologis studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some tricyclic drugs (e.g., linipramine, clomiptramine, desipramine) and selective serotomin reuptake inhibitors. Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing methylphenidate. Serious adverse events have been reported in concomitant use of methylphenidate with coindine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alphe-2-agonists has not been systematically evaluated.

a-2-agonists has not been systematically evaluated. inogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenicity studies of transdermal methylphenidate have been performed. In a lifetime carcinogenicity study of oral methylphenidate carried out in B6CSF1 mice, methylphenidate ed an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of wimately 60 my/kg/day. Hepatoblastoma is ar leatively rare rodent malignant tumor type. There was no increase in total gnant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors and the significance of events ho humans is unknown.

Mart Replatic LIMOIS. The mouse stream used is sensitive to the decomposition of the decomposition of the methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in administered methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in at; the highest does used was approximately 45 mg/kg/day. 4 veek oral carcinogenicity study in the transgenic mouse strain p53^{ac}, which is sensitive to genotoxic carcinogens, was no evidence of carcinogenicity. In this study, male and female mice were fed diets containing the same tration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 direct conthetenidete. Imprentate. was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lympho assay, and was negative *in vivo* in the mouse bone marrow micronucleus assay. Sister chromatid exe aberrations were increased, indicative of a weak clastogenic response, in an *ivritro* assay in cultured

hamster ovary cells. Methyphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day.

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cal development program for Daytrana™ included exposures in a total of 1,158 participants in clinic

The pre-marketing clinical development program for Daytrana^{er} included exposures in a total or 1, too part trials (758 pediatric patients and 400 healthy adult subjects). These participants received Daytrana^{er} in participants are considered and the participants and a clinical patients (age 6 to 16 years) were evaluated in 6 controlled clinical table clinical studies, and 4 clinical pharmacology studies. Adverse reactions were assessed by collecting ad the results of physical examinations, vital signs, weights, laboratory analyses, and ECGs. Refer to the Full Prescribing Information for details of adverse event data collection.

Is of physical examinations, vital signs, weights, laboratory anaryses, and c-ucos, the Full Prescription Information for deals of adverse event data collection. Findings in Clinical Trials With Daytrana[™] *Events Associated With Discontinuation of Treatment:* In a 7-week double-blind, parallel-group, placebo-controlled children with ADHD conducted in the outpatient setting, 7.1% (7/98) of patients treated with Daytrana[™] discontinued diverse events compared with 1.2% (1/05) receiving placebo. The reasons for discontinuation among the patients ith Daytrana[™] were application site erythema, application site reaction, contisuonal state, crying, tics, headaches, in flectious mononucleosis, and viral infection. *Events Occurring at an Incidence of 5% or More Among Patients Treated With Daytrana[™]*: Table 1 enumerates ence of treatment-emergent adverse events reported in a 7 week double-blind, parallel-group, placebo-controlled children with ADHD conducted in the outpatient setting.

TABLE 1: Most Commonly Reported Treatment-Emergent Adverse Events (≥ 5% and 2x Placebo) in a 7-week Placebo-controlled Study Mumber (5) of Subjects Mith ≥ 1 Adverse Events Adverse Event Daytran³⁴ Placebo Mumber of Subjects With ≥ 1 Adverse Event (N = 98) Mumber of Subjects With ≥ 1 Adverse Event (N = 98) Mumber of Subjects With ≥ 1 Adverse Event (N = 98) Mumber of Subjects With ≥ 1 Adverse Event (N = 98) Mumber of Subjects With ≥ 1 Adverse Event (N = 98) Mumber of Subjects With ≥ 1 Adverse Event (N = 98) Mausea 12 (12) 2 (2) Number (5) 2 (2) Subjects Mith ≥ 1 Adverse Event (N = 98) Mausea 12 (12) 2 (2) Mumber (5) 2 (2) Mumber (6) 2 (2 Nausea Vomiting Nasopharyngitis Weight decreased Anorexia Decreased appetite Affect lability* Diagnosis of allergic contact dern be corroborated by appropriate dir ing (see WARNINGS – Contact Se Adverse Fvents With Ihe Long-Daytrana⁷⁹: In a long-term open-up to 40-month duration in 191 ADHD, the most frequently report emergent adverse events in pedi treated with Daytrana⁷⁷ for 12 hou anorexia (87 subjects, 46%), insor jects, 30%), viral infection (54 su nor from the study because of treatm ation site reaction (12 subjects, 6%) Nasal congestion

Six subjects had affect lability, all judged as mild and described as increased emo-tionally sensitive, emotionality, emotional instability, emotional lability, and inter-

dache (53 subjects, 28%). A total of 45 (24%) subjects were withd events. The most common events leading to withdrawal were app

In the most had 17 subjects, and 10 with the second sec

occlusion efinite causal relationship has not been established, the following have been reported in pat-ter. Blood/ymphatic: leukopenia and/or anemia. Hepatobiliary: abnormal liver function, n-elevation to hepatic coma; Psychiatric: transient depressed mood; SkinSubeutaneous: Scaliguans Syndrome: Very rare reports of neuroleptic malignant syndrome (MMS) have been rec-patients were concurrently receiving therapies associated with MMS. In a single report, a ten-year on methylphenidate for approximately 18 months experienced an MMS-like event within 44 irst dose of veniataxine. It is uncertain whether this case represented a drug-drug interaction, a ne or some other cause. e elevation to nepatic com Malignant Syndrome: Ver e, patients were concurrent king methylphenidate for st of these, patients were concurrent I been taking methylphenidate for esting his first dose of venlafaxine. er drug alone, or some other cause UG ABUSE AND DEPENDENCE

dermal system), like other methylphenidate products, is

dependence information.
OVERDOSAGE
Signs and Symptoms: Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects. may include the following: vomiting, aglation, tremors, hyperreflexia, muscle twitching, convulsions (may be following): euphoria, contuision, halucinations, delirum, sweating, flushing, headache, hyperryrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydrasis, and dryness of muccus membranes.
Recommended Treatment: Remove all patches immediately and cleans the area(s) to remove any remaining adhesive. The continuing absorption of methylphenidate from the skin, even after removal of the patch, should be considered when treating patients with overdose. Treatment consists of appropriate supportive measures. The patient must be protocled against settral situal in the world agravate oversimulation already present. Intensive care musts be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia. Effecacy of pertoneal dialysis or extracorporeal hemodialysis of to Daytram⁴⁰ overdosage has not been established.
Poisso Control Center: As with the management of all overdosages, the possibility of multiple drug ingestion should be considered when develosage with methylphenidate.
Do not store patches unpouched. Store at 25 C (77 F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Once the tray is opened, use contents within 2 months. Apply the patch immediately upon removal from the protective pouch. Do not store patches unpouched.

the protective pouch. Do not store patches unpoucneu. rui tensorment account. REFERENCE American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: Manufactured for Shire US Inc., Wayne, PA 19087 by Noven Pharmaceuticals, Inc., Miami, FL 33186. For more information call 1-300-628-2088 or wist tww.shire.com. Description of the activation of Noven Pharmaceuticals, Inc. risit <u>www.shire.com</u>. iceuticals, Inc. euticals Ireland Limited. ™ is a trademark of Noven Pha '' is a trademark of Shire Pharn

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"When we're talking about confusion, for the most part we're not talking about a little bit of confusion," said Dr. Rothner, a pediatric neurologist and director of the Pediatric/Adolescent Headache Clinic at the Cleveland Clinic.

As an example, he described the case of a 14-year-old girl who experienced an aura followed by a bifrontal headache and a 5hour period of progressive disorientation, confusion, incontinence, bizarre behavior, and extreme combativeness that included kicking, screaming, scratching, and attempting to bite medical personnel. She was unresponsive to benzodiazepines. Once the confusion passed, the patient had no recollection of these events.

Her parents recalled two previous episodes that were less severe and involved nausea and vomiting. "There seems to be

Boys aged 5-12 years, followed by boys aged 13-17 years, were most often affected. Head trauma was present in more than one-third of cases.

something special about this group of patients that predisposes them to recurrent attacks of a very, very unusual phenomenon," Dr. Rothner noted.

Toxicology screens in 76 patients were all negative, as were examina-

tions of cerebrospinal fluid in 29. Computed tomography or MRI in 63 patients was normal in 57 and showed unrelated abnormalities in 6. Electroencephalograms were performed in 55 patients and were abnormal in 44, with the majority showing unilateral or bilateral slowing.

"The differential diagnosis can be the most difficult and problematic issue," Dr. Rothner explained. "If there is any doubt regarding the condition, transportation to an emergency room or trauma center is wise."

In the short term, "Care must be taken to make sure that one does not overlook a more ominous problem, like an epidural or subdural hematoma," he said in an interview following the meeting.

A careful description of the injury may be helpful in ruling out concussion. "Concussion often but not always involves a bigger hit and often but not always, immediate loss of consciousness," he said.

In these cases, mild trauma often occurred quite some time before the development of migrainelike symptoms, and then confusion. Visual disturbances were much more prevalent in patients with acute confusional migraine than in children with typical migraines.

Until the etiology is known, he cautioned against sedating patients, although he acknowledged that the agitation and confusion can be difficult to manage. Dr. Rothner also hesitates to prescribe triptans in the presence of a neurologic deficit.

Providing pain relief and antiemetics are key in the acute setting, and patients and families should be counseled about the high rate of recurrence of acute confusional migraine.