

Correspondence



The Effectiveness of the Varicella Vaccine

To the Editor: The findings of Vázquez et al. (March 29 issue)¹ on the effectiveness of the varicella vaccine were reassuring. However, we are concerned by the finding that only 74 percent of the suspected cases of chickenpox were confirmed by the polymerase chain reaction (PCR). Relying on information from a parent or diagnosis by a physician results in 26 percent of the children with a clinical diagnosis of chickenpox remaining susceptible and not undergoing vaccination. If these data are reexamined according to vaccination status, 92.5 percent of the clinical cases among unvaccinated children were confirmed by PCR, supporting the current practice of accepting information from a parent or diagnosis of chickenpox by a health care provider as a condition for exemption from vaccination. Furthermore, the case definition used (a positive PCR test) may have led to the exclusion of some cases among vaccinated children, therefore overestimating the effectiveness of the vaccine.^{2,3} The effectiveness of the vaccine would be lower if any vaccinated children without positive PCR tests had true cases of chickenpox.

Varicella vaccine is effective in preventing chickenpox, but reliance on PCR for confirmation of cases can result in an overestimation of the effectiveness of the vaccine, as may have been the case in the study by Vázquez et al. Cases of chickenpox among vaccinated persons (“breakthrough cases”) may be less likely to be associated with positive PCR results.

AISHA O. JUMAAN, PH.D., M.P.H.
 JANE SEWARD, M.B., B.S., M.P.H.
 National Immunization Program
 Atlanta, GA 30333
 aojl@cdc.gov

1. Vázquez M, LaRussa PS, Gershon AA, Steinberg SP, Freudigman K, Shapiro ED. The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med* 2001;344:955-60.
2. Storsaeter J, Hallander H, Farrington CP, Olin P, Mollby R, Miller E. Secondary analyses of the efficacy of two acellular pertussis vaccines evaluated in a Swedish phase III trial. *Vaccine* 1990;8:457-61.
3. Schlesselman JJ. Case control studies: design, conduct, analysis. New York: Oxford University Press, 1982.

The authors reply:

To the Editor: In our study, there were 208 unvaccinated children with potential cases of chickenpox, of whom 187 (90 percent) had a positive PCR test. By contrast, among the 122 children with potential cases who had received varicella vaccine, only 56 (46 percent) had a positive PCR test. The information necessary to make these calculations was not reported in the paper. We believe the explanation for this difference is that vaccinated children with an atypical rash are less likely to have chickenpox and not that the PCR test is less sensitive in vaccinated children. Certainly, there were many vaccinated children (56) with a rash in whom the PCR test was positive for varicella-zoster virus. Children with potential cases who were classified as negative for chickenpox had a negative result for varicella-zoster virus by the PCR test but had a positive result for a 268-bp fragment of the human β -globin gene, which indicated that there was amplifiable DNA in the sample. We believe these to be true negative results. The PCR assay is very sensitive; it gives a positive result for the presence of varicella-zoster virus in samples with as little as 100 fg of varicella-zoster virus DNA extracted from in vitro culture in 10 μ l of diluent.¹ In addition, in other studies the PCR test was used successfully to detect the vaccine strain of varicella-zoster virus in vaccinated subjects with zoster-like rashes, which in general are less likely to be vesicular than are disseminated rashes.²

The rates of vaccination among the children with potential cases of chickenpox in whom the PCR test was not positive were similar to those among their matched controls — as one would expect if the children with potential cases did not have chickenpox. Children with either a negative or an indeterminate PCR test were significantly less likely to have had a recognized exposure to someone with chickenpox than were children with a positive PCR test. Moreover, none of the parents of the 71 children whose PCR test was either negative or indeterminate reported that chicken-

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Your letter must be typewritten and triple-spaced. •Its text, not including references, must not exceed 250 words if it is in reference to a recent *Journal* article, or 400 words in all other cases (please provide a word count). •It must have no more than five references and one figure or table. •It must not be signed by any more than three authors. •Letters referring to a recent *Journal* article must be received within four weeks of its publication. •Please include your full address, telephone number, fax number, and e-mail address. •You may send us your letter by standard mail, fax, or e-mail.

Our address: Letters to the Editor • *New England Journal of Medicine* • 10 Shattuck St. • Boston, MA 02115

Our fax numbers: 617-739-9864 and 617-734-4457

Our e-mail address: letters@nejm.org

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. We are unable to provide prepublication proofs. Financial associations or other possible conflicts of interest must be disclosed. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal's* various print and electronic publications and in collections, revisions, and any other form or medium.

pox subsequently developed in a close contact of their children, whereas 30 percent of parents of 195 children whose PCR test was positive reported that chickenpox had developed in a close contact. Both of these findings support our contention that the children who did not have a positive PCR test were not infected with varicella-zoster virus.

MARIETTA VÁZQUEZ, M.D.
EUGENE D. SHAPIRO, M.D.

Yale University School of Medicine
New Haven, CT 06520-8064
eugene.shapiro@yale.edu

PHILLIP S. LARUSSA, M.D.

Columbia University College of Physicians and Surgeons
New York, NY 10032

1. LaRussa P, Lungu O, Hardy I, Gershon A, Steinberg S, Silverstein S. Characterization of a restriction site polymorphism present in DNA from the vaccine strain of varicella zoster virus. Presented at the 15th International Herpes Virus Workshop, Washington, D.C., August 2, 1990. abstract.
2. LaRussa P, Steinberg SP, Shapiro E, Vazquez M, Gershon AA. Viral strain identification in varicella vaccinees with disseminated rashes. *Pediatr Infect Dis J* 2000;19:1037-9.

Effect of Early or Delayed Tympanostomy-Tube Insertion for Persistent Otitis Media

To the Editor: Clinicians pondering the negative results of Paradise et al. (April 19 issue)¹ should note that 82 percent of the children had unilateral or discontinuous middle-ear effusions. Although the timing of insertion of tympanostomy tubes had no effect on developmental outcomes, the laterality and continuity of the effusions (63 percent were unilateral, and 66 percent were discontinuous) would not be expected to cause developmental delays in otherwise healthy children. Furthermore, the ability to detect differences is blunted when 18 percent of the children randomly assigned to early tube placement never received tympanostomy tubes and 48 percent received the tubes only after a delay of two to six months.

The results of this study are not applicable to children with bilateral, continuous middle-ear effusion plus hearing loss (a common indication for tube placement), because they made up less than 20 percent of the study group. The results also are not applicable to children who were excluded from the study, such as those with recurrent acute otitis media, anatomical changes in the tympanic membrane, or cognitive, speech, language, or developmental delay at base line. Unjustified application of the findings by Paradise and colleagues to such children could deprive them of the benefits of tympanostomy-tube placement.^{2,3}

A final problem in generalizing the results is the limited description of hearing. No data are given for mean baseline hearing levels in the treatment groups other than that hearing loss was present in 75 percent of the children with bilateral middle-ear effusions and 50 percent of those with unilateral middle-ear effusions. Applying these estimates to the group as a whole indicates that at least 40 percent would have had normal hearing at base line. Without additional details, it is difficult to accept the conclusion of Paradise et al.

that their results apply to children with middle-ear effusion and “its usual, attendant mild-to-moderate hearing loss.”

RICHARD M. ROSENFELD, M.D., M.P.H.

SUNY Downstate Medical Center
Brooklyn, NY 11203
richrosenfeld@msn.com

1. Paradise JL, Feldman HM, Campbell TF, et al. Effect of early or delayed insertion of tympanostomy tubes for persistent otitis media on developmental outcomes at the age of three years. *N Engl J Med* 2001;344:1179-87.
2. Bluestone CD, Lee D. What to expect from surgical therapy. In: Rosenfeld RM, Bluestone CD, eds. Evidence-based otitis media. Hamilton, Ont., Canada: B.C. Decker, 1999:208-21.
3. Rosenfeld RM, Bhaya MH, Bower CM, et al. Impact of tympanostomy tubes on child quality of life. *Arch Otolaryngol Head Neck Surg* 2000;126:585-92.

To the Editor: Paradise et al. did not address three variables that may be important predictors of which children with persistent otitis media with effusion might need early intervention. One is age, since younger children would be expected to have more extensive developmental delay than those who are older. Another variable is the degree of hearing loss. Children who hear sound at 20 dB would be expected to function significantly better than children who hear sound at greater than 30 dB. A third is that children with unilateral hearing loss should not be grouped with children who have bilateral hearing loss. Extrapolation of the study conclusions to older children must be done with extreme caution. Children over the age of three years, who are more aware than younger children of subjective sensation and who function in more situations in which there is competing noise, might demonstrate reduced speech and language or difficulty in school or in social interactions.

RONALD A. HOFFMAN, M.D.

JANE R. MADELL, PH.D.

Beth Israel Medical Center
New York, NY 10003
rhoffman@bethisraelny.org

The authors reply:

To the Editor: Middle-ear effusion was more generally pervasive in the children we studied than it appears at first glance. In 73 percent of the children who were enrolled on the basis of having unilateral effusion, bilateral effusion had been present for more than 25 percent of the preceding six-month period. Similarly, many of the children who were enrolled on the basis of the presence of discontinuous effusion had also had substantial periods of continuous effusion. Furthermore, of the children in our late-treatment group, 64 percent and 45 percent continued to have effusion for more than 50 percent of the 6-month and 12-month periods after randomization, respectively.

The assertion that unilateral or discontinuous effusion “would not be expected to cause developmental delays” contradicts the recent position statement of the Joint Committee on Infant Hearing, which refers explicitly to potential adverse developmental effects of unilateral hearing loss and of fluctuating hearing loss associated with persistent or recurrent otitis media.¹

Of 402 children who underwent developmental testing, 362 (90 percent) had hearing tests during one or more episodes of effusion before randomization. The results were abnormal (as defined in the article) during one or more episodes in 301 of these children (83 percent).

We analyzed the results within subgroups of children categorized according to the laterality and sequence of effusion that served as the basis for their meeting randomization criteria (bilateral, continuous; bilateral, discontinuous; unilateral, continuous; and unilateral, discontinuous) and in the 362 children with prerandomization hearing tests, categorized with the use of specified demarcations (no test vs. one or more tests with abnormal results, or with a pure-tone average ≥ 30 dB, ≥ 35 dB, or ≥ 40 dB). There were no significant differences in scores on any developmental measure favoring children who received early treatment in these subgroups.

The proportion of tested children assigned to the early-treatment group who received tympanostomy tubes after a delay of two to six months was 15 percent, not 48 percent. Our analyses did take age at randomization into account. We cautioned that our results were particularly applicable to children with persistent effusion who were otherwise healthy and were not applicable to children with recurrent acute otitis media or anatomical changes in the tympanic membrane. We also cautioned that developmental testing of our children at later ages may yield different results.

JACK L. PARADISE, M.D.
HEIDI M. FELDMAN, PH.D., M.D.
Children's Hospital of Pittsburgh
Pittsburgh, PA 15213
jpar@pitt.edu

HOWARD E. ROCKETTE, PH.D.
University of Pittsburgh Graduate School of Public Health
Pittsburgh, PA 15213

1. Joint Committee on Infant Hearing. Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics* 2000;106:798-817.

Fluvoxamine for the Treatment of Anxiety Disorders in Children and Adolescents

To the Editor: It is with concern that I read the article by the Research Unit on Pediatric Psychopharmacology Anxiety Study Group (April 26 issue)¹ promoting the treatment of young children with potent psychotropic drugs, adding to the several million American children who are already taking such medications. The Surgeon General's 1999 report on mental health, which states that "approximately one in five children and adolescents experiences the signs and symptoms of a DSM-IV [*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, revised] disorder during the course of a year,"² emphasizes that we have increasingly relabeled troublesome behavior and emotional distress in children as mental illness, which can and should be treated with drugs. The large number of researchers making these claims cannot offer any evidence that psychopharmacologic treatments do not affect the developing brains of young children, over the short or long term.

What is more troubling about this study, however, is

that it originates from departments of child psychiatry that attribute the difficulties of childhood to the defective genes or neurologic systems of the children themselves and that do not deal with questions of poor schools, stress on families, or other environmental factors. Although small numbers of severely disturbed children may need drug treatment, we are pacifying millions of our children to avoid dealing with larger social issues.

EILEEN ISAACS, M.D.
385 Palisade Ave.
Yonkers, NY 10703
eisacs@pol.net

1. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med* 2001;344:1279-85.

2. Mental health: a report of the Surgeon General. Rockville, Md.: Public Health Service, 1999.

The authors reply:

To the Editor: Dr. Isaacs suggests that our study promotes the use of psychotropic drugs, psychiatrists inappropriately label some forms of behavior as mental disorders to be treated with drugs, these drugs might harm the developing brain, and our departments misattribute children's difficulties to genetic or neurologic factors and neglect social and environmental factors.

First, our study was designed to test the safety and efficacy of a potentially useful treatment, not to promote the treatment. Second, it is essential to differentiate normal behavior from symptoms of mental disorders. Anxiety is a normal part of childhood; anxiety disorders are not. Anxiety disorders involve persistent irrational fears that cause marked distress and limitations in functioning, and they impair children's well-being, often to the same degree as other serious conditions such as asthma.^{1,2} Moreover, children with anxiety disorders have a high risk of long-term impairment.³ The children in our study had severe anxiety, which had resulted in social isolation and absence from school. It is crucial to recognize the pain experienced by children with anxiety disorders, given that in the past the impact of major mental disorders has been trivialized. Our study demonstrated that drugs represent one efficacious treatment for these children. Discouraging such studies limits our ability to provide children with effective treatment.

Third, no harmful neurologic effects of selective serotonin-reuptake inhibitors have emerged in research on their use in children, but studies examining this issue have just begun. Although studies in animals suggest that these drugs may affect brain development, other studies suggest that the developing brain may have increased sensitivity to stress, which accompanies anxiety disorders.⁴ By not considering the potential effect of anxiety disorders on brain development, Dr. Isaacs ignores the possibility that withholding appropriate treatment may carry its own risks.

Finally, Dr. Isaacs misrepresents our views concerning the causes of anxiety disorders. Anxiety disorders in children have many causes and cannot be attributed to purely genetic, neurobiologic, social, or other environmental factors. Although the ultimate causes remain incompletely understood, consensus has emerged that social and emotional fac-

tors and neurobiologic factors have key roles in the pathogenesis of these disorders.^{1,5}

DANIEL S. PINE, M.D.

National Institute of Mental Health
Bethesda, MD 20892
daniel.pine@nih.gov

JOHN T. WALKUP, M.D.

Johns Hopkins University
Baltimore, MD 21287

LAURENCE GREENHILL, M.D.

Columbia University
New York, NY 10032

FOR THE RESEARCH UNIT ON PEDIATRIC
PSYCHOPHARMACOLOGY ANXIETY STUDY GROUP

1. Klein RG, Pine DS. Anxiety disorders. In: Rutter M, Taylor E, Hersov L, eds. Child and adolescent psychiatry: modern approaches. 4th ed. London: Blackwell Scientific (in press).
2. Ialongo N, Edelsohn G, Werthamer-Larsson L, Crockett L, Kellam S. The significance of self-reported anxious symptoms in first grade children: prediction to anxious symptoms and adaptive functioning in fifth grade. *J Child Psychol Psychiatry* 1995;36:427-37.
3. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch Gen Psychiatry* 1998;55:56-64.
4. Francis DD, Caldji C, Champagne F, Plotsky PM, Meaney MJ. The role of corticotropin-releasing factor–norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. *Biol Psychiatry* 1999;46:1153-66.
5. Merikangas KR, Avenevoli S, Dierker L, Grillon C. Vulnerability factors among children at risk for anxiety disorders. *Biol Psychiatry* 1999;46:1523-35.

Spontaneous Dissection of the Carotid and Vertebral Arteries

To the Editor: In the review article on spontaneous dissection of the carotid and vertebral arteries (March 22 issue),¹ Dr. Schievink recommends therapeutic anticoagulation unless the dissection extends intracranially. Intraarterial angiography is often necessary to establish whether such an extension is present. It is believed that there is an increased risk of intracranial bleeding on anticoagulation of an intracranial arterial dissection. However, there is no good evidence to support this view. In the absence of hard data, this approach is largely empirical. It would be appropriate to qualify this recommendation until better data are available.

ROBERT KALB, M.D.

Yale University School of Medicine
New Haven, CT 06520-8018
rgk2@email.med.yale.edu

1. Schievink WI. Spontaneous dissection of the carotid and vertebral arteries. *N Engl J Med* 2001;344:898-906.

To the Editor: Although the title of Schievink's review of cervical arterial dissection uses the words "spontaneous dissection," the author includes "minor precipitating event[s]," such as sudden neck movements, as causes of dissection. We believe that in the context of dissection the word "spontaneous" is a misnomer, since this diagnosis is entirely dependent on the patient's history.

In a prospective study being undertaken by the Canadian Stroke Consortium,¹ careful history taking in patients with so-called spontaneous dissection has invariably revealed minor trauma. Most people experience sudden inadvertent neck movements during everyday activities, but the hallmark of dissection seen so far in 99 of 119 of our patients (83 percent) is sudden, often severe, and immediate neck pain over the site of the dissection. These arterial tears are often surprisingly painful.

There is clearly a spectrum of injury, varying from trivial injuries, such as those due to swinging a golf club, to serious, direct trauma to the neck. Underlying congenital arterial abnormalities, such as fibromuscular dysplasia, are very relevant. Such abnormalities were seen on 21 of 119 angiograms (18 percent) in our cases, but subtle changes in the arterial wall not visible on angiography are probably more common.

VADIM BELETSKY, M.D., PH.D.

JOHN W. NORRIS, M.D.

University of Toronto
Toronto, ON M4N 3M5, Canada
neuroteam@netscape.net

FOR THE CANADIAN STROKE CONSORTIUM

1. Norris JW, Beletsky V, Nadareishvili ZG. Sudden neck movement and cervical arterial dissection. *CMAJ* 2000;163:38-40.

Dr. Schievink replies:

To the Editor: Dr. Kalb is correct in stating that I do not recommend anticoagulation in patients with intracranial extension of a carotid-artery or vertebral-artery dissection. Because there is no external elastic lamina in intracranial arteries and because the media in these arteries is attenuated as compared with that of extracranial arteries, anticoagulation is likely to increase the risk of intracranial bleeding. This approach to therapy is largely empirical, and better data are certainly needed. In my experience, arteriography is generally not necessary to show intracranial extension of a dissection, since it is often better visualized by magnetic resonance imaging.

Drs. Beletsky and Norris object to the use of the term "spontaneous." As I state in my article, there is a distinction between minor precipitating events, such as coughing and sneezing, and the serious head or neck injuries encountered in motor vehicle crashes. It is likely that the etiology and pathogenesis of spontaneous carotid-artery and vertebral-artery dissections are multifactorial and that mechanical factors, such as sudden neck movements, and underlying arteriopathy have a role. The underlying arteriopathy may be transient and may be related to a recent infection, or the arteriopathy may be related to a genetic abnormality.

WOUTER I. SCHIEVINK, M.D.

Cedars-Sinai Medical Center
Los Angeles, CA 90048
schievinkw@cshs.org

Epilepsy

To the Editor: In their review article on epilepsy, Browne and Holmes (April 12 issue)¹ state that electroencephalo-

graphic studies should be performed 48 hours or more after a suspected seizure. We disagree. Studies of chronic partial epilepsy show that interictal epileptiform activity is more frequent after seizures (postictal activation).² Sundaram et al.³ reported an increased probability of finding interictal discharges (up to 77 percent) when patients were studied within two days after a seizure. In a recent study of 300 consecutive patients with a first unexplained seizure in whom electroencephalography was performed within 24 hours after the seizure, epileptiform abnormalities were identified in 39 percent of adults and 59 percent of children, whereas in studies of patients in whom electroencephalography was performed 48 hours or more after the seizure, epileptiform abnormalities were identified in 10 to 27 percent of adults and 32 to 43 percent of children.⁴

Electroencephalographic studies should also not be delayed in patients with a prolonged confusional state or agitation after a seizure, since it is important to distinguish between postictal encephalopathy and generalized nonconvulsive status epilepticus in order to treat the latter condition promptly.⁵ In our opinion, performing electroencephalography within 24 hours after a suspected seizure is a valuable approach to increase diagnostic sensitivity.

ALBERTO PRIMAVERA, M.D.
LUCA ROCCATAGLIATA, M.D.
Università di Genova
16132 Genoa, Italy
neurolab@cisi.unige.it

1. Browne TR, Holmes GL. Epilepsy. *N Engl J Med* 2001;344:1145-51.
2. Gotman J, Marciani MG. Electroencephalographic spiking activity, drug levels, and seizure occurrence in epileptic patients. *Ann Neurol* 1985;17:597-603.
3. Sundaram M, Hogan T, Hiscock M, Pillay N. Factors affecting interictal spike discharges in adults with epilepsy. *Electroencephalogr Clin Neurophysiol* 1990;75:358-60.
4. King MA, Newton MR, Jackson GD, et al. Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. *Lancet* 1998;352:1007-11.
5. Fagan KJ, Lee SI. Prolonged confusion following convulsions due to generalized nonconvulsive status epilepticus. *Neurology* 1990;40:1689-94.

To the Editor: Drs. Browne and Holmes recommend that patients who are free of seizures be prohibited from driving for at least four months after discontinuing antiepileptic medication. The reference they cite to support this approach is an American Academy of Neurology practice parameter on discontinuing antiepileptic medication, which does not mention driving.¹ My colleagues and I individualize instructions about driving. Most patients consider relinquishing driving too steep a price to pay for stopping medication. When driving is essential and the risk of a recurrent seizure is not all that low, it may make more sense to continue antiepileptic medication for some years.

The authors state that "the usual first-line drugs for primarily generalized tonic-clonic seizures are divalproex sodium and phenytoin." Both of the articles cited in support of this statement, however, describe divalproex sodium as the drug of choice for primarily generalized epilepsy.^{2,3} In patients with juvenile myoclonic epilepsy, phenytoin (and carbamazepine) may aggravate myoclonic seizures.⁴ When possible, tonic-clonic seizures should be considered part of either a primarily generalized or a partial (localization-

related) epilepsy, as they are in the International League against Epilepsy classification of seizures. There is confusion among primary care physicians about the term "generalized seizures." At our seizure clinic, primary care trainees learn about primarily generalized epilepsy and its response to broad-spectrum agents such as divalproex sodium.

FREDERICK LANGENDORF, M.D.
Hennepin County Medical Center
Minneapolis, MN 55415
lange002@tc.umn.edu

1. Practice parameter: a guideline for discontinuing antiepileptic drugs in seizure-free patients — summary statement: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1996;47:600-2.
2. Mattson RH. Medical management of epilepsy in adults. *Neurology* 1998;51:Suppl 4:S15-S20.
3. Pellock JM. Treatment of seizures and epilepsy in children and adolescents. *Neurology* 1998;51:Suppl 4:S8-S14.
4. Genton P, Gelisse P, Thomas P, Dravet C. Do carbamazepine and phenytoin aggravate juvenile myoclonic epilepsy? *Neurology* 2000;55:1106-9.

The authors reply:

To the Editor: The basis for our statement that electroencephalographic studies should be performed 48 hours or more after a suspected seizure is a practice parameter put forward by the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society.¹ This practice parameter states: "It is not clear what the optimal timing should be for obtaining an [electroencephalogram]. Although an [electroencephalogram] done within 24 hours of a seizure is most likely to show abnormalities, physicians should be aware that some abnormalities such as postictal slowing that can be seen on [electroencephalography] done within 24 to 48 hours of a seizure may be transient and must be interpreted with caution." In this review for primary care physicians we selected the least complex option for the timing of electroencephalography. When an expert is available to evaluate the importance of electroencephalographic abnormalities in the postictal period, there are advantages to performing electroencephalography soon after a seizure.

We stated explicitly that the decision to discontinue antiepileptic drugs should be individualized on the basis of several considerations, including the importance of driving to the patient. If antiepileptic drugs are to be discontinued, the patient should stop driving for a period that reflects the risk of a recurrent seizure. Many seizures recur during the period of withdrawal of antiepileptic drugs, and 75 to 80 percent of recurrences occur during the first year after withdrawal.²⁻⁴ The four-month figure is the minimal amount of time that driving should be prohibited after the discontinuation of antiepileptic drugs, and a case can be made for making one year the minimum.

Phenytoin and valproic acid have both been used successfully for decades to treat primarily generalized tonic-clonic seizures. There are no studies comparing phenytoin and valproic acid in the management of primarily generalized tonic-clonic seizures. The choice depends primarily on the side effects. Primarily generalized tonic-clonic seizures often begin in the teens. The weight gain induced by valproic acid and the drug's reproductive and teratogenic side effects may not make it an ideal drug for young women.

The juvenile myoclonic epilepsy syndrome is associated with tonic-clonic and other types of seizures. Space did not permit a discussion of all the syndromes that may include tonic-clonic seizures. The differences between primarily generalized and secondarily generalized tonic-clonic seizures are enumerated in Table 1 of our article.

THOMAS R. BROWNE, M.D.
GREGORY L. HOLMES, M.D.

Boston University School of Medicine
Boston, MA 02118
tbrowne@bu.edu

1. Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluating a first nonfebrile seizure in children: report of the Quality Standards Subcommittee of the American Academy of Neurology, The Child Neurology Society, and The American Epilepsy Society. *Neurology* 2000;55:616-23.
2. Buna DK. Antiepileptic drug withdrawal — a good idea? *Pharmacotherapy* 1998;18:235-41.
3. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomized study of antiepileptic drug withdrawal in patients in remission. *Lancet* 1991;337:1175-80.
4. Shinnar S, Berg AT, Moche SL, et al. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. *Ann Neurol* 1994;3:534-45.

“Invisible” Synthetic Opiates and Acute Psychosis

To the Editor: Many acute psychotic episodes encountered in emergency situations are related to addictive substances. Nalbuphine is a synthetic opiate agonist-antagonist, chemically related to both the opioid antagonist naloxone and the analgesic oxymorphone.¹ It has been widely prescribed in Mexico for palliative care and in the United States for obstetrical analgesia.¹⁻³ Nalbuphine is a low-priced analgesic and is not a tightly controlled substance.

We wish to report the case of a 53-year-old man with no known psychiatric or substance-abuse history. Police found him walking public streets unclothed and apparently responding to internal stimuli. He was taken to the emergency room, where he was found to have slurred speech, generalized tremors, and an altered level of consciousness. In the initial medical workup, the results of a lumbar puncture and a computed tomographic scan of the head were normal; the creatine kinase level was 2008 U per liter. The urine toxicology screen was negative on two occasions over a 48-hour period. The creatine kinase level normalized, but the patient continued to be delirious and psychotic. He received risperidone, 1 mg twice daily for two days, and showed dramatic improvement. After his mental status returned to normal, he reported that he had been crossing the border between the United States and Mexico to obtain nalbuphine, which he had been taking for many months for chronic back pain.

Nalbuphine has been reported to have an analgesic potency equivalent to that of morphine. The most commonly reported side effects are sedation and euphoria. Delusions and hallucinations have also been reported.^{1,3}

It has been reported that nalbuphine has less addictive potential than codeine or propoxyphene and therefore in many countries it is not a tightly controlled substance.¹⁻³ This assumption needs revisiting. Another striking fact is that nalbuphine may interfere with enzymatic methods for the detection of specific opiates, and it is virtually invisible

to routine toxicologic tests,^{1,4} as in the case we report. When there is suspicion of nalbuphine intoxication, routine screening for opiates should be supplemented with a more specific assay such as gas chromatography-mass spectrometry.

Given the widespread use of nalbuphine in Mexico and the increasing number of prescriptions for it in the United States, it is important for emergency room physicians to be alert for this “invisible opiate” as a possible cause of acute psychosis. The problem may not be confined to regions near the Mexican border but may be more widespread. A recent report, for instance, noted abuse of nalbuphine among body-builders who treat themselves for chronic pain.⁵

ALVARO CAMACHO, M.D.
SCOTT C. MATTHEWS, M.D.
JOEL E. DIMSDALE, M.D.

University of California, San Diego
La Jolla, CA 92093
acamacho@ucsd.edu

1. Nubain product information. Chadds Ford, Pa.: Endo Pharmaceuticals, September 1999.
2. Montejo Rosas G, Bruera E. Palliative care in Mexico. *J Palliat Care* 1993;9:35-6.
3. Hoover RC, Williams RB. Survey of butorphanol and nalbuphine diversion in US hospitals. *Am J Hosp Pharm* 1985;42:1111-3.
4. Kintz P, Tracqui A, Mangin P. Determination of nalbuphine using high-performance liquid chromatography coupled to photodiode-array detection and gas chromatography coupled to mass spectrometry. *J Chromatogr* 1992;579:172-6.
5. Wines JD Jr, Gruber AJ, Pope HG Jr, Lukas SE. Nalbuphine hydrochloride dependence in anabolic steroid users. *Am J Addict* 1999;8:161-4.

Web Sites with Misinformation about Illicit Drugs

To the Editor: As part of our research on the relation between the Internet and substance abuse, we have identified several Web sites that promulgate information about illicit drugs. These “partisan” Web sites are easily identified by common search engines if one uses the names of illicit substances as search terms.¹ With some pages viewed more than 160,000 times per day, partisan sites appear to be effective in reaching adolescents and young adults. In a recent study, 24 percent of college students used the Internet to obtain information on illicit substances, and 27 percent of Internet-using college students reported that Internet use increased the likelihood that they would use drugs.²

The popularity of partisan Web sites may arise from their plausible descriptions of the preparation, dose, administration, and psychoactive effects of drugs (Table 1). Partisan sites also offer recommendations for management of the adverse effects of illicit drugs. As one partisan site says, “it is up to the drug user to stay out of [the physician’s] hands.”¹¹ To evaluate the quality of such information, we conducted a survey of seven partisan Web sites. With high interobserver reliability ($\kappa=0.81$) between experts unaware of the source of the information, we found that every partisan site made potentially harmful recommendations for the management of the adverse effects of illicit drugs. Information from partisan sites has been linked to adverse outcomes: some partisan sites have described their own role in the deaths of drug users and some have been implicated in poisoning from 1,4-butanediol.^{12,13}

TABLE 1. FEATURES OF PARTISAN WEB SITES AS OF MAY 24, 2001.*

NAME (URL)	FEATURES	EXAMPLES OF TEXT FROM SITE	COMMENTS
The Vaults of Erowid (http://www.erowid.org)	Describes the illicit use of over 200 substances in over 4000 pages, is visited more than 160,000 times per day, and describes detailed protocols for the use of illicit substances.	"And if you're really concerned . . . most or all of the serotonin system reduction may be prevented by taking Prozac (fluoxetine) 0-6 hours after taking the MDMA. One might speculate that other SSRI drugs (Zoloft, Paxil) may work too. Note, however, that some people report that Prozac taken before or in the early part of an MDMA session lessens some of the desirable effects of the MDMA."	The combined use of SSRIs or monoamine oxidase inhibitors with drugs possessing serotonergic activity such as MDMA has led to serotonin syndrome in selected patients. ³ For a large number of illicit substances, Erowid offers pharmacokinetic data in both tabular and graphical form, so that potential users can predict their own dose-response curves for a particular substance. Furthermore, the first-person descriptions of the effects of illicit substances ("trip reports") frequently list the dose and body weight of the reporter, so that the observed clinical effects can be reproduced or avoided.
Dancesafe (http://www.dancesafe.org)	Promotes "non-abstentionist" drug-related health and safety information; provides "services [to] help people use as safely as possible"; offers to test pills, free of charge, to identify those that do not contain ecstasy; and contains a table that compares the risks associated with daily activities with the risks associated with use of illicit substances.	"High pressure levels in the [nitrous oxide] tank can shoot the gas out at a dangerously fast speed and damage the lungs. It is safer to inhale from a balloon than from a tank." "Many tablets sold on the illicit market as 'ecstasy' actually contain substances far more dangerous than MDMA." States that the risk of using "amphetamines, GHB, and cocaine" is comparable to the risk associated with "travel by airplane."	Nitrous oxide inhaled from a secondary source was the cause of deaths of college students in the Boston area. ⁴ Dancesafe proposes that the majority of medical emergencies attributed to amphetamines are instead due to dextromethorphan. The two substances have distinct toxicities and clinical presentations. ⁵ The Web site also states that the level of risk from the use of nitrous oxide is comparable to the risk of "spontaneous combustion."
Ecstasy.org (http://www.ecstasy.org)	Contains a question-and-answer section with replies from "experts," some of whom are physicians.	"I would like to know if it is safe to mix Ecstasy and Viagra? Expert Reply: I understand that there have now been two cases reported to Pfizer, the manufacturers of Viagra, of priapism associated with the use of Viagra together with ecstasy. The mechanism may be that inhibitors of the drug metabolising enzyme system P450-3A4 are known to increase the concentration of sildenafil. . . . I can see why some users might want to try taking [ecstasy] and Viagra together. [I]f you must, try half a dose of each. . . ." "Drink lots of water to replenish body fluids."	Ecstasy.org is one of several partisan Web sites to apply toxicogenomic principles to the use of illicit drugs. Other drug-drug effects commonly mentioned are the interactions of CYP3A4 inhibitors (such as HIV-protease inhibitors) with MDMA (ecstasy) and of monoamine oxidase inhibitors with MDMA. ⁶
Ecstasy info (http://come.to/ecstasy)	Offers a direct entry into chat rooms in which the use of illicit drugs such as MDMA is discussed.		Because it is an amphetamine with serotonergic activity, MDMA suppresses both appetite and thirst. To prevent dehydration, several partisan sites suggest ingestion of water. This practice carries the risk of water intoxication and hyponatremia leading to seizures, cerebral edema, and death. ⁷
The Shroomery (http://www.shroomery.org)	Proposes several "cures" for <i>Amanita phalloides</i> poisoning, which arises from the ingestion of misidentified mushrooms.	"Liver-damaging substances such as carbon tetrachloride can be used to stop uptake of phallotoxins, but the 'cure' is not much better than the affliction."	Carbon tetrachloride is a known cause of fulminant hepatic necrosis. ⁸
The Lycaeum (http://www.lycaeum.org)†	Hosts several Web sites, including those of Rhodium (an underground chemist), Beehive (a compendium of syntheses for illicit substances), and GHB FAQ.	"If [taking GHB] makes you feel anxious: some Clonazepam (1-2 mg) will help. (If you can still keep it in by that time . . . better take some before.) You may also best sleep for a while (to find yourself waking up . . . refreshed!)" "Users wishing to employ GHB for immediate detox can follow the model of the experiment above. Begin with 50 mg/kg GHB 3 times each day, and reduce by 30% each day after the third. This should be done during a dedicated recovery period. . . . It is vital to have another person assist in this process, who can absolutely ensure that the subject does not drink."	The combination of two sedative-hypnotic agents — clonazepam and GHB — carries a risk of severe respiratory depression and loss of airway protective reflexes. ⁹
GHB FAQ (http://users.lycaeum.org/~ghbfaq/contents.html)†	Offers a brief form designed to be printed and carried to the site of drug use that describes the dose, effects, and management of overdose of GHB; the site also describes the dosing protocols for the use of GHB in the treatment of other clinical conditions, such as the alcohol withdrawal syndrome.		Prolonged or excessive use of GHB itself is capable of producing a withdrawal syndrome similar to the alcohol withdrawal syndrome. ¹⁰

* MDMA denotes methylenedioxymethamphetamine, SSRI selective serotonin-reuptake inhibitor, GHB γ -hydroxybutyric acid, and HIV human immunodeficiency virus.

† This Web site is not currently available.

Unfortunately, Internet-based efforts to prevent drug use may not deflect visitors from partisan Web sites. We performed five separate searches using identical key words (“GHB” [γ -hydroxybutyric acid], “ecstasy” [methylenedioxymethamphetamine or MDMA], and “psychedelic mushrooms”) over a period of 10 months. Our first two searches listed 8 partisan and 2 federal antidrug Web sites in the top 10 results. The third search identified nine partisan sites and one federal site, whereas the final two searches identified eight partisan and no federal sites. In all searches, antidrug sites from the federal government failed to appear as often as the partisan sites, which dominate the search results. Moreover, sites of the Federal Website Initiative, part of a billion-dollar multimedia program for the prevention of drug abuse, did not appear in any of the search results. These data suggest that the U.S. government, despite extensive and costly efforts, currently does not provide effective alternative sources of information about drugs on the Web, where partisan sites still get the attention of both search engines and users.

EDWARD W. BOYER, M.D., PH.D.
 MICHAEL SHANNON, M.D., M.P.H.
 PATRICIA L. HIBBERD, M.D., PH.D.
 Children's Hospital
 Boston, MA 02115
 edward.boyer@tch.harvard.edu

1. Nelson LS. A guide to clinical toxicology resources available on the Internet: drugs of abuse. *J Toxicol Clin Toxicol* 2000;38:85-6.
2. Wax P, Reynolds N. Just a click away: student Internet surfing for recreational drug information. *J Toxicol Clin Toxicol* 2000;38:531. abstract.
3. Mueller PD, Korey WS. Death by “ecstasy”: the serotonin syndrome? *Ann Emerg Med* 1998;32:377-80.
4. Toxic Exposure Surveillance System. Massachusetts Poison Control Center Data, 2000. *Am J Emerg Med* (in press).
5. Boyer EW, Quang L, Woolf A, Shannon M, Magnani B. Dextromethorphan and ecstasy pills. *JAMA* 2001;285:409-10.
6. Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and γ -hydroxybutyrate. *Arch Intern Med* 1999;159:2221-4.
7. O'Connor A, Cluroe A, Couch R, Galler L, Lawrence J, Synek B. Death from hyponatraemia: induced cerebral oedema associated with MDMA (“Ecstasy”) use. *N Z Med J* 1999;112:255-6.
8. Zimmerman HJ. Chemical hepatic injury. In: Haddad LM, Shannon MW, Winchester JF, eds. *Clinical management of poisoning and drug overdose*. 3rd ed. Philadelphia: W.B. Saunders, 1998:149-74.
9. Osborn HH. Sedative-hypnotic agents. In: Goldfrank LR, ed. *Goldfrank's toxicologic emergencies*. 6th ed. Stamford, Conn.: Appleton & Lange, 1998:1001-22.
10. Dyer JE, Roth B, Hyma BA. GHB withdrawal syndrome: eight cases. *J Toxicol Clin Toxicol* 1999;37:650. abstract.
11. Cohn M. GHB mini FAQ. 1998. (<http://www.lycaem.org> [Web site may not be currently available.]
12. Second reported 2C-T-7 death. Erowid, 2001. (Accessed July 24, 2001, at http://www.erowid.org/chemicals/2ct7/2ct7_death2.shtml.)
13. Zvosec DL, Smith SW, McCutcheon JR, Spillane J, Hall BJ, Peacock EA. Adverse events, including death, associated with the use of 1,4-butanediol. *N Engl J Med* 2001;344:87-94.

Correspondence Copyright © 2001 Massachusetts Medical Society.

IMAGES IN CLINICAL MEDICINE

The *Journal* has resumed consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal's* Web site at <http://www.nejm.org>. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.
