



Generic substitution of antiepileptic drugs: What's a clinician to do?

Khichar Shubhakaran, MBBS, MD, Rekha Jakhar Kihichar, Jodhpur, India: We read with interest the article by Dr. Privitera¹ on generic substitution of antiepileptic drugs. The US Food and Drug Administration's approval of any drug is meaningful worldwide. The issues raised in the article are practical ones. In India, 10 to 11 million people are estimated to have epilepsy and approximately 4% to 5% of the Indian population is estimated to fall below the poverty line because of costs for treatment of various medical ailments. The government of India provides free medicine to those below the poverty line, and gradually every citizen is likely to be provided—free of charge—drugs that are considered essential. There is also a provision to provide drugs free of charge in special/exceptional cases, for which there is also separate funding. Various standard pharmaceutical companies are claiming their products to be superior to their competitors' brands regarding manufacturing, packing and dispensing, and efficacy. Rigorous prospective trials are needed, from procurement to dispensing, to periodic monitoring and surveillance.

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Author Responds: Michael Privitera, MD, University of Cincinnati Neuroscience

Institute: I thank Drs. Shubhakaran and Kihichar for their thoughtful comments on our article.¹ In the United States, we often forget how our regulatory decisions may have far-reaching impact on health policy elsewhere in the world. Our studies are designed to determine whether doing generic equivalence testing using subjects with epilepsy and combining single and chronic dose studies will improve generic quality. Widespread generic substitution will markedly reduce health care costs worldwide, but our patients with epilepsy need to be assured that generic substitution and generic product switches will not adversely affect seizure control or side effects.

Disclosures: M. Privitera serves on a DSMB for Upsher Smith and as a consultant for Eli Lilly, serves on the editorial board for *Annals of Pharmacotherapy*, has served on the Speakers' Bureau for UCB and Pfizer, and receives research support from UCB, Eisai, Neuren Pharmaceuticals, the NIH, and the FDA.

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1. Privitera M. Generic substitution of antiepileptic drugs: what's a clinician to do? *Neurol Clin Pract* 2013;3:161–164.

Sports-related concussion: Truth be told

Nitin K. Sethi, MD, New York-Presbyterian Hospital: I read with interest the editorial by Hainline et al.¹ commenting on the study by Torres et al.,² who conducted an anonymous survey of sports-related concussion in a collegiate athletic cohort. The Torres et al. survey confirmed what has long been suspected—that athletes frequently avoid reporting concussions to their athletic trainers and the team physician on the sideline. For an athlete, there are obvious conflicts of interest when it comes to reporting a concussion. On one hand, it ensures that he or she receives appropriate and timely medical evaluation and management of the head injury sustained on the field, but it also risks the high likelihood that he or she shall be sidelined until cleared by a medical doctor to return to play. For a professional athlete, the loss of salary, winnings, bonuses, and endorsement income may be prohibitive. For an

amateur athlete, it may be the potential loss of an athletic scholarship. The vast majority of sports-related concussions involve no objective loss of consciousness and their detection depends upon accurate reporting of concussive symptoms by the injured athlete. While sideline concussion assessment tests such as Standardized Assessment of Concussion, Balance Error Scoring System, and King-Devick aid in diagnosis, none is exclusively sensitive or specific. Until the above conflicts of interest are adequately addressed, concussions will continue to be underreported by athletes.

Disclosures: N. Sethi serves as Associate Editor for *The Eastern Journal of Medicine*.

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Authors Respond: Brian Hainline, MD, FAAN, FACS, William W. Dexter, MD, FACS, John DiFiori, MD, National Collegiate Athletic Association; American College of Sports Medicine; American Medical Society for Sports Medicine: We agree with Dr. Sethi that athletes must receive medical care that is transparent and without a conflict of interest. We stated such in our editorial.¹ There is a palpable shift in this direction because of a combination of a heightened awareness regarding conflict of interest problems in sport and because medical organizations are working together to address this issue. Equally important, and also addressed by Dr. Sethi, is the search for objective biomarkers of concussion that correlate with diagnosis and prognosis. So long as concussion diagnosis is driven by clinical symptoms, there will exist a “relativity scale” among athletes, sports medicine clinicians, parents, and coaches regarding the perceived importance of each symptom.

Disclosures: B. Hainline reports no disclosures. W.W. Dexter serves as Web Alert Editor for *Current Sports Medicine Reports* and on the editorial board of the *Clinical Journal of Sports Medicine*, receives publishing royalties from UpToDate, is the Director of Sports Medicine at Maine Medical Center, and serves on the advisory board for Cambria Health. J.P. DiFiori serves as an Associate Editor of the *Clinical Journal of Sports Medicine* and as a Section Editor for *Current Sports Medicine Reports*.

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2. Torres DM, Galetta KM, Phillips HW, et al. Sports-related concussion: anonymous survey of a collegiate cohort. *Neurol Clin Pract* 2013;3:279–287.

Recommendations for the safe administration of donepezil

Leilani Doty, PhD, Kenneth M. Heilman, MD, University of Florida Cognitive & Memory Disorder Clinics: Safe administration of a medicine depends on individual differences in tolerance and appropriate, consistent instructions from the physician, pharmacist, and package directions. When patients receive written and oral dosing directions that disregard individual differences and are inconsistent, the therapeutic benefits of the medication may be reduced and adverse effects may result.

A specific example occurs with the written and oral directions to patients (and caregivers) for the administration of donepezil. The Aricept Patient Package Insert (paper) under the section “How should the patient take ARICEPT?” instructs as follows: “Give ARICEPT one time each day. ARICEPT can be taken with or without food.”¹ In the same package, the second larger insert reads: “Full Prescribing Information, 2) Dosage and Administration”: “ARICEPT should be taken in the evening, just prior to retiring.”²

Shortly after the 1996 Food and Drug Administration (FDA) approval of donepezil (Aricept, Eisai Inc., Woodcliff Lake, NJ) for possible mild or moderate Alzheimer disease (AD)

(FDA approval included severe AD in 2006), our physicians prescribed (as the Physicians' Desk Reference guided) a starting dose of 5 mg before bedtime. After several patients complained of restless sleep, nightmares, nausea, vomiting, or diarrhea, we suggested a post-breakfast dose. Soon thereafter, the first author (L.D.) contacted the Scientific Advisor of Eisai/Pfizer about modifying their directions with the post-breakfast dose alternative. The Scientific Advisor reported that changes necessitated additional Eisai research and FDA reapproval; therefore, they would maintain the status quo.

Now thousands of patients later, our prescriptions for donepezil³ indicate a post-breakfast dose, titrating "lower and slower" (from 2.5 mg to 5 mg to 7.5 mg to 10 mg daily on a monthly titration schedule). Good tolerance from 2.5 mg to 5 mg titrates to 10 mg. Patients intolerant of more than 5 mg or 7.5 mg daily typically remain at the lower, tolerated dose.

When patients referred to our clinic for a more comprehensive evaluation have stopped donepezil because of intolerable nightmares, nausea, vomiting, or diarrhea, invariably families report that their physicians' instructions and the packaged directions recommended a bedtime dose, with or without food. While some patients who have not tolerated donepezil have transitioned smoothly to rivastigmine or galantamine, many others, based on their donepezil experiences, have avoided further anticholinesterase attempts.

The recurring dilemma of nighttime dosage leading to sleep problems or continued gastrointestinal upset prompted us to again phone Eisai (February 22, 2013). The Eisai Medical Services Product Safety Specialist, Margaret Morris, RN, requested our completing an Adverse Event Information Form for their FDA report. Reporting Adverse Events & Events of Special Interest differs from our proposals to 1) expand directions about an alternative post-breakfast dose; 2) provide consistent directions; and 3) attend to individual differences regarding titration.

An important treatment for mild to severe AD, anticholinesterase, such as donepezil, must have appropriate, safe, consistent administration directions, carefully attuned to individual differences.

Disclosures: L. Doty reports no disclosures. K. Heilman has taught many courses and has had many visiting professorships as well as speaking engagements at societies and scientific meetings; serves/has served on editorial boards for *ACTA Neuropsychologia*, *The Journal of Contemporary Neurology*, *Journal of the International Neuropsychological Society*, *Neurocase*, *Neuropsychiatry*, *Neuropsychology and Behavioral Neurology*, *Cognitive and Behavioral Neurology*, *Neuropsychologia*, *Brain and Cognition*, *Journal of Clinical and Experimental Neuropsychology*, *Neurology*, *Brain and Language*, *eMedicine-Neurology*, *Journal of Neuropsychology*, and *Journal of Clinical Neurology*; receives publishing royalties for authoring or editing books from Oxford University Press, Taylor and Francis Books, and Appleton-Century-Croft; receives research support from the State of Florida, Department of Elder Affairs Memory Disorder Clinics, and NIDCD/NIH T-32 grant; receives license fee payments from the University of Florida; and has served as an expert witness in medico-legal cases.

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1. Aricept directions reviewed February 2013: a) patient package insert: a 2-sided page, 2 × 24 3/4 inches with the bar code 202258 (Aricept, Eisai); b) full prescription information (larger package insert): 2-sided page, 9 1/2 × 24 inches, with the bar code 202257 (Aricept, Eisai).
2. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. In: *The Cochrane Collaboration: The Cochrane Library*. Hoboken: John Wiley & Sons; 2009:1–165.
3. Baskys A, Hou AC. Vascular dementia: pharmacological treatment approaches and perspectives. *Clin Interv Aging* 2007;2:327–335.

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