Vinpocetine: An Unapproved Drug Sold as a Dietary Supplement

To the Editor: In the United States, the law governing dietary supplements permits vitamins and minerals, botanical products, amino acids, and protein powders to be sold as supplements. The laws regulating supplements have one safeguard to give the US Food and Drug Administration (FDA) the opportunity to intervene before manufacturers introduce an unapproved drug as a supplement: before introducing a new ingredient into supplements, the manufacturer is required to submit a "new dietary ingredient notification" to the FDA. The FDA assesses the application and responds as to whether the ingredient is appropriate for sale as a dietary supplement.

If a manufacturer proposes selling an unapproved prescription drug, the FDA would be expected to inform the manufacturer that it is not a legal dietary supplement ingredient. However, the FDA has not always enforced the law. An example is vinpocetine, a pharmaceutical agent prescribed in Germany, Russia, China, and other countries at dosages from 5 mg to 40 mg for acute stroke and cognitive impairment.[1] Vinpocetine has never been approved by the FDA as a prescription drug in the United States. Data regarding vinpocetine's neuroprotective effects are conflicting, with a recent Cochrane review suggesting no benefit,[1] and vinpocetine can lead to flushing, headaches, and decreased blood pressure.[2]

In 1997, a supplement manufacturer submitted a new dietary ingredient notification for vinpocetine to the FDA.[3] Rather than responding that an unapproved drug may not be sold as a supplement, the FDA permitted the introduction of vinpocetine into supplements. Today, more than 340 brands of supplements contain vinpocetine.[4] The FDA may have assumed that vinpocetine was a botanical extract, but it is not. Vinpocetine can be synthesized from vincamine, an alkaloid extracted from the leaves of the lesser periwinkle (*Vinca minor*).[1] However, to my knowledge, vinpocetine itself has never been identified in lesser periwinkle or any other plant.

Recently, my colleagues and I analyzed all supplements labeled as containing vinpocetine that are available for purchase online from GNC (General Nutrition Centers, Inc) or The Vitamin Shoppe, two of the largest supplement retailers in the United States.[5] Vinpocetine supplements were most commonly sold as sports supplements, brain enhancers, and weight loss supplements. We found that only 6 of the 23 supplement labels (26%) provided consumers with accurate dosages of vinpocetine.[5]

The FDA has permitted an unapproved new drug with unproven efficacy and known adverse effects to be sold directly to consumers. By permitting the sale of a drug as a dietary supplement, the FDA has created a dangerous precedent by which new drugs can bypass the rigorous drug approval process and be sold directly to consumers without FDA approval. When this happens, consumers are unable to obtain accurate dosing information and are not aware of adverse effects. The FDA should not permit unapproved drugs, even semisynthetic derivatives of natural compounds, to be sold as dietary supplements.

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1. Bereczki D, Fekete I. Vinpocetine for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2008;(1): CD000480.
2. National Toxicology Program. Chemical information review document for vinpocetine [CAS No. 42971-09-5]. http://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/vinpocetine091613_508.pdf. Published September 2013. Accessed August 10, 2015.
3. Tanner J. 75-Day Premarket Notification for New Dietary Ingredients [vinpocetine]. US Food and Drug Administration website. http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0012_01.pdf. Published August 29, 1997. Accessed August 10, 2015.
4. Natural Medicines Comprehensive Database. http://www.naturaldatabase.com. Accessed August 10, 2015.
5. Avula B, Chittiboyina A, Sagi S, Wang Y-H, Wang M, Khan IA, Cohen PA. Identification and quantification of vinpocetine and picamilon in dietary supplements sold in the United States: drug testing and analysis. *Drug Testing Analysis*. doi: 10.1002/dta.1853.

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Teachable Action for Leaders Committed to Improving Physician Work Life: Continuing Education

To the Editor: We read with great interest the article by Shanafelt et al[1] on the impact of organizational leadership on physician burnout and satisfaction published in the April 2015 issue of *Mayo Clinic Proceedings*. In their article, the authors identified several specific leadership qualities of physician supervisors as predictors of physician burnout and career satisfaction, including encouraging physicians to develop their talents and skills. We recently conducted a survey of the approximately 1850 clinically active academic physicians at Massachusetts General Hospital focused on physician burnout, career satisfaction, and administrative burden (response rate, 96% [1774]). Our results similarly support the finding that physician leaders can improve the well-being of physicians. In our study, physicians who were satisfied with the control they have over their practice environment, their call and coverage schedule, and their overall workload were less likely to report symptoms of burnout. Each of these factors, with the exception of call and coverage schedule, was also predictive of career satisfaction.

In addition, a majority of our physicians (1227 of 1758 [70%]; 16

non-respondents) reported high levels of satisfaction with continuing medical education (CME) opportunities offered in their departments. Fewer (995 of 1760 [57%]; 14 non-respondents) were satisfied with time and resources provided for CME, but those who were satisfied with both of these aspects of CME reported higher degrees of overall career satisfaction (odds ratio, 1.30). Previous studies have established the relationship between opportunities for professional development and career satisfaction among physicians.[2,3] For physicians, continuing education programs can be intellectually engaging, provide opportunities to connect with colleagues, and support their pursuit of excellent care for patients. However, without sufficient resources, CME requirements can be a burden. Together, our findings and those of Shanafelt et al introduce 3 specific actions related to continuing education that physician leaders can take today to improve physician well-being: (1) encourage (or even require) physicians to pursue educational opportunities and new skills,[1] (2) create time in physician schedules for such activities, and (3) provide resources (tuition and travel reimbursement or locally developed programs).

Recent attention to physician burnout is likely a reflection of rapidly changing times—payment reform, electronic medical records, and board certification requirements, for example. While leaders focus on guiding physicians through these tumultuous and distracting times, the surveys that we and Shanafelt et al conducted suggest that by paying closer attention to one of the oldest traditions of the medical profession—continuing education—leaders can help physicians weather the storm.

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Editor's Note: When publishing a letter that comments on an article published previously in *Mayo Clinic Proceedings*, it is the journal's policy to invite the author(s) of the referenced article to publish a response. Dr Tait Shanafelt was invited to respond, and although he was supportive of this letter, he felt the content of the letter did not require a reply.

1. Shanafelt TD, Gorringe G, Menaker R, et al. Impact of organizational leadership on physician burnout and satisfaction. *Mayo Clin Proc*. 2015; 90(4):432-440.
2. Bovier PA, Perneger TV. Predictors of work satisfaction among physicians. *Eur J Public Health*. 2003;13(4):299-305.
3. Bunton SA, Corrice AM, Pollart SM, et al. Predictors of workplace satisfaction for U.S. medical school faculty in an era of change and challenge. *Acad Med*. 2012;87(5):574-581.

http://dx.doi.org/10.1016/j.mayocp.2015.07.020

Nonictal Near Sudden Unexpected Death in Epilepsy

To the Editor: The presence of epileptiform discharges and seizures is routinely monitored by electroencephalography (EEG) during Wada testing. Spontaneous cardiac arrhythmias are unexpected.[1] Malignant cardiac arrhythmias, including asystole, are rare complications that occur in patients with focal seizures and have been implicated in sudden unexpected death in epilepsy (SUDEP).[2] We report a case of nonictal near-SUDEP.

Report of a Case. A 30-year-old man with drug-resistant, localization-related epilepsy underwent an evaluation for surgical treatment. Recurrent focal seizures with dyscognitive features and focal seizures evolving to convulsions had continued despite a trial of 4 antiseizure drugs. Video-EEG monitoring captured 3 left temporal seizures characterizing the localization during a presurgical evaluation. Electrocardiography (ECG) revealed normal sinus rhythm with sinus tachycardia during the seizures. An initial Wada test was invalid because of oversedation from amobarbital. During preparation for a repeated study and prior to catheterization, bradycardia and subsequent asystole occurred with generalized tonic stiffening that was first suspected to represent a seizure. Subsequent review of the ECG confirmed asystole causing convulsive syncope. A precordial thump prompted immediate resolution (after 64 seconds) without the need for antiarrhythmic medication. Outpatient Holter monitoring subsequently recorded a 33-second episode of spontaneous asystole. This episode resolved without clinical signs, and a permanent cardiac pacemaker was implanted without recurrence.

Discussion. This patient with drug-resistant focal seizures exhibited spontaneous cardiac asystole undetected during seizure monitoring. Had the Wada test not revealed in-hospital cardiac asystole, sudden cardiac death may have occurred without intervention. Cardiorespiratory disturbances are normally controlled by the autonomic nervous system and in many cases are associated with seizures.[3] A disturbed cerebral-cardiac relationship from brainstem dysregulation of cardiac sympathetic-parasympathetic activity may be the foundation for near death from a malignant arrhythmia in some patients with epilepsy. However, without EEG and ECG monitoring, it would have been difficult during Wada testing to conclude that the witnessed event was nonepileptic. An event misdiagnosed as an epileptic seizure would have been disastrous because of a missed treatment of a malignant cardiac arrhythmia.

Cardiac arrhythmias may account for a substantial number of cases of