



Figure. Age and odds ratio (OR) for diversion and death. *Reference group for diversion. †Reference group for death.

deaths. Passengers who were reported to be unconscious were 33 times more likely to require diversion and 234 times more likely to die during flight. Passengers who required the use of an AED were 35 times more likely to be diverted.

Diagnostic category was associated with diversions but not deaths. Neurological (39.1%), cardiac (23.9%), and obstetric and/or gynecological (13.0%) problems accounted for most of the diversions. Obstetric and/or gynecological cases had a diversion rate of 10.7%, which was higher than the rate for neurological (2.5%) or cardiac (4.4%) cases.

Comment. Public access to AEDs has been implemented with various successes in a number of airlines,^{1,2} and it has been shown to be cost effective in one study.³ Over the 5-year period of our study, the AED very rarely detected a shockable rhythm. Further study of AED use is necessary to more clearly define their role in emergency care on aircrafts.

Although it is not possible to change most of the risk factors for medical flight diversions and deaths identified in our study, they have important public health implications in relation to prevention and event mitigation. Previous studies have suggested that 65% of in-flight medical events are related to pre-existing problems⁴ and that preflight medical clearance may be effective in reducing in-flight medical events.⁵ In our study, advancing age was found to be a major risk factor for diversion and death, and obstetric conditions had the highest risk for diversion. It may be that implementing a proactive prevention strategy including pre-flight screening for these groups of passengers may reduce diversions.

Being unconscious on initial examination was another major risk factor for both death and diversion in-flight. Because basic assessment of consciousness level requires training and practice, it might be worthwhile considering incorporating simple training like the ACUDU (Alert, Confused, Drowsy, Unresponsive) scale⁶ into the first aid course for flight attendants.

Kevin K. C. Hung, MBChB, MPH
 Emily Y. Y. Chan, SM PIH(Harvard), MBBS
 Robert A. Cocks, MD
 Rose M. Ong, MD
 Timothy H. Rainer, MD
 Colin A. Graham, MD, MPH

Author Affiliations: Accident & Emergency Medicine Academic Unit (Drs Hung, Cocks, Rainer, and Graham) and School of Public Health and Primary Care (Drs Hung, Chan, and Ong), The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong.

Correspondence: Dr Graham, Accident & Emergency Medicine Academic Unit, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong (cagraham@cuhk.edu.hk).

Author Contributions: Dr Hung had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Hung, Cocks, and Graham. *Acquisition of data:* Cocks and Ong. *Analysis and interpretation of data:* Hung, Chan, Cocks, Rainer, and Graham. *Drafting of the manuscript:* Hung and Cocks. *Critical revision of the manuscript for important intellectual content:* Hung, Chan, Cocks, Ong, Rainer, and Graham. *Statistical analysis:* Hung, Chan, and Graham. *Obtained funding:* Hung and Graham. *Administrative, technical, and material support:* Rainer and Graham. *Study supervision:* Chan, Cocks, and Graham.

Financial Disclosure: Drs Cocks and Ong both hold appointments with the Hong Kong-based airline that is the subject of this study.

Funding/Support: MedAire Inc (Tempe, Arizona) provided technical assistance for this study. Funding was obtained from the Hong Kong College of Emergency Medicine research grant (2008-2009).

Disclaimer: The airline that is the subject of this study did not influence the reporting or analysis of the results in any way.

- O'Rourke MF, Donaldson E, Geddes JS. An airline cardiac arrest program. *Circulation.* 1997;96(9):2849-2853.
- Page RL, Joglar JA, Kowal RC, et al. Use of automated external defibrillators by a U.S. airline. *N Engl J Med.* 2000;343(17):1210-1216.
- Groeneveld PW, Kwong JL, Liu Y, et al. Cost-effectiveness of automated external defibrillators on airlines. *JAMA.* 2001;286(12):1482-1489.
- Qureshi A, Porter KM. Emergencies in the air. *Emerg Med J.* 2005;22(9):658-659.
- Jorge A, Pombal R, Peixoto H, Lima M. Preflight medical clearance of ill and incapacitated passengers: 3-year retrospective study of experience with a European airline. *J Travel Med.* 2005;12(6):306-311.
- McNarry AF, Goldhill DR. Simple bedside assessment of level of consciousness: comparison of two simple assessment scales with the Glasgow Coma scale. *Anaesthesia.* 2004;59(1):34-37.

Effect of Enzyte on QT and QTc Intervals

Dietary supplements represent a distinct class of biologically active compounds which, unlike prescription and over-the-counter products, have been available to the public without regulatory oversight

*See Invited Commentary
 at the end of this letter*

for nearly 15 years and are responsible for more than 13 000 adverse events annually.^{1,2} Like many dietary supplements, Enzyte (Vianda, Cincinnati, Ohio)—a dietary supplement marketed for “male enhancement,” a euphemism for

Table. Effects of Enzyte on the Corrected QT Interval

Variable	Milliseconds, Mean (SD)				P Value, ANOVA	P Value, Interperiod (vs Placebo)
	Placebo	0.5 Tablet	1 Tablet	2 Tablets		
Bazett Correction Formula						
Baseline	385 (33)	392 (38)	402 (31)	390 (20)	.44	NA
1 h	384 (19)	415 (30)	418 (29)	420 (18)	<.001	All periods, <.05
3 h	380 (18)	412 (31)	420 (19)	422 (22)	<.001	All periods, <.05
5 h	388 (25)	424 (23)	425 (26)	406 (22)	<.001	All periods, <.05
Framingham Linear Correction Formula						
Baseline	361 (27)	366 (18)	369 (29)	371 (26)	.44	NA
1 h	362 (29)	388 (16)	392 (32)	394 (29)	<.001	All periods, <.05
3 h	366 (37)	391 (21)	400 (31)	398 (28)	.01	1 Tablet and 2 tablet periods, >.05
5 h	370 (17)	393 (35)	388 (27)	370 (17)	.01	1 Tablet period, <.05

Abbreviations: ANOVA, analysis of variance; NA, not applicable.

erectile dysfunction—is a multicomponent preparation marketed to consumers without stringent regulatory oversight or premarketing evaluation of pharmacokinetics, pharmacodynamic, or drug interaction studies, including thorough QT and corrected QT (QTc) studies to assess proarrhythmic risk. Considering this information, we conducted a randomized, double-blind, double-dummy, placebo-controlled, dose-ranging, crossover study of the effects of Enzyte on the electrocardiographic (ECG) parameters including the QTc interval.

Methods. Consenting healthy male volunteers were randomized using a double-blind, double-dummy (ie, masking the difference in shape, appearance, and dosing schedule of the active and placebo preparations), placebo-controlled, dose-ranging, crossover study design approved by the institutional review board at Midwestern University, Downers Grove, Illinois. Active capsules contained the contents of one-half of a pulverized Enzyte immediate-release tablet. Lactose-containing placebo capsules were prepared in the pharmaceuticals laboratory at Midwestern University. Because interlot variability has been reported with preparations of various dietary supplements and could impact results, we limited the study of Enzyte to tablets purchased from a single lot. Exclusion criteria included the following: risk factors for torsades de pointes,³ concurrent use of potentially interacting drugs (anticoagulants, monoamine oxidase inhibitors, over-the-counter medications containing pseudoephedrine, or any dietary supplements), female sex, or unwillingness to sign informed consent.

The primary ECG end point was the maximum postdosing QTc interval attained at 1, 3, and 5 hours between the placebo and each of the dosing periods. Maximum postdosing QTc interval was prospectively defined as the longest QTc interval from all evaluable leads in each of the 3 postdosing ECGs. The maximum postdosing QTc interval was assessed because the time to maximal absorption of the compounds in the dietary supplements have not been established. The QTc interval was calculated using the Bazett formula [$QTc = QT / (R-R)^{1/2}$] for the primary analysis, since it is the most commonly used clinically. The hazard ratio was calculated based on the mean R-R interval using the following formula: $60 / (R-R \text{ interval} / 1000)$.

Interperiod analysis of continuous data was performed using a repeated measures analysis of variance with post hoc Bonferroni correction. The study was conducted using a power analysis under the assumption that an interperiod difference in the QTc interval by 6 ± 3 milliseconds (ms) would be significant.

Results. Fifty subjects were approached for recruitment. Thirty-seven subjects declined enrollment, and 4 met study exclusion criteria. Nine male subjects (2 Asian and 7 white; mean [SD] age, 28.7 [11.3] years; and mean [SD] body mass index, 26.8 [4.4] [calculated as weight in kilograms divided by height in meters squared]) were randomized and completed the entire study protocol.

At baseline, there were no interperiod differences in the QTc interval. Following ingestion, the QTc interval increased at all dosages (**Table**). When subjects received the single-tablet dose (as is indicated on the product labeling), the QTc increased by 8.4% (95% CI, 8.01%-60.01%) or 32 ms ($P < .05$) at 3 hours after dosing and 11% (95% CI, 10.31%-69.70%) or 37 ms at 5 hours after dosing ($P < .05$). The results were of the same magnitude and direction when the Framingham Linear Corrected Formula was used. Aside from QT and QTc intervals, there were no changes in any other electrocardiographic end point during the study (data not shown). There were no cases of atrial or ventricular arrhythmias. Of the 9 subjects enrolled, 4 (44%) developed profound cutaneous flushing consistent with the effect of niacin, which is found in the preparation. Subjects reported no other adverse effects including prolonged erection.

Comment. Although guidelines for the clinical measurement of the QT interval are not yet adopted in the United States, procedures used for the assessment of QT prolongation in clinical trials indicate that changes in QTc from baseline greater than 30 or 60 ms signify an increased risk for the development of the polymorphic ventricular tachycardia, torsades de pointes.³ Indeed, the US Food and Drug Administration has exhibited a stricter policy germane to drug-induced QTc prolongation with the removal of cisapride and terfenadine from the market after increased reports of drug-induced sudden death despite mean increases in the QTc interval of 13 and 17

ms, respectively.^{4,5} Despite the presence of risk factors leading to exaggerated drug-induced QT prolongation (ie, bradycardia, heart disease, hypomagnesemia, hypokalemia), the risk of drug-induced torsades des pointes is imprecise and remains highly stochastic even among patients with the same risk profile and equivalent QT intervals.⁶ Because most male patients are embarrassed to report erectile dysfunction, the use of QTc prolonging supplements, such as Enzyte, are likely to be underreported to health care providers. This creates a relatively anonymous patient population at an elevated risk for drug-induced sudden death.

This study has some important limitations primarily due to safety precautions. The majority of subjects enrolled in this study were young healthy male volunteers, which lowered the mean QTc interval observed at baseline. Since patients with erectile dysfunction are older than our study subjects and may have some form of underlying cardiovascular disease (eg, atherosclerosis, hypertension), their baseline QTc intervals, and thus proarrhythmic risk, may be higher. Although prolonged QTc intervals are a risk factor for sudden cardiac death, we did not study the effect of Enzyte on all-cause or cardiovascular mortality. Finally, our assessment of noncardiac adverse effects is limited by the lack of case reports. Clearly, more studies are needed to establish the safety of Enzyte in the population to which it is marketed. Clinicians should advise patients to refrain from using Enzyte until more information is known.

Mark Phillips, DO
Bridgette Sullivan, PharmD
Brenda Snyder, DO
Paul J. Allegretti, DO
Brian F. McBride, PharmD

Author Affiliations: Chicago College of Osteopathic Medicine, Chicago College of Pharmacy Midwestern University, Downers Grove, Illinois (Drs Phillips, Sullivan, Snyder, and Allegretti); and Marcella Niehoff School of Nursing and Stritch School of Medicine, Loyola University Chicago (Dr McBride).

Correspondence: Dr McBride, Marcella Niehoff School of Nursing, Loyola University Chicago, 2160 S First Ave, Bldg 102, Room 4602, Maywood, IL 60153 (Bf.mcbride@comcast.net).

Author Contributions: *Study concept and design:* Sullivan, Allegretti, and McBride. *Acquisition of data:* Phillips, Sullivan, Snyder, and McBride. *Analysis and interpretation of data:* Phillips and McBride. *Drafting of the manuscript:* Phillips, Sullivan, Snyder, Allegretti, and McBride. *Critical revision of the manuscript for important intellectual content:* Phillips and McBride. *Statistical analysis:* Phillips and McBride. *Obtained funding:* McBride. *Administrative, technical, and material support:* Sullivan, Snyder, Allegretti, and McBride. *Study supervision:* Allegretti and McBride.

Financial Disclosure: None reported.

1. Morrow JD. Why the United States still needs improved dietary supplement regulation and oversight. *Clin Pharmacol Ther.* 2008;83(3):391-393.
2. Morrow JD, Edeki TI, El Mouelhi M, et al; American Society for Clinical Phar-

macology and Therapeutics. American Society for Clinical Pharmacology and Therapeutics position statement on dietary supplement safety and regulation. *Clin Pharmacol Ther.* 2005;77(3):113-122.

3. Food and Drug Administration, HHS. International Conference on Harmonization; guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; availability: notice. *Fed Regist.* 2005;70(202):61134-61135.
4. Wang SH, Lin CY, Huang TY, Wu ES, Chen CC, Tsai S. QT interval effects of cisapride in the clinical setting. *Int J Cardiol.* 2001;80(2-3):179-183.
5. Gillen MS, Miller B, Chaikin P, Morganroth J. Effect of supratherapeutic doses of ebastine and terfenadine on the QTc interval. *Br J Clin Pharmacol.* 2001; 52(2):201-204.
6. Li EC, Estery JS, Pohl S, Scott SD, McBride BF. Drug-induced QT prolongation. *Pharmacotherapy.* In press.

INVITED COMMENTARY

The Safety of Dietary Supplements

According to a National Center for Complementary and Alternative Medicine report, in 2007, Americans spent \$14.8 billion on “non-vitamin, non-mineral natural products.”¹ To put this in context, this is approximately one-third of US out-of-pocket spending for prescription drugs. Dietary supplements are popular with American consumers.

But with popularity comes concerns about safety. In 2003, dietary supplements containing the herb ephedra were pulled from the market amidst concerns that they contributed to cardiovascular deaths among young people.² Kava-containing dietary supplements have been associated with liver failure, supplements containing red yeast rice and marketed for the control of cholesterol were found to have been adulterated with lovastatin,^{3,4} and more recently a report from the Government Accounting Office found that 92% of a sample of herbal supplements contained trace amounts of lead and 80% had at least one other contaminant, such as mercury.⁵

In this issue of the *Archives*, Phillips and colleagues add to this list of concerns by documenting worrisome electrocardiographic changes in 9 healthy young male subjects given the dietary supplement Enzyte, which is marketed as “the once daily tablet for natural male enhancement” (<http://www.enzyte.com/>). Enzyte is promoted as containing *Ginkgo biloba*, “horny goat weed extract,” Korean ginseng, L-arginine, *Tribulus terrestris* extract, and 30 mg of niacin and zinc and 15 mg of copper. In specific, Phillips and colleagues, in a double-blind experiment, found prolongation of QT and QTc intervals, a finding which in other populations has been associated with an increased risk of torsades de pointes ventricular tachycardia.

What should physicians and consumers make of this finding? One limitation is that we do not know who uses Enzyte, and thus do not know the degree to which the studied population of young healthy men is representative of the user population, which could be older and sicker. Second, Phillips and colleagues did not conduct their study long enough to be able to assess adverse health outcomes—outcomes that people can feel or experience. The QT/QTc outcome is a proxy outcome for other,

43. Unützer J, Katon W, Callahan CM, et al; IMPACT Investigators. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA*. 2002;288(22):2836-2845.
44. Kroenke K, Spitzer RL, Williams JBW, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med*. 2007;146(5):317-325.
45. Perkins AJ, Kroenke K, Unützer J, et al. Common comorbidity scales were similar in their ability to predict health care costs and mortality. *J Clin Epidemiol*. 2004;57(10):1040-1048.
46. Brown LF, Kroenke K, Theobald DE, Wu J, Tu W. The association of depression and anxiety with health-related quality of life in cancer patients with depression and/or pain. *Psychooncology*. 2010;19(7):734-741.
47. Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Med Care*. 2004;42(12):1194-1201.
48. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Med Care*. 1989;27(3)(suppl):S178-S189.
49. Carr D, Goudas L, Lawrence D, et al. *Management of Cancer Symptoms: Pain, Depression, and Fatigue*. Rockville, MD: Agency for Healthcare Research and Quality; 2002. Evidence Report/Technology Assessment No. 61; AHRQ publication 02-E032.
50. Bottomley A. Depression in cancer patients: a literature review. *Eur J Cancer Care (Engl)*. 1998;7(3):181-191.
51. Caraceni A, Portenoy RK; International Association for the Study of Pain. An international survey of cancer pain characteristics and syndromes: IASP Task Force on Cancer Pain. *Pain*. 1999;82(3):263-274.
52. Portenoy RK, Lesage P. Management of cancer pain. *Lancet*. 1999;353(9165):1695-1700.
53. Kroenke K. The interface between physical and psychological symptoms. *J Clin Psychiatry Primary Care Companion J Clin Psychiatry*. 2003;5(suppl 7):11-18.
54. Patrick DL, Ferketich SL, Frame PS, et al; National Institutes of Health State-of-the-Science Panel. National Institutes of Health State-of-the-Science Conference Statement: Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15-17, 2002. *J Natl Cancer Inst*. 2003;95(15):1110-1117.
55. Kroenke K, Spitzer RL, deGruy FV III, Swindle R. A symptom checklist to screen for somatoform disorders in primary care. *Psychosomatics*. 1998;39(3):263-272.
56. Rief W, Martin A, Klaiberg A, Brähler E. Specific effects of depression, panic, and somatic symptoms on illness behavior. *Psychosom Med*. 2005;67(4):596-601.
57. Kroenke K, Sharpe M, Sykes R. Revising the classification of somatoform disorders: key questions and preliminary recommendations. *Psychosomatics*. 2007;48(4):277-285.
58. Kroenke K. Somatoform disorders and recent diagnostic controversies. *Psychiatr Clin North Am*. 2007;30(4):593-619.
59. Löwe B, Spitzer RL, Williams JB, Mussell M, Schellberg D, Kroenke K. Depression, anxiety and somatization in primary care: syndrome overlap and functional impairment. *Gen Hosp Psychiatry*. 2008;30(3):191-199.
60. Barsevick AM. The elusive concept of the symptom cluster. *Oncol Nurs Forum*. 2007;34(5):971-980.
61. Barsevick AM, Whitmer K, Nail LM, Beck SL, Dudley WN. Symptom cluster research: conceptual, design, measurement, and analysis issues. *J Pain Symptom Manage*. 2006;31(1):85-95.
62. Barsevick AM. The concept of symptom cluster. *Semin Oncol Nurs*. 2007;23(2):89-98.
63. Raine R, Haines A, Sensky T, Hutchings A, Larkin K, Black N. Systematic review of mental health interventions for patients with common somatic symptoms: can research evidence from secondary care be extrapolated to primary care? *BMJ*. 2002;325(7372):1082-1085.
64. Smith RC, Lein C, Collins C, et al. Treating patients with medically unexplained symptoms in primary care. *J Gen Intern Med*. 2003;18(6):478-489.
65. Jackson JL, O'Malley PG, Kroenke K. Antidepressants and cognitive-behavioral therapy for symptom syndromes. *CNS Spectr*. 2006;11(3):212-222.
66. Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. *Lancet*. 2007;369(9565):946-955.
67. Kroenke K. Efficacy of treatment for somatoform disorders: a review of randomized controlled trials. *Psychosom Med*. 2007;69(9):881-888.
68. Jacobsen PB, Jim HS. Psychosocial interventions for anxiety and depression in adult cancer patients: achievements and challenges. *CA Cancer J Clin*. 2008;58(4):214-230.
69. *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*. Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting. Washington, DC: National Academies Press; 2008.

Correction

Error in Byline. In the Research Letter titled "Effect of Enzyte on QT and QTc Intervals" by Philips et al, published in the August 9/23 issue of the *Archives* (2010; 170[15]:1402-1404), an error occurred in the spelling of the first author's surname in the signature block, author affiliations, and author contributions at the end of the letter. The name should have been spelled "Mark Philips, DO."