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.

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Financial Disclosure: None reported.

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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 "nonvitamin, 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 *Gingko 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,

serious health outcomes, and whether these would actually occur is not yet established.

Still, Phillips and colleagues' findings must be taken as a signal that there is something potentially lurking beyond our current eyesight regarding the safety of Enzyte. Their conclusion that clinicians should advise their patients to avoid this dietary supplement until more evidence is available seems justified and prudent. Their report adds to the increasingly loud drumbeat of safety concerns about dietary supplements.

What can be done to ensure that consumers are not exposed to dietary supplements that are unsafe? The Dietary Supplement Health and Education Act of 1994 (DSHEA)[6] posits that dietary supplements are "presumed safe" until proven to be otherwise. Clearly, the body of evidence accumulated since 1994 indicates that this assumption is no longer in the public interest and needs to be revised. What needs to happen? First, we need to determine what we mean by "safe." All things have potential risks: excess salt intake is associated with hypertension, water is necessary for life yet too much water intake can cause dangerous hyponatremia, and too much oxygen can cause various lung and eye conditions. So "safe" cannot equal "no risk at all." How much risk is too much? This is where the "benefit" comes into play. As a primary care physician, I commonly prescribe pharmaceuticals that I know to have risks, sometimes serious risks, but I do so when the evidence supports that the expected benefit (such as the mortality reduction in patients with systolic heart failure treated with angiotensin-converting enzyme inhibitors) exceeds the expected risks (eg, angioedema, renal failure) by a sufficiently large margin indicating that the prescription is appropriate. What is the benefit of taking a dietary supplement? Under the DSHEA,[6] dietary supplements cannot claim to treat medical conditions, meaning that Enzyte cannot claim to treat erectile dysfunction. Rather, dietary supplements may only make "structure/function" claims, ergo, Enzyte promotes "male enhancement." This distinction is probably lost on many if not most consumers. Furthermore, even to promote "male enhancement" implies a biologically active mechanism for the ingredients in Enzyte. I believe that if a biologically active effect is stated, then there needs to be evidence that this is indeed the case. Disturbingly, in many recent rigorous trials of dietary supplements, they have been found to be no more effective than placebo.[7-10] We are left, then, in the situation where evidence of benefit is slim to nonexistent, which then makes any level of risk—even if it is simply a signal and not evidence of the risk itself, as in the case of Enzyte—a sufficient concern to warrant a recommendation against using it.

Second, the public needs better evidence of the benefits as well as the risks of dietary supplements. In the absence of benefit, no risk is acceptable. It is in the interest of the responsible dietary supplement manufacturers to do more to convince the public that their products are safe and effective. When properly performed, such work could rely on the market to reward manufacturers of safe and effective supplements, while driving out the less-responsible manufacturers. Examples abound where consumers are willing to pay more for "quality" if they have confidence in the evidence of that quality. If the dietary supplement manufacturers do not respond to this challenge, the American public will demand federal regulation.

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Financial Disclosure: None reported.

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COMMENTS AND OPINIONS

Nursing Home Culture Discourages Physician Involvement

In her excellent recent editorial, Johnson[1] describes the vital role of the physician in changing the culture of nursing homes in a positive direction. The problem is that, in recent history, it has been very difficult in many places to entice physicians to become and remain involved, as either medical directors or attending physicians, in providing medical care to nursing home residents. In a research project a several years ago, I tried to identify some of the explanations for the complex "missing in action" phenomenon[2] largely characterizing physician noninvolvement in nursing homes. The primary impediments to physicians' willingness to care for nursing home residents appeared to be a lack of pertinent professional training and acculturation, strong financial disincentives, the relatively low status of nurs-