The Supplement Paradox
Negligible Benefits, Robust Consumption

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**Dietary supplements** encompass a wide variety of products from vitamins, minerals, and botanicals to probiotics, protein powders, and fish oils.1 During the past 2 decades, a steady stream of high-quality studies evaluating dietary supplements has yielded predominantly disappointing results about potential health benefits, whereas evidence of harm has continued to accumulate. How consumers have responded to these scientific developments is not known. In this issue of JAMA,2 the report by Kantor and colleagues sheds light on this important question.

To place the results of the study by Kantor et al in context, it is helpful to understand the regulatory changes predating their study. In the late 1980s, 36% of men and 48% of women used vitamins, minerals, and other supplements.3 These high consumption levels increased further after the passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA), a law that continues to define supplement policy to this day. Under DSHEA, all supplements are assumed to be safe until the US Food and Drug Administration (FDA) detects evidence of harm,4 usually only after consumers have been extensively exposed to the product. The lax DSHEA requirements for proof of product safety led to a rapid increase in the number of supplements in the marketplace, from an estimated 4000 in 1994 to 55,000 in 2012.4 Dietary supplements had grown into a greater than $32 billion industry by 2012.5

The period Kantor and colleagues studied, 1999 through 2012, was an era of intense investigation into the health effects of supplements. The National Institutes of Health (NIH) invested more than $250 million to $300 million per year funding dietary supplement research.4,5 Many major clinical studies were published, but the results generally failed to demonstrate beneficial effects on health. According to a recent summary of this extensive investment: “most of the larger NIH-supported clinical trials [of dietary supplements] failed to demonstrate a significant benefit compared to control groups.”6 Prominent examples of high-quality studies published during this era and showing no benefits of supplements include an evaluation of multivitamins to prevent cancer and heart disease,6 echinacea to treat the common cold,7 St John’s wort to treat major depression,8 and vitamin E to prevent prostate cancer.9

At the same time, the health risks of supplements were also becoming better understood. In the late 1990s and early 2000s, supplements containing ephedra were linked to many serious adverse events including myocardial infarctions, seizures, strokes, and sudden deaths.10 By 2002, national poison centers were receiving more than 10,000 calls related to ephedra poisonings per year.10 Long-term risks began to be recognized as well, for example, beta-carotene supplements were found to actually increase the risk of lung cancer among smokers.11

Not all supplements, of course, lack evidence of efficacy. Many supplements, including vitamins, minerals, and probiotics, are important components of modern health care. Supplements are essential to treat vitamin and mineral deficiencies, and there are indications for multivitamins as well, for example, a specific combination of vitamins and minerals can delay progression of early age-related macular degeneration.12 But even supplements that are useful in treating certain conditions are frequently overused among the general population to “improve” or “maintain” health, and only about one-quarter of consumers use supplements based on the advice of their clinicians.13 For the majority of adults, supplements likely provide little, if any, benefit.

It might have been expected that the string of negative studies involving supplements, along with the increasing safety concerns, would have triggered a decrease in supplement use in the late 1990s and early 2000s. But this is not what Kantor and colleagues found. Instead, using cross-sectional data from 37,958 interviews obtained over 7 cycles of the National Health and Nutrition Examination Survey (NHANES), Kantor et al found that supplement use was stable during this period, with 52% (95% CI, 49%-54%) of US adults in the 1999-2000 survey and 52% (95% CI, 49%-55%) in the 2011-2012 survey reporting having used supplements in the prior 30 days.

Although overall supplement use remained constant, there were some noteworthy changes in use of specific supplements. Multivitamin use, for example, declined from 37% to 31%, and rates of vitamin C, vitamin E, and selenium use decreased, perhaps in response to research findings showing no benefit. Other products continued to be used at the same rate despite major studies demonstrating no benefit over placebo. Following the negative results of the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) published in 2006,14 use of glucosamine and chondroitin remained essentially the same in the 1999-2000 and 2011-2012 surveys. Other supplements increased in use during the study period, including omega-3 fatty acids, lycopene, vitamin D, and probiotics. Overall, major research findings sometimes appeared to lead to modest effects on consumption of individual supplements but had no effect on overall use of supplements.

Why would consumers continue to use supplements after high-quality trials found many of these products to be no more effective than placebos? One factor may simply be that consumers are not aware of these negative results, and so continue to use the products...
they have been using for years. In these cases, the onus is on clinicians to inform patients when the evidence has changed. Other consumers might not have faith in the scientific process, in which case counseling is unlikely to result in significant changes in supplement use.

Another factor may be that these findings are counterintuitive: avoiding a multivitamin seems to run counter to everything patients have been taught about the importance of consuming enough vitamins and minerals. Physicians can help remind patients that there is no benefit of obtaining vitamins from a pill rather than from conventional food.

A third factor is that the law affords manufacturers significant leeway to advertise supplements for a broad spectrum of conditions. DSHEA permits the promotion of supplements using “structure/function claims.” For example, claims such as “supplement X will preserve heart health” or “supplement Y will maintain mental alertness” are permitted without premarketing authorization from the FDA. Such claims must be accompanied by a disclaimer: “These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.” However, the disclaimer appears to have minimal effect on consumer understanding of the advertised claim.

Moreover, even after high-quality studies that show no meaningful clinical differences between supplements and placebos are published, the law provides manufacturers latitude to continue advertising their products based on earlier, lower-quality data. For example, Ginkgo biloba continues to be sold “to support mental sharpness” despite a large, high-quality NIH-funded study that found evidence to the contrary. In the study by Kantor et al, when the consumption of some products declined over time, consumption of other products increased and made up for the deficit. It might be that companies refocused advertising from one supplement to another. In response to research findings showing no substantial benefit for garlic and glucosamine, for example, manufacturers may have turned to preliminary findings to promote coenzyme Q10 for heart health or methylsulfonylmethane for joint health.

What are the conclusions from this new analysis? It is now well documented that more than half of US adults use supplements. Physicians should include supplements when they review medications with all patients and also consider supplements when symptoms raise the possibility of a supplement-related adverse effect. It is now known that many supplements contain pharmaceutically active botanicals, which can have important clinical effects. For example, red yeast rice, yohimbe, and caffeine all have pharmacological effects, and although ephedra has been banned, a variety of synthetic drugs have replaced ephedra as stimulants in many sports and weight loss supplements. Reporting suspected adverse effects of supplements is also critical. The FDA relies on physicians and consumers to report adverse events via MedWatch to remove hazardous supplements from the marketplace.

The current study by Kantor et al should also lead funders and legislators to reconsider their priorities with respect to supplements. Given the current regulatory framework, even high-quality research appears to have only modest effects on supplement use. Future efforts should focus on developing regulatory reforms that provide consumers with accurate information about the efficacy and safety of supplements and on improving mechanisms for identifying products that are causing more harm than good.

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REFERENCES