

The Rational Use of Dietary Supplements and Nutraceuticals in Clinical Medicine

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Abstract

The rational use of dietary supplements and nutraceuticals (DS/N) is based on objective evaluation of the clinical evidence as well as subjective evaluation of the risks, benefits, economic costs, and potential drug interactions. Since the use of DS/N has skyrocketed, physicians must learn about them in order to better communicate with and care for their patients. There are many evidence-based and rational uses for DS/N, but profiteering and quackery must be avoided at all costs.

Key Words: Dietary supplements, nutraceuticals, alternative care.

Introduction

THE PRACTICE OF CLINICAL MEDICINE spans a range of methodologies from disciplined scientific investigation to an impressionistic system of health care. Creative solutions to clinical problems incorporate subjective, humanistic qualities that cannot always be scientifically tested. However, the advocacy of unproven therapies, heralded as standards of care or appropriate interventions, cannot be condoned. Such is the case for many of the published indications for dietary supplements and nutraceuticals (DS/N) and their seemingly widespread recommendation for a host of ailments. The purpose of this article is to present a framework for the rational, safe and beneficial use of DS/N. A technical review of the data supporting or refuting the use of specific DS/N is beyond the scope of this article, but may be found in the American Association of Clinical Endocrinologists' Clinical Practice Guidelines on the topic (1).

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Defining the Problem

Several key concepts need to be defined first. The practice of medicine that strays from the basic tenets taught in American medical schools is termed "alternative," "complementary," "unconventional," "integrative" or "holistic." This paradigm incorporates two other features: (a) addressing symptoms rather than diagnoses of diseases and (b) relying on lesser levels of scientific substantiation or none at all, i.e., anecdote and testimonial. One of the major problems of this second feature is that the "placebo-effect" can clearly account for purported benefits. The major issue is not whether these alternative medical practices are "right" or "wrong," but rather whether they cause harm. This issue is difficult to address, because the line between traditional standards of care and quackery is blurred.

Why is alternative care popular? People become disenchanted with the medical profession and flock to alternative medicine when complaints, such as pain or fatigue, cannot be adequately treated, or diseases, such as certain forms of cancer, cannot be cured. In addition, alternative care is promoted by the media, especially over the Internet, which is an ever-increasing source of health care advice and information. An impetus for the promotion by the media is the profit motive. The public may seek traditional medicines when they are *sick*, but they also seek DS/N when they want

to *promote health*. To some extent, many people use DS/N to self-treat, almost as if they are personally challenging the traditional medical system. Alternative care practitioners and their customers promulgate the concept that *natural* products are superior to and safer than *synthetic* products or *drugs*. This distinction, in the context of treating disease states, is not based on scientific data and may be viewed as irrational.

Many DS/N advertisements lead the public to believe that the scientific evidence for the efficacy of the product is comparable to that required for FDA-approved drugs, when in fact the DS/N data are clearly inferior. In addition, advocates of alternative care use medical pseudojargon and elaborate physiologic theory very persuasively. Moreover, patients can become confused when the distinction between traditional and alternative care becomes blurred: some traditional doctors prescribe pharmaceuticals to treat diseases in ways that are unproven (e.g., statins for osteoporosis) and they also prescribe DS/N to treat diseases in ways that are proven (e.g., calcium and vitamin D for osteoporosis). However, to be fair, if patients are not receiving successful treatments using the traditional route, and if they seek an alternative care approach that is relatively harmless, regardless of benefit, and if the cost for these interventions is fair and not exploitative, then the practice of alternative medicine can be potentially valuable. The problem is the “ifs.”

For years, the Food and Drug Administration (FDA) required extensive paperwork from manufacturers that was seen by some as impeding the prompt availability of DS/N to the general public. In 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA) to facilitate the investigation and appropriate use of DS/N (Table 1). However, despite these regulations, tremendous qualitative and quantitative variability exists in the composition of DS/N products.

Nutraceuticals have been defined as dietary supplements that contain a concentrated form of a presumed bioactive substance originally derived from a food, but now present in a nonfood matrix, and used to enhance health in dosages exceeding those obtainable from normal foods (2). Examples would be vitamin supplements, ipriflavone tablets for osteoporosis or fish-oil capsules for lipid disorders. To be more precise, perhaps, the term “*nutraceuticals*” refers to compounds containing many bioactive substances, not necessarily nutrients, targeting multiple physiologic actions with many “healing effects” and “*nutri-ceuticals*” refers to compounds containing one nutrient promoting one healing effect (3). *Functional foods* are foods and

TABLE 1
Features of the Dietary Supplement Health and Education Act (DSHEA)

Authorizes increased funding for the Office of Alternative Medicine at the National Institutes of Health.
Provides for increased investigations of DS/N by the Cochrane-Controlled Trials Register.
Defines dietary supplements as: <ul style="list-style-type: none"> • a vitamin or mineral • an herb or other phytochemical • an amino acid • a dietary substance to supplement the diet by increasing the total dietary intake (e.g., enzymes, organ tissue or glandular tissue) • a concentrate, metabolite, constituent or extract of any of the above • not foods in their natural form • not meal substitutes like Ensure® or Boost®
Permits 3 types of claims on labels: <ul style="list-style-type: none"> • nutrient-content (“high in calcium”) • structure-function or nutrition support (“calcium builds strong bones”) • disease-treatment claims (“calcium treats osteoporosis”)—must have FDA authorization based on scientific data
Allows the FDA to monitor adverse reports, issues warnings to the general public, intervene and regulate DS/N
Shortcomings: <ul style="list-style-type: none"> • FDA receives inadequate scientifically based data regarding product safety • FDA receives inadequate scientifically based data regarding product benefit • FDA is unable to address the observed <i>potential</i> to do harm • FDA is unable to verify manufacturing processes

FDA = Food and Drug Administration; DS/N = dietary supplements and nutraceuticals.

beverages with claimed health benefits based on scientific evidence. For simplicity, in this review, “DS/N” refers to dietary supplements, nutraceuticals, nutriceuticals, and functional foods (Figure).

The DSHEA was designed with the goal of saving health care dollars by promoting self-healing as a vehicle to diminish costly doctor visits, drugs and diagnostic procedures. While there are obvious merits in patients assuming a primary responsibility for their own health, as exemplified by the USDA Dietary Guidelines for Americans (4), current data on the role of preventive medicine suggest that “self-healing” should not supplant physician visits and standards of care for screening, diagnostic testing and drug use. To illustrate the magnitude of this problem, expenditures for alternative medicine professional services increased 45% from 1990 to 1997, totaling \$21 billion in 1997, \$12 billion of which was paid for “out-of-pocket” expenses (5). An alarming 72% of patients availing themselves of alternative care failed to disclose this to their physicians (6). One can only

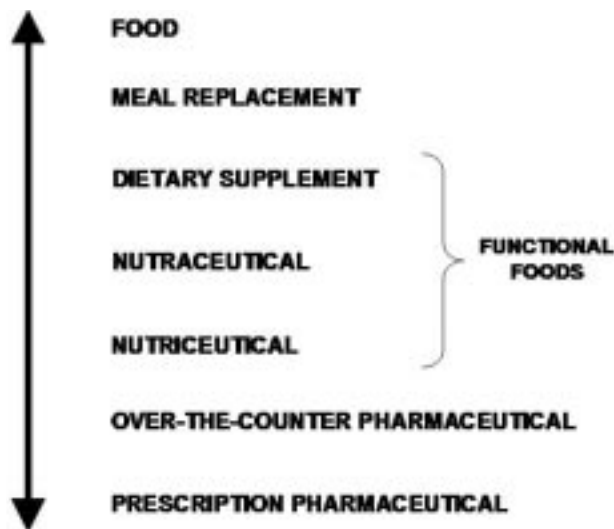


Figure. Spectrum of nutritional substances.

imagine the extent of this problem now, a decade later.

Moreover, as a result of DSHEA, there has been an explosion of commercially available DS/N, which has resulted in worrisome consequences. The FDA has recently succeeded in removing ephedra-containing products from the market. However, many other agents with reported adverse effects have not (yet) been banned. Until further legislation occurs that fairly reconciles the need of the general public to have access to safe DS/N, with their need to be protected from unsafe or inappropriate DS/N, physicians bear the responsibility to (a) educate themselves and their patients, (b) prescribe DS/N in a rational manner, (c) conduct research protocols to investigate the scientific merits of various DS/N, and (d) police the use of unproven therapies.

Another type of alternative care that has attracted traditional doctors is termed “functional medicine.” This branch of alternative medicine focuses on the treatment of chronic diseases and symptoms, as well as preventive medicine and healthy aging. Though the use of traditional medicine is not prohibited, the use of DS/N is clearly favored. The rationale is predicated on physiologic theory, which can be quite intricate, as well as *in vitro* and preclinical studies, but without strong clinical data. However, there is a component of functional medicine that deserves mention. The use of genomic medicine in the realm of nutrition, so-called “nutrigenomics,” represents an emerging field in traditional medicine that will one day, it is hoped, be commonplace. Specifically, gene arrays could be used to identify individualized nutritional needs to prevent diseases that would potentially occur later in life, such as type-2 diabetes mellitus,

metabolic syndrome, cardiovascular disease, and various cancers, to name a few. The question is, “How appropriate would it be to start DS/N therapy for patients at risk for certain diseases?” The answer centers squarely on the presence and quality of clinical data to justify their use, and not simply theory, *in vitro* data, preclinical data, or imaginative aspirations.

“Evidence-based medicine” has become a frequent expression on hospital rounds and in heated debates on the relative merits of DS/N. Proponents of evidence-based medicine argue that all clinical decision-making must incorporate some level of scientific data to differentiate standard patient care from clinical investigations or purely impressionistic practices. Moreover, proper informed consent, risk-benefit analyses, and cost-effectiveness analyses can be based on the strength of the scientific evidence at hand and lead to formal recommendation grades (Table 2). Critics argue that one cannot extrapolate data from prospective, randomized controlled trials to a single patient, necessitating the incorporation of impressionistic, subjective attributes into any clinical decision. Besides, it is also asserted, even anecdote and testimonial constitute a form of “evidence.”

Thus, the problem is: “When is it appropriate to prescribe or recommend DS/N?”

Navigating a Course towards the Answer

The rational use of DS/N has been approached via two converging methodologies. On the one hand, clinical investigators in traditional medicine have been reporting adverse events, case reports of apparent successes and relatively small prospective, randomized controlled trials for the use of DS/N for specific diseases. On the other hand, some alternative care practitioners have diligently conducted well-designed clinical studies to evaluate the safety and efficacy of many DS/N. The net result is an accrual of data that supports the use of some DS/N based on science and not hearsay (Table 3). Unfortunately, there are still many health care providers, both traditional and alternative, who recommend unproven (recommendation grade D) therapies, and practice quackery and profiteering. Patients who select these practitioners and substitute unproven therapies for standard medical care, must accept responsibility for their own choices and actions. Moreover—and this is a crucial point—even if a DS/N product is proven to be safe and effective with level I scientific evidence, there is no guarantee whatsoever that the commercially manufactured product actually contains: (a) the proper chemical structure of the main

TABLE 2
Levels of Scientific Substantiation

Level of Evidence	Recommendation Grade	Description
I		Well-controlled, generalizable, randomized trial Adequately powered Well-controlled multicenter trial Large meta-analyses with quality ratings All-or-none evidence
II		Randomized controlled trial—limited body of data Well-conducted prospective cohort study Well-conducted meta-analysis of cohort studies
III		Flawed randomized clinical trials Observational studies Case-series or case-reports Conflicting evidence with weight of evidence supporting the recommendation
IV		Expert consensus Expert opinion based on experience “Theory-driven conclusions” “Unproven claims”
	A	Homogeneous evidence from multiple, well-designed, randomized controlled trials with sufficient statistical power Homogeneous evidence from multiple, well-designed, cohort-controlled trials with sufficient statistical power ≥1 conclusive Level I publication demonstrating benefit >> risk “first-line treatment”
	B	Evidence from at least one large, well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis No conclusive Level I publication; ≥ 1 conclusive Level II publication demonstrating benefit >> risk “second-line treatment”
	C	Evidence based on clinical experience, descriptive studies, or expert consensus opinion No conclusive Level I or II publication; ≥ 1 conclusive Level III publication demonstrating benefit >> risk No conclusive risk at all and no conclusive benefit demonstrated by evidence “no objection to use”
	D	Not rated No conclusive Level I, II, or III publication demonstrating benefit >> risk Conclusive Level I, II, or III publication demonstrating risk >> benefit “do not use”

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ingredient; (b) the quantity of main ingredient indicated on the label; and/or (c) no other interfering substances or deleterious ingredients. Thus, the general, unregulated use of DS/N, particularly without the scrutiny of an individual’s physician, confers more risk than benefit.

Clearly, additional scientific studies need to be conducted, so that eventually, level I meta-reviews can be generated to provide the basis for evidence-based recommendations for DS/N. In addition, a revamping of DSHEA, manufacturing processes of DS/N and the role of the FDA regarding DS/N are required.

TABLE 3
Summary of Results of Clinical Practice Guidelines for
Some DS/N

DS/N	Indication	Recommendation Grade
Calcium	osteoporosis	A
Fiber	decreased risk of cancer and CAD	A
Folic acid	decreased risk of neural tube defects	A
Psyllium	decreased risk of CAD	A
Soy protein	decreased risk of CAD	A
n-3 fatty acids	cardiovascular disease	A
	hypertriglyceridemia	B
	inflammatory bowel disease	C
Chondroitin	osteoarthritis	B
Glucosamine	osteoarthritis	B
Probiotics	chronic pouchitis	B
	antibiotic-related diarrhea	C
Saw palmetto	benign prostatic hypertrophy	B
Ipriflavone	osteoporosis	B
Taurine	chronic alcoholism	B
	TPN-induced hepatopathy	C
α -lipoic acid	diabetic neuropathy	B
Coenzyme Q10	mitochondrial disorders	C
Creatine	performance enhancement	C
Androstenedione	performance enhancement	D
DHEAS	anti-aging	D
Melatonin	cancer	D
<i>Ginkgo biloba</i>	intermittent claudication	D

DS/N = dietary supplements and nutraceuticals; TPN = total parenteral nutrition; CAD = coronary artery disease; DHEAS = dehydroepiandrosterone sulfate.

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Summary of Recommendations

DS/N should be used in accordance with recommendations from clinical practice guidelines based on a technical review of the literature. Physicians should be aware that many DS/N have proven indications and that many others have no proven indications. Does this mean that DS/N must always have “strong” evidence demonstrating benefit in order to be rationally used? The answer is no. In some cases, the clinical evidence may demonstrate clear safety but unproven benefit (recommendation grade C). In this case, physicians should not actively recommend the use of the particular DS/N, but they need not instruct the patient to stop using it.

In situations where such clinical practice guidelines are not available, the individual practitioner should recommend DS/N only when a diligent literature search supports benefit exceeding risk and the patient has been fully apprised of these risks and benefits.

All patients should be asked about their use of DS/N, in addition to conventional medications, as part of routine history-taking.

Only DS/N manufactured properly should be used. Due diligence should be employed by the physician to verify that DS/N products meet this criterion. If a product cannot be verified, then the patient should be advised not to use it. Patients who choose to take unverified products would do so at their own risk.

Interactions between DS/N products—or between such products and food or medication—should be known by the physician. If there is any interaction that has potential for harm, the agent should not be recommended.

If a DS/N product is recommended, appropriate follow-up must be performed.

Physicians should receive formal education regarding DS/N in medical school, postgraduate training and continuing medical education programs. This will enable prudent and evidence-based decision-making, as well as facilitate communication with patients.

Research projects on DS/N with sound experimental design should be encouraged.

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