Chapter 2
25+ Observations Over 25+ Years for Surviving and Thriving in the Dietary Supplement Quality Control and/or Perception Versus Reality World

Introduction

"Vitamin E is dangerous!" "Herbal products have no evidence!" _____ does not treat or cure advanced cancer"? "Supplements don't do anything, so don't waste your money!" For almost 30 years I have watched not just patients, but especially some influential clinicians generalize, embellish, and misconstrue data on dietary supplements. This type of commentary just mirrors the lack of objective education in this area, does nothing to improve the clinician and patient relationship, and arguably sends countless individuals to less credible sources for information and misguided sales pitches (as it did through the years for many of my own family members). At the same time, I have watched many in the supplement industry embellish data and supplement efficacy and promote a "we vs. them" contentious milieu that only continues to confuse the public. Again, this acrimonious dichotomy or profound polarization does nothing for overall patient care [1].

A good example of the ongoing dual cacophony was a New York (NY) Times front-page article on quality control testing of dietary supplements. The New York State attorney general (NYAG) accused four national retailers (GNC, Target, Walgreens, and Walmart) of selling dietary supplements that were fraudulent and, in numerous cases, "contaminated with unlisted ingredients" [2]. A total of four out of every five products tested contained none of the herbs advertised on the label! And it seemed for critics of the supplement industry this added fuel to the ongoing fire while advocates for the industry fought back and stated that the NY state attorney general's office commissioned an independent testing group that actually performed the wrong test. And they have proof that exactly what is advertised in their products is what is in the products [3]. The NY investigation and accusation was based on testing of herbal products using "DNA barcoding." It is a very reliable method, but here is the key—it needs to be performed on the appropriate material. In other words, herbal extracts found in many supplements contain DNA but it is often of a low quality and broken down or degraded to a level that could make it

M.A. Moyad, *Integrative Medicine for Breast Cancer*,
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really difficult to prove what is in the bottle based on this specific testing method. There is a chance that the supplement companies were primarily in compliance and the NY office was too quick in reaching a verdict. The problem at the time of this writing is that there has been no communication or release of the testing commissioned by the NYAG. In fact, NYAG has now shifted some of the focus on health claims made by these supplement companies and also quality control. This has all the makings of a reality TV show. Recently, research out of Canada showed similar findings of quality control issues but they also utilized DNA barcoding [4]. Regardless of who is right or who is wrong or semi-wrong there is little doubt that many supplements still have issues so perhaps the end will justify the mean with the NYAG situation. Even if the NYAG investigation was botched there appeared to be gluten for example found in "gluten free" advertised supplements.

Thus, I wanted to provide multiple rules or steps, questions I am asked, or really observations that have helped me when making a recommendation or finding the right product for patients that are as true today as they were almost 25+ years ago. This is critical because timeless advice is needed in this field rather than the need or desire to be attracted to the latest and greatest option only to be disappointed or taken to the cleaners so to speak. These will help you (health care professional, patient, …) in getting something desperately needed when reviewing the latest "groundbreaking" (how cliché are those words) supplement or dietary or lifestyle changes, and that is something called "objectivity." This what is desperately needed in the teaching of integrative medicine and especially dietary supplements, which is a business today, and I am glad it is a business because it initiating more and more research and interest, but the down side of that business is the nebulousness or demarcation of objectivity and subjectivity (of course conventional medicine is also as guilty at times of this problem). More and more health care professionals then ever before are selling or recommending supplements and get paid for doing so, and more and more consumers are selling them. This does not disqualify their expertise but makes it more difficult than ever before for a non-polarizing, non-royalty, or non-endorsing objective and experienced current up-to-date source of information, although I had my brief moments over my long career of having been often tempted or even succumbing temporarily to a disease called "JD" or "judgmental dysfunction," but at least I (or others) quickly reminded me of how to find the cure, which is actually appreciating the honor or privilege and trust you hold and earned over time with the public, patients, and health care professionals. Here in this chapter at least you will find that source of current information that I wish I had when I was starting my career as a complete greenhorn.

• The difference between a clinically effective drug and supplement is perception and not reality. So, what are the rules or even politics of what becomes a supplement or a drug? What about FDA current Good Manufacturing Practices (cGMP) now required by supplement companies in the USA? Does that help to give a supplement drug like quality?

In the words of the FDA: "A dietary supplement is a product intended for ingestion that contains a dietary ingredient intended to add further nutritional value to (supplement) the diet. A dietary ingredient may be one, or any combination, of the

following substances: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by people to supplement the diet by increasing the total dietary intake, a concentrate, metabolite, constituent, or extract …" [5]. What?! And keep in mind that dietary supplements are not intended to diagnose, treat, cure or prevent and disease, but the FDA states that some supplements can be used to "help you reduce your risk of disease" [5]. What?!

Okay, now from those definitions above try and tell me the difference of what can become a supplement or a drug? It is pretty nebulous, which is why for example you can sell fish oil or omega-3 in the USA or you can also get it as a prescription drug (Epanova®, Lovaza®, Vascepa® …) [1]. Thus, in my opinion the difference is usually researched based or the requirements of strict clinical trials for FDA approval (a drug) or no trials needed at all (a supplement) and political with an "us" versus "them" mentality which is why it is tough to regulate. In other words, in Congress you have staunch past and current advocates of legislation to maintain supplements as a standalone category (Senator Hatch from Utah, Senator Harkin from Iowa … Republican and a Democrats joined together). And then you have others politically that are on the other side that are more quiet in general but try and monitor public concern, and since most Americans take supplements of some kind and most politicians I have met (hundreds over the years) consume supplements, then I think it is an unpopular position politically to suggest supplements should be tested or regulated like drugs.

The idea that there is no enforced safety net for pills that you consume is a little concerning. So, with some public pressure mounting on quality control the FDA came up with current good manufacturing practices (cGMP or GMP) rule many years ago, in 2007, that supplement companies are supposed to follow. However, if I told you the speed limit was 55 MPH but you knew there were few cops on the highways to enforce this law, then what speed would you drive? In other words, FDA does not have the person power to enforce cGMP so some companies say they are cGMP, but the public has no idea until they are actually inspected by the FDA or an outside third party (for example like NSF or USP). So, there are still a small number of companies operating with an "innocent until they catch me doing something wrong" mentality.

Still, I do not believe supplements should become prescriptions but at the same time anyone that wants to start a supplement company should have to abide by some credible third party independent quality control group like NSF. It makes no sense that tomorrow I could simply set up the "Dr Moyad supplement company" and there would be no one that could stop me or require me in some credible manner to prove that what I was proffering was at least safe (and do not get me started on the scientific part that also requires zero proof for some companies to start selling pills).

On the other side of the debate, you have the anti-drug movement folks and this is a reality. Some drugs today are so ridiculously and embarrassingly expense that this is why the name "big pharma" has become part of the US vernacular or lexicon and that term is obviously not complimentary. I had a colleague of mine at Harvard (notice how I threw in the word Harvard to impress the reader on my personal regular range of peers or colleagues) lean over to me at a lecture and tell me that sildenafil

(Viagra) was 40 dollars a single pill (at the time) for some men suffering from a medical condition (erectile dysfunction) after prostate surgery for example [1]. And by the way there is no justification for some of these prices such as Viagra's cost because research and development (R&D) was not that expensive for this once shelved drug to justify this ongoing cost. So, thanks to higher drug prices and I am sure numerous other reasons like shifting the profit to another source, there is also a strong movement that is anti-big pharma, which helps keep strong political advocacy in favor of NOT changing the supplement rules because what is the perceived antithesis of big pharma? In my opinion, the mom and pop supplement company or holistic practitioner just trying to sell their natural products to help people, and look at big pharma deliberately or personally getting in the way like some vendetta, or try to minimize the little alternative guy or gal (of course sarcasm because some of the biggest supplement companies are now pharmaceutical brands from Bayer to Pfizer and some of the biggest out of pocket profiting is from selling your own line of supplements/recommending them).

Supplements are a many billion-dollar industry (arguably 35–40 billion/year) [6, 7], and in some ways (ironically) it has taken on its own big pharma feel, and money doesn't talk but shouts! So, in reality there are massive money and political movements behind keeping things status quo. When I started 30 years ago in supplements and even in medical school, doctors would tell me all the time that a supplement might not help but "can't hurt" but we know that is not true anymore. *They can help, hurt or do nothing* (just like any other pill). The sheer amount of profit in the industry combined with the lack of good objective education to health care professionals and the public, and throw in the political forces, and you have somewhat of a blurred line between what can become or mimic a supplement and/or a drug. The bottom line again, is that the real difference to me is perception and reality, and also one is required to pass some threshold of evidence and the other does not have to pass a threshold of evidence (it is up to the individual company in the case of a supplement if they even want to risk their business model with something as silly as research—again sarcasm).

So, remember, there is no difference between an effective supplement and a drug. Some of the most widely used supplements in the USA are treated like regulated drugs in other countries. Ever heard of melatonin [1]? Alpha-Lipoic Acid [1]? S-adenosyl-methionine (SAM-e) or Zinc gluconate [1]?!

• "This product is not intended to diagnose, treat, cure, or prevent any disease" is what most dietary supplements or commercials on supplements have to claim, because only a drug can make this claim. Excuse me? What? Yet this is precisely why physicians recommend them or not, and why many patients use them (or not)! The ongoing bane of the "structure/function" FDA allowed claims ("maintains," "promotes," or "supports" _____ Note: just fill in the organ system of interest and add the word "health" to it like breast, colon, immune, prostate health …).

Under the FDA Code of Federal Regulations, title 21, volume 2, the rules for dietary supplements are quite clear despite voluminous language. Under part 101, subpart F and section 101.93 (I am not kidding here) and stated under number 2 part C

"Text for disclaimer." It states that the rules are "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." The problem with this language is it also serves to provide a confusing chasm between reality and perception for families or individuals dealing with minor to devastating diseases. I often tell audiences that most of the effective supplements in the USA are actually prescription drugs or regulated like drugs in other countries such as S-adenosyl-methionine (SAM-e) for depression or osteoarthritis [8–10]. Thus, the line between an effective drug and supplement is only perception and not reality. Instead, what is permitted by the FDA for dietary supplements are what is known as "structure/function claims" (as long as some level of anemic general evidence is provided), which are non-disease claims and companies are allowed to suggest that something contributes or benefits "general well-being" or reduces "nutrient deficiency" or how a nutrient acts to "maintain such structure or function" [11].

In my experience, many companies have tried to follow structure/function claims by mentioning one of three words in advertising, so for example the suggestion that a supplement product may "maintain" or "promote" or "support" prostate health. For example, saw palmetto can advertise that it "supports prostate health," which is not only confusing vernacular to the consumer, but it is arguably now completely inaccurate (see below) [1, 12]. Thus, again these rules do not serve to provide clarity for clinicians and patients but rather perplexity. The current rules or system are scientifically confusing and health care professionals in everyday practice need to better educate the public and patients. Therefore, it is imperative to review a series of situations where supplements are utilized like a drug or not (clear demarcation), and why not allow over-the-counter exceptions or situation where some companies could advertise the benefits (especially when a part of clinical guidelines for a specialty) especially if they were part of the objective phase-3-like trial, while not allowing any suggestion of benefit for other products that have clearly failed phase-3-like trials. The solution does not have to be that difficult and it does not imply that supplements have to be strictly regulated by the government. *I am talking about rewarding the research (more on this later)!*

• Please provide a review of some of the dietary supplements that are utilized as drugs (or not) by health care professionals and patients in the USA for specific diseases/medical conditions.

Alzheimer Disease (AD) or completely different medical conditions known as "NAFLD" (non-alcoholic fatty liver disease) and "NASH" (non-alcoholic steatohepatitis) have somE-thing in common—vitamin E

Individuals with mild to moderate Alzheimer disease taking 2000 IU of vitamin E (DL-alpha-tocopheryl acetate or "synthetic" vitamin E from DSM Nutritional Products, Heerlen, Netherlands) per day in addition to standard medications—the acetylcholinesterase inhibitors (AChEI) drugs, experienced an over 6 month reduction in functional decline and reduced caregiver time by 2 h a day in one of the longest and best clinical trials conducted in the USA (known as the "TEAM-AD VA cooperative randomized trial" and published January 1, 2014 in the Journal of the American Medical Association) [13]. It is noteworthy that this is the second such

phase-3-like trial to demonstrate this clinical benefit in Alzheimer patients with 2000 IU of vitamin E (again DL-alpha-tocopherol from Hoffman-LaRoche, Nutley, NJ) daily and the first trial was published on April 24, 1997 in the New England Journal of Medicine [14]!

AD patients need more options as exemplified by the recent Cleveland Clinic report that 99.6 % (244 out 245) of the Alzheimer's clinical trials have failed over the past decade [15], so why not? It is remarkable that no vitamin E supplement company is able to advertise these results (not even the company that provided the product for the clinical trial) so the only individuals that potentially suffer from this lack of objective information are the patients afflicted by Alzheimer disease and the other individuals that care about or for them.

It is also disconcerting that some practitioners have not been recommending vitamin E to Alzheimer patients because these supplements have been suggested to have shown some toxicity in other areas of medicine [16], so why utilize them in Alzheimer disease? This myopic thinking again somehow places an effective supplement for a devastating disease in a different category than how things would be treated for an effective drug with some standard limitations. If acetylcholinesterase inhibitors showed some toxicity in other disease scenarios, which they have significantly done already in mild cognitive impairment or Alzheimer patients (nausea, vomiting and diarrhea) [17, 18], then would practitioners quit using all these medications? This appears doubtful because the benefit exceeds the risk for many patients, which is similar to the situation with vitamin E. Additionally, in the TEAM-AD VA Cooperative Trial and in the first phase 3 trial published in 1997, the adverse effects of vitamin E were similar overall to placebo [13, 14]. Interestingly, vitamin E supplements have not shown an ability to prevent Alzheimer's or help those with mild cognitive impairment (MCI) at a dosage of 2000 IU per day (from DSM Nutritional Products, Heerlen, Netherlands) [19], but for those with mild to moderate or moderately severe impairment from Alzheimer's it should be discussed with a physician.

Interestingly, this situation and benefit is arguably similar to a different disease scenario occurring with NAFLD (non-alcoholic fatty liver disease) or NASH (non-alcoholic steatohepatitis) where 800 IU daily (400 IU twice a day) of vitamin E appears to have benefited children/young adults (age 8–17 years) and more clearly benefited adult patients from two major clinical trials (PIVENS trial used "natural" form vitamin E or D-alpha-tocopherol from Nature Made®, Pharmavite, LLC, Mission Hills or Northridge, CA and TONIC children/young adult trial also used Nature Made® vitamin E at the same dosage and form used in the PIVENS trial) [1].

Age-Related Macular Degeneration (AMD)

Individuals with intermediate to advanced stages of age-related macular degeneration (AMD) are now recommended to use a dietary supplement as one of the primary treatments for this disease, which can also prevent vision loss. The exact formulation recommended by the National Eye Institute (NEI) was derived from two phase-3 government funded trials known as AREDS1 (supplements provided by Bausch & Lomb, Bridgewater, NJ) conducted at 11 medical centers and AREDS2 [supplements from DSM Nutritional Products, Inc., Sisseln, Switzerland

manufactured the constituents of the AREDS2 formulations and raw materials for active ingredients and placebos were produced into tablets (lutein + zeaxanthin) and gelatin capsules (EPA + DHA ethyl esters) by Tishcon Corp, Westbury, NY and Alcon Research Ltd, Fort Worth, TX provided raw materials for the four AREDS-type supplements and added into gelatin capsules Banner Pharmacaps Europe BV (Tilburg, the Netherlands)] conducted at 82 medical centers [20–22]. The following dosage is now a standard clinical recommendation for ophthalmologists dealing with AMD:

- 500 mg of vitamin C (ascorbic acid)
- 400 IU of vitamin E (DL-alpha-tocopheryl acetate)
- 25 or 80 mg of zinc (zinc oxide)
- 2 mg (cupric oxide—to prevent potential anemia with high-dose zinc)
- 10 mg Lutein
- 2 mg zeaxanthin

(Note: The lutein source was *Tagetes erecta*/Aztec marigold and zeaxanthin was synthesized at DSM via a patented process and omega-3's EPA + DHA failed to show a benefit in the AREDS2 clinical trail and all participants taking a multivitamin were required to switch to Centrum Silver®, now Pfizer, New York, NY, which was also provided to them, and in the AREDS1 trial the multivitamin allowed was Centrum®, Whitehall-Robins Healthcare, Madison, NJ and now Pfizer.)

Interestingly, this and a similar formula have not shown an ability to prevent this disease but appear to help those with the intermediate to advanced stages. Thus, it is critical that I reiterate the fact that this has become one of the primary or standard treatments for AMD (dry and wet form) along with conventional medicine to help preserve vision. Again, no direct advertisements or benefits are allowed by the companies that provided these products for the clinical trial despite the fact that they are a standard part of medical treatment. I am often frustrated by the fact that I am educating some patients with macular degeneration about these results and the specific formulation that they require, and immediately with the approval of their ophthalmologist they are utilizing these pills. There must be a better method of general education, right?

Antiaging?

Aging is not a medical condition per se, but some in the antiaging movement appear to be advertising that they are combating the aging process. High on this list is a dietary supplement known as "resveratrol." Resveratrol is a supplement that can cost 50–100 dollars a month and it is touted to have dramatic antiaging effects like increasing telomere length and other impressive vernacular, but the reality outside of the laboratory, is that many of the recent human studies have been a large disappointment. And even when preliminary clinical trials on the supplement were published [23], or a large pharmaceutical company (GlaxoSmithKline) invested heavily (arguably up to 750 million dollars for a resveratrol-like compound) it also turned out to be a preliminary disappointment [24]. I often tell patients to save their money until someone can actually prove it does something besides shrink your wallet, which ultimately can increase your stress and can accelerate the aging process [1, 25]. Why some practitioners are allowed

to sell these expensive supplements and others out of their office, and profit from an overall lack of consistent beneficial evidence is concerning, especially based on the ongoing recent evidence [26]. Thus, when a supplement has drug-like efficacy it should be allowed to advertise to patients but at the same time if it fails to show overall efficacy then not even structure–function claims should be permitted.

BPH (Benign Prostatic Hyperplasia or non-cancerous prostate enlargement)—the story of saw palmetto and two phase-3-like and very well-done trials, or the story of chronic non-bacterial prostatitis: a tale of two urologic cities

One of the largest past reviews of clinical studies of saw palmetto for benign prostatic hyperplasia (BPH) found some interesting results in 1998 [27]. This analysis reviewed a total of 18 randomized trials ($n = 2939$ men) and found that most of the studies were limited by their short duration and study design. However, the existing evidence suggested that this herbal product improves urologic symptoms and flow measures. Compared with the FDA approved drug finasteride for this condition, saw palmetto produced similar improvement in urinary tract symptoms and urinary flow, with less side effects. However, saw palmetto had only been compared to current drug therapies for a maximum of approximately 12 months (still not a bad endorsement). More data was needed on this herbal product. Interestingly, the dosage of saw palmetto used in most randomized trials at this point in time was 320 mg/day and this dosage had no effect on PSA levels.

Four years after this notable 1998 review was published another one by similar authors added three new trials with 230 added male participants that translated into a meta-analysis of 21 randomized trials and the conclusions were similar stating that "The results of this update are in agreement with our initial review" [28]. In other words that saw palmetto could be an option that works as well as some pharmacologic agents but with less side effects.

The authors then updated their original meta-analysis again in 2009 and came to this conclusion "Serenoa repens was not more effective than placebo for treatment of urinary symptoms consistent with BPH" [29]. Next, in 2012 another follow-up review by similar authors concluded with the following comment on subjective and objective benefits of saw palmetto by noting: "Serenoa repens therapy does not improve LUTS or Q(max) compared with placebo in men with BPH, even at double and triple the usual dose" [30].

What happened that caused such a reversal in a long-standing recommendation or endorsement for saw palmetto? In the more recent meta-analysis for example there were nine new trials added to the analysis that included 2053 more men (about 65 % increase), and overall there were 5222 subjects from 30 randomized trials of a 4–60 week duration utilized for example [29, 30].

However, the answer to the question of what caused such a reversal in the saw palmetto enthusiasm lies in what is known as well-done non-biased or objective phase-3-like research. The first trial was a US government funded trial called "STEP" (The Saw palmetto for Treatment of Enlarged Prostates) [31], followed by the results of a more recent trial called "CAMUS" (Complementary and Alternative Medicine for Urological Symptoms) [32]—two outstanding phase-3 like trials that arguably should have settled the majority of the debate on saw palmetto itself.

The STEP trial was simply a very well done clinical trial [31], and the researchers and participants in this study should be commended for being a part of one of one the better herbal studies ever completed in medicine. Saw palmetto enjoys a tremendous amount of sales around the world. Some areas of Europe have made this herbal product a prescription, but in the USA there are literally hundreds of over-the-counter (OTC) brands. Florida and several coastal states are some of the largest exporters of this herbal product. This herbal product is so well known that it continues to be one of the more popular supplements taken by men to prevent prostate cancer despite having no relevant evidence that it prevents prostate cancer [33, 34]. Okay, another reason why a structure and function claim such as "supports prostate health" can confuse the public even more than it can clarify, and this is very concerning, because saw palmetto again never had any credible data that it reduces the risk of prostate cancer. So, then why are all these men taking it? Is it because they do not get enough saw palmetto in their diet, or could it be that when something supports prostate health it is very logical to assume that it may have some research against prostate disease prevention, including cancer? Regardless, all of the preliminary data was for the improvement of BPH symptoms. Some researchers suggest it has a finasteride (a drug approved for BPH) type effect, but unlike finasteride (also known as Proscar®) it has not been shown to have any impact on PSA levels. Regardless, there was an ample need to conduct a non-industry or non-biased supported clinical trial to determine if saw palmetto really does have some efficacy. And of course I was pulling for saw palmetto to work and work well given the lack of low cost options with reduced side effects at the time.

The STEP trial was funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and by the National Center for Complementary and Alternative Medicine (NCCAM) [31]. In the STEP trial a total of 225 men with moderate-to-severe BPH symptoms were randomized to saw palmetto extract at a dosage of 160 mg twice a day (320 mg a day total) or placebo [31]. The primary outcomes were the change in score on the American Urological Association Symptom Index (AUASI, a subjective measurement completed by patients) and the maximal flow rate (an objective measure completed by the physician). There were also a number of secondary outcomes including: change in the prostate size, urine volume left in the bladder after urinating, quality of life, laboratory values and side effects. When the trial ended after 12-months of treatment there was no difference between saw palmetto and placebo in all the major areas of study including:

- AUASI score (only 0.04 point difference)
- Maximal urinary flow rate (only 0.43 ml difference)
- Prostate size or volume (only 1.22 ml difference)
- Residual volume after urinating (only a 4.51 ml difference)
- No difference in quality of life, PSA, or side effects

Interestingly, critics abound from these trials and it appears will do anything to shred a major well-done objective phase-3-like clinical trial. For example, some of the popular alternative medicine consumer books and websites had espoused for years the use of a saw palmetto with either 80–95 % combination of fatty acids and

sterols or 85–95 % fatty acids and greater than 0.2 % sterols. The herbal extract used in this trial demonstrated consistent 90–92 % fatty acids and 0.33 % sterols and this was actually verified [31], which means it was right on target or even above the standards of what has been recommended in the past for effectiveness. Even the placebo had an odor similar to saw palmetto so that the participants could not tell the difference, which is always needed in a well-done clinical trial but had not been done in several past saw palmetto trials so I believe some of the participants could tell the difference. The placebo contained polyethylene glycol-400, which is a bitter-tasting liquid with an oil makeup. It contained no free fatty acids, and a brown coloring agent was used in order to ensure no difference in appearance between saw palmetto and placebo.

Some critics then argued that the study should have tested men with mild BPH symptoms or larger prostate glands. Perhaps including men with more mild BPH symptoms and not those with moderate-to-severe BPH would have been a better study, and perhaps men with larger prostates would have also been a better group. The reason for this is due to the suggestion that saw palmetto works similar to a drug (finasteride) that shrinks larger prostate glands. However, again in defense of the researchers in this trial, studying only mild BPH would have been filled with problems such as a large placebo effect, and the encouragement of medicating a condition that for many men needs no immediate intervention (aka overtreatment). Regardless, when the researchers looked at the small number of men with more or less symptoms than the average or with small or larger prostate glands there was still no difference between saw palmetto and placebo [31].

Additionally, what also did not receive attention from this trial was the fact that all of the potential participants in this trial were first placed in a 1-month, single-blind, placebo run-in phase and were not permitted in the trial unless they took 75 % or more of the placebo capsules [31]. In other words, in order to really determine who was committed to being compliant with the pills throughout this entire trial, the participants had to take placebo pills for 1-month prior to the start of the official study. It is interesting that there was actually a significant despite small improvement (or decrease) in symptom scores (AUASI) during this 1-month period! This demonstrates the impressiveness of the placebo effect, especially with BPH and it has to be accounted for, and the researchers made a good effort accounting for it.

Critics also complained of the short length of the trial. Yet this trial was one of the longest saw palmetto versus placebo trials in the history of medicine. The majority of the past trials were about 3 months or shorter [27, 28]. BPH trials of 6 months to 1 year or more are more than adequate to determine if a medication is effective. The researchers could have done this trial over 6 months, but in my opinion 1-year was the perfect duration to determine if saw palmetto was better than placebo. In fact, participants had eight clinic visits during the trial [31], which was also more than sufficient to determine the impact of saw palmetto.

If the STEP trial results were a surprise then the CAMUS results were arguably even more surprising in my opinion because of the higher doses of saw palmetto utilized [32]. Basically, the CAMUS researchers found that low (320 mg), moderate (640 mg), and high doses (960 mg) of saw palmetto given over 72 weeks did not

work better than a placebo for BPH/LUTS. Saw palmetto was again as safe as a placebo, but not more effective than a placebo in the follow-up North American study to the STEP trial. CAMUS was a double-blind, multicenter, placebo-controlled randomized trial conducted at 11 North American clinics including Ontario, Canada [32]. A total of 369 men, approximate mean age, AUASI, peak urinary flow rate, and PVR (post-void residual) of 61 years, 14.5, and 14.9 ml/s and 41 ml were given escalating doses of saw palmetto or placebo over 72 weeks. Again, the intervention consisted of 1–3 chocolate covered gelcaps (320 mg each), and the starting dosage was 320 mg/day with a dose escalation at 24 (640 mg/day) and 48 weeks (960 mg/day) with the trial ending at 18-months of intervention compared to placebo. The saw palmetto used in CAMUS consisted of 85–95 % fatty acids, and it was a lipidic ethanolic extract of ripe, dried saw palmetto berries manufactured by Rottapharm/Madaus, Cologne, Germany, and sold as PROSTA-URGENIN UNO capsules. The placebo contained 375 mg of polyethylene glycol and a matched weight (475 mg), and participants were told to take all gel caps at same time.

Again, in the CAMUS trial the baseline and 72-week results found no significant differences between saw palmetto and placebo for any parameter [32]. For example, no differences were found for all of the following (impressive list):

- AUASI (primary outcome),
- BPH impact index,
- AUA SI QOL,
- Nocturia,
- Peak flow rate,
- Postvoid residual,
- PSA,
- IIEF (International Index of Erectile Function),
- Sleep dysfunction scale,
- Incontinence scale or
- NIH CPSI (Chronic Prostatitis Symptom Index).

Many items actually favored placebo except for the difference in AUASI for non-Caucasian participants, which favored saw palmetto (non-significantly). Some critics suggested the extraction process of saw palmetto was faulty resulting in an impure product. However, the STEP trial used a carbon dioxide extraction procedure for their saw palmetto preparation [31], compared to an ethanolic extraction procedure in the CAMUS trial [32]. In other words, some internet criticisms of the extraction procedure for saw palmetto after the STEP trial was addressed in the CAMUS trial and did not produce better results. This is again a beautiful testament to the researchers for these trials (many of them I know and respect, as is the case with many of the other clinical trials in this book that I thought I would mention to mildly impress the reader).

Interestingly, the most notable saw palmetto supplement/drug in the world (Permixon®) with the most positive clinical research (popular in Europe) apparently either did not or could not participate in this trial [35–38], despite being requested to participate by the North American researchers. Thus, the researchers were left

with another agent from a different manufacturer in this trial, which again arguably demonstrated that North American saw palmetto rigorous studies do not demonstrate efficacy of this herbal product compared to placebo. However, should researchers discount the more positive European studies utilizing Permixon? Not necessarily, but since the most notable product outside the USA are not for sale in the USA, then both the STEP and CAMUS trial suggests that saw palmetto should not be allowed to make any prostate health claim without some future positive research. This would seem appropriate based on the fact that two of the most rigorous trials ever done in medical history showed no benefit over placebo. Regardless of the type of supplement and whatever the medical condition, if most of the rigorous trials result in failure then why is a structure/function claim still permitted?

Still, in order to maintain objectivity in this discourse, patients are left with unmet needs when it comes to prostate enlargement prescription FDA approved medications because numerous men are not able to tolerate them or they could be dangerous for some elderly men [39]. And recent costly drug combinations approved by the FDA did not even include a placebo arm and were still given FDA approval [40]? Also, in discussions with some of the researchers from the CAMUS trial there appeared to be no volunteers (despite being requested) from the pharmaceutical world to be placed up against saw palmetto or placebo when the original trial was being designed. Again, the patients get lost in this shuffle, so BPH is an area of medicine that would benefit from some dietary supplement that works modestly or moderately better than a sugar pill. And although there are some candidates like beta-sitosterol [25], it has been difficult to initiate more recent and rigorous clinical trials to determine if these agents are truly effective. Instead, high-priced combinations of ingredients are used in prostate health supplements that include beta-sitosterol and some of these companies use the old beta-sitosterol clinical data (normally a low cost single ingredient) as evidence as to why their product is effective? However, their product contains countless compounds and beta-sitosterol is just one of them and yet they are allowed to promote their product using the publications of beta-sitosterol as a stand-alone intervention? What?! This issue is not only symptomatic of some urologic supplements but symptomatic of the larger disease found with supplements in almost every medical specialty [1]. Some are bad and should never be allowed any claim, and others do not get the credit they deserve because research does not get rewarded enough in the world of dietary supplements so let's reward some more research before finishing this section.

On the other hand, it is fascinating and perplexing that in another area of urology, chronic non-bacterial prostatitis there are some dietary supplements (Cernilton pollen extract from a variety of sources such as Graminex LLC products, Deshler, OH; and quercetin generic and quercetin complexes from Farr Labs, Beverly Hills, CA such as Prosta-Q and Q-Urol) with adequate clinical evidence and no consistently effective FDA approved drugs [1, 25, 41, 42]. And countless clinicians from the Mayo Clinic to UCLA utilize and recommend these dietary supplements and yet no one is allowed to advertise their benefits?! And chronic non-bacterial prostatitis, by the way, consists of the vast the majority of the global cases of prostatitis, not infectious prostatitis [25].

Breast and Prostate Cancer Prevention/Treatment/Side Effects

Interestingly, there is no supplement that has shown evidence to reduce the risk or recurrence of these two common cancers. And, in fact, there is now plenty of evidence to suggest that getting too many supplements when completely healthy could increase the risk of these cancers, especially prostate cancer. For example, higher-dosages of selenium supplements (200 μg or more) when already ingesting ample selenium from dietary sources could increase the risk of aggressive prostate cancer [25, 43]. Additionally, the evidence of vitamin E supplements and an increased prostate cancer risk as well as potentially high-dose folic acid cannot be ignored [25]. Currently, there is no single supplement that could be considered to have ample evidence in the area of breast cancer prevention or recurrence. And the past 30 years are replete with supplements that claimed such a potential distinction or were deemed to potentially benefit by "experts" in the field. However, the evidence for dietary supplements to reduce the risk of side effects or treat side effects from breast and prostate cancer treatment are impressive (see Chap. 7).

Dry Eye and/or High Triglycerides

Fish oil has been touted for countless conditions but overall has failed most recent clinical trials from cardiovascular disease prevention to macular degeneration [22, 44, 45]. However, it continues to garner increasing research and recommendations in the area of dry eye syndrome [46–49], which is commendable because prescription drugs for this condition can be quite expensive. In the most recent meta-analysis of seven independent studies and almost 800 participants concluded with the following: "Consequently, our findings suggest that omega-3 fatty acids is an effective therapy for dry eye" [49].

These studies have attracted enough interest to initiate a large phase-3 like trial in collaboration with the National Eye Institute (NEI) at over 20 medical centers (2000 mg EPA and 1000 mg DHA) to determine if omega-3 can improve moderate to severe dry eye disease. This trial is known as "DREAM" (Dry Eye Assessment and Management Study) [50]. It will be interesting because the placebo contains olive oil, which also has some known anti-inflammatory properties (a controversial choice). Ophthalmologists are using this option in clinical practice but again how do patients in general discover this information [1]? And what of a cancer patient that experiences this specific problem as a side effect from conventional treatment. Why not try this low-cost option?

Interestingly, the American Heart Association (AHA) guidelines suggest 2–4 g of EPA + DHA (omega-3 from marine sources) per day provided as capsules under a physician's care for hypertriglyceridemia (500 mg/dl+) or simply "patients who need to lower triglycerides" [51]. Currently, three omega-3 prescription drugs have been approved by the FDA for the reduction of triglycerides and they include: Lovaza (approved in 2004), Vascepa (2012), and Epanova (2014) [52, 53]. However, the question remains whether low-cost over-the-counter omega-3 products (fish oil) are the same, better, or worse at lowering triglycerides compared to the more expensive prescription brands. In my experience, there is no difference except in price and the perception of quality control assurance, but most of the over-the-counter fish oil products

have outstanding quality control based on serendipity [25]. This is due to the finding that fish oils are usually derived from short-lived nontoxic harboring fish such as anchovies, sardines, and mackerel. Most of the krill, shrimp, salmon, and even green-lipped mussel fish oils are also well-known for their high quality control, and ease of use/utilization compared to larger fish oils pills, but also high price in some cases, and lack of an impressive number of more rigorous trials with hard clinical endpoints found with low cost (aka cheap) fish oil supplements [1]. And if there is a reason to take fish oil but one needs to avoid large pills, then a children's flavored liquid easily suffices in terms of taste, quality control, concentration, and ease of use compared to any many fish oil pills or capsules.

Erectile Dysfunction (ED)

L-citrulline (an amino acid derived from watermelon rind) is arguably the most promising supplement for ED at 1500 mg/day because it can significantly raise nitric oxide (NO) levels better than the most commonly used products for this same purpose (L-arginine) [25, 54]. And preliminary clinical research demonstrates that it (L-citrulline free form) may be an adequate option for mild or moderate ED. Many other supplements touted for ED have little to no research. And in many parts of the USA some of ED prescription drugs are approximately 10–40 dollars a single pill. This will moderately change with sildenafil becoming generic but in the meantime other viable options to be utilized with and without prescription medications are being utilized by physicians. L-citrulline malate (or even free form) also has the potential to help with legal athletic enhancement (improve muscle blood flow/oxygenation and remove metabolic waste products to allow muscles to function longer) [55]. And since the only primary dietary source of citrulline is watermelon rind, supplementation is the only option for a medical condition [1, 25].

High LDL Cholesterol (aka "Statin intolerance")

Individuals with high cholesterol that cannot tolerate statin drugs have the option of using red yeast rice extract (RYR). However, in one of the more bizarre rulings by federal officials companies are NOT allowed to standardize the active ingredient known as "monacolin K" (basically identical to isolated lovastatin), which is responsible for the lowering of LDL cholesterol in RYR [25].

A meta-analysis of 9625 patients in 93 randomized trials involving three different commercial variants of RYR has summarized this alternative option for patients [56]. The mean reduction in total cholesterol, LDL, triglyceride, and increase in HDL was respectively the following: −35 mg/dl (−0.91 mmol/L), −28 mg/dl (−0.73 mmol/L), −36 mg/dl (−0.41 mmol/L), and +6 mg/dl (+0.15 mmol/L).

"Xuezhikang" is a commercial RYR product evaluated in a large, randomized, placebo-controlled clinical trial with robust endpoints [57]. The China Coronary Secondary Prevention Study (CCSPS) enrolled 4870 participants (3986 men, 884 women) with a previous myocardial infarction (MI), and a baseline mean total cholesterol, LDL, triglyceride, and HDL of approximately 208 mg/dl (5.38 mmol/L), 129 mg/dl (3.34 mmol/L), 165 mg/dl (1.85 mmol/L), and 46 mg/dl (1.19 mmol/L). Participants received RYR 600 mg twice daily (1200 mg total, monacolin K 2.5–3.2 mg/capsule) or matching placebo and followed for 4.5 years. The trial was conducted from May 1996 to December 2003 in 65 hospitals in China. The primary end point was nonfatal MI or death from coronary or cardiac causes. Secondary end

points included total mortality from CV disease, total all-cause mortality, need for coronary revascularization procedure, and change in lipid levels. Fasting blood samples were drawn at baseline, 6–8 weeks after randomization, and at 6-month intervals. There were two interim analyses, and the second one demonstrated a significant difference for the primary endpoint. The study was stopped in June 2003. A total of 98 % of the participants completed the study. It is of interest that a plethora of clinical endpoints were significantly reduced with the exception of a nonsignificant reduction in fatal MI (see Chap. 4). Cancer mortality and all-cause mortality were reduced. Lipids were also modestly and significantly reduced. No serious adverse events were observed during this trial. Total adverse events and treatment cessation numbers were similar for RYR and placebo. The number needed to treat (NNT) to prevent a primary end-point over the 4.5 year duration of the trial is 21, which favorably compares to the NNT range (19–56) observed in previous secondary prevention trials [58]. Subsequent subgroup evaluations from the CCSPS trial have found equivalent benefits with RYR among diabetics [59], elderly (mean age 69 years) [60], and hypertensive participants [61]. Potential anticancer benefits found in the overall trial with RYR were also found among the elderly (significant reduction in cancer deaths) [57, 60], and included a 51 % reduction in cancer incidence [60]. Thus, the data has been consistent that RYR reduces lipid parameters, especially LDL [62–64], and appears to have a favorable impact on clinical endpoints [57]. Reviews of past studies in statin intolerant patients have demonstrated efficacy and safety [65], including a preliminary study in breast cancer patients where RYR was a primary ingredient in one supplement [66], so it could be an interesting current or future option in some cancer patients. The catch … searching for a supplement used in a positive clinical trial that one can rely on and some are mentioned in this text (for example, Sylvan Bioproducts at www.sylvaninc.com/bio/healthCare.html).

Low Testosterone (all perception and minimal to no reality)

There are currently no effective dietary supplements that can consistently increase low testosterone in men [12], and even when testosterone pills were utilized in drugs in many other countries there were health concerns, which is arguably why this form of testosterone was never FDA approved in the USA [1, 25]. In fact, many of the best selling supplements in this category contains fenugreek (*Trigonella foenum-graecum*), which has not only not worked consistently, but actually showed a significant reduction in free testosterone in one study [67]. Fenugreek was famous/infamous over a decade ago when female breast enhancement supplements used this as their primary ingredient (and it did not work in this situation either) [25]. Fenugreek the food has health benefits but the supplement being linked to testosterone or even estrogen consistent increase needs quality research and I am not optimistic despite the fact that having a supplement to increase testosterone would be well-received if safe because some forms of prescription testosterone replacement are expensive.

Insomnia

Melatonin is a well-known supplement that can help with jet lag but it can also help with occasional bouts of insomnia and has an excellent safety record [1]. Most melatonin supplements are immediate release, which means they do not remain in the body for long (short half-life), but they have still demonstrated efficacy. Currently

there is another option known as PR (prolonged release) melatonin that has shown some benefit and is regulated like a drug in some European countries (known as "Circadin®") and it is approved in multiple counties for primary insomnia for individuals 55 years and older [68].

The preliminary benefit in utilizing melatonin for breast cancer patients with insomnia or even depressive symptoms with similar side effects to placebo also should be preliminarily impressive (for example one 3 mg melatonin supplement from Rugby Laboratories—a subsidiary of Watson Laboratories in Duluth, GA, USA—used in a Harvard study, or another 6 mg melatonin from Pharma Nord, Vejle, Denmark) [69, 70]. It is critical to continue to find short-term insomnia solutions especially since some of the prescription drugs have come under some scrutiny lately (for example eszopiclone and FDA concerns) because in rare situations higher dosages can lead to fugue states or "impairment," where the person performs activities, such as driving a vehicle, and does not recall them [71]. And it should be kept in mind that unintentional prescription drug abuse is a leading cause of mortality in the USA with opioids, antianxiety and then insomnia prescription drugs as the top three (in that order) medications that the CDC has identified as a source of this epidemic issue [1].

Migraine Prevention

Prescription drugs and painkillers work well for some migraine sufferers but what does a patient do when suffering from them regularly in terms of prevention? The American Academy of Neurology (AAN) guidelines recommend butterbur extract (Petadolex® brand licensed to multiple companies including Linpharma Inc., Oldsmar, FL—not identified by AAN, but utilized in the clinical trials) as having class A evidence (one of its highest recommendations) as a method to prevent migraine [72]. Additionally higher dosages of vitamin B2 (generic riboflavin) have excellent preliminary data (Level B recommendation) [72]. Yet how exactly does the patient figure all of this out without a reputable and highly specific source [1]?

Parkinson's Disease (PD): Another tale of two supplements—one promising and the other not so promising supplement

There are no effective treatments that slow the progression of this disease but few realize that one of the most interesting options being utilized now by some clinicians and tested in large clinical trials is inosine (from initial research funded by the Michael J. Fox Foundation, US Government/NIH and others and called "SURE-PD" Trial and inosine supplements were obtained from Kyowa Hakko USA Inc., New York, NY) to slow the progression of this disease by raising uric acid levels (making sure patients are monitored carefully by a health care professional because taking too much can increase the risk of kidney stones) [1, 73]. Inosine is also receiving research currently in Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS) [1].

Creatine monohydrate is commonly associated with exercise enhancement but it was also being studied at 10 g a day in arguably one of the largest and well done trials in PD to potentially slow clinical decline and improve quality of life (45 clinical sites in the USA and Canada for a minimum of 5 years) [74]. After reviewing the data from an interim analysis of 955 patients enrolled at least 5 years in this trial there was no observation of efficacy, so the study was appropriately stopped [75].

Urinary Tract Infections (UTI)

Chronic antibiotic use for the prevention of recurrent UTIs may have efficacy but also have potential toxicity and the development of resistance. Cranberry dietary supplements have worked as well as cranberry juice in preventing UTI for individuals that suffer from recurrent UTIs but this is still preliminary data [76, 77]. Regardless, cranberry supplements only contain a few calories whereas cranberry juice contains about 125–150 calories per 8 ounces, which can increase your weight and waist, which in the long-term could theoretically increase the risk of UTIs [25]. Supplements with higher concentrations of the active ingredients, PAC-A (proanthocyanidin A), need more research [77, 78], but are arguably an option being utilized currently for antibiotic-intolerant patients based on benefit over risk ongoing research [25, 77–79]. Looking for reasonable priced supplement with a higher concentration of PAC or especially PAC-A is important since there is no stand out product from a major clinical trial (numerous products exist in Europe such as Anthocran, Cysticlean, Monoselect Macrocarpon-enteric-coated that are regulated).

Weight Loss

Green coffee bean extract, Garcinia cambogia, acai berry … there are a countless list of weight loss supplements that are controversial. However, protein powder isolates (no sugar or lactose) contain as much as 25 g of protein per 100 calories far exceeds what can be accomplished with almost any protein bar or dietary option [1]. It should be "first do no harm" when dealing with weight loss and dietary supplements. Research continues to accumulate that this or another protein powder is a potential option to encourage weight/waist loss and enhance lean muscle mass in association with resistance exercise/exercise and moderate calorie reduction from an analysis of 14 randomized trials [80]. Cancer patients experiencing sarcopenia from treatment should at least be informed of this data. Additionally, alpha-lipoic acid (ALA) has received some interesting rigorous trial results and it may just function as a less potent metformin mimic (see Chap. 6), but ALA is a regulated drug in many countries but it is a supplement in the USA (from multiple easy to access companies) [1].

• Aspirin for up to 50 dollars a month?! Most dietary supplements are initially sold as generics and not patented compounds versus pharmaceuticals that start as patented compounds and then ultimately become generic. Watch for the old "bait and switch" when concerning dietary supplement prices based on this tactic. Adding a celebrity and more ingredients is not always tantamount to a better product but can dramatically increase the price, confusion and obscure the question of whether or not high-quality research was performed on the product itself.

Excuse the distraction for a moment on the discussion of plant sterols (also see Chap. 4), but it is not only educational on some specific dietary supplements and nutrient added to foods and beverages (plant sterols and stanols) to lower cholesterol, but demonstrates what has become somewhat common when utilizing someone else's research to promote a new product that in and of itself has little to no research.

Phytosterols are found in a variety of plants and plant oils [81]. Phytosterols are similar in structure to cholesterol except for minor structural differences. They are not synthesized in humans and minimally absorbed, excreted more rapidly from the liver compared to cholesterol, and not found in high concentrations in human tissues. The main phytosterols found in diet are sitosterol, stigmasterol, and campesterol. Beta-sitosterol is arguably the phytosterol found in largest quantity in the diet (please keep this in mind). Phytosterols block the uptake of exogenous cholesterol from dietary and bile sources in the intestinal tract. LDL cholesterol is reduced by phytosterols, and HDL and triglycerides are not impacted. The blockage of cholesterol absorption may produce a relative cholesterol pool reduction that is followed by up regulation of cholesterol synthesis and LDL receptors, which can increase LDL removal. This is somewhat similar to how some healthy dietary fats found in many healthy foods such as almonds or pistachios may also reduce LDL and improve some health outcomes [82, 83].

An ample quantity (over 40) of clinical trials utilizing phytosterols themselves has been conducted that have ranged from 1 to 12 months in duration [81, 84, 85]. Plant sterols added to foods such as yogurt, margarine, orange juice, mayonnaise, olive oil, and milk have been shown to reduce LDL by approximately 10–15 % (mean of 10–11 %) when approximately 2000 mg or more per day is ingested. And 1600–3000 mg of plant sterol supplemental or tablet consumption can also reduce LDL approximately 4–15 %. Plant sterols may also reduce the absorption of some fat-soluble vitamins, so there has been some debate as to whether multivitamin consumption should occur with the use of these products, and I agree that one multivitamin per day should also be encouraged.

It is interesting that the primary mechanism of action of these sterols via cholesterol uptake reduction and a minor anti-inflammatory mechanism suggests, in my opinion, that they are weaker or less potent mimics of the drug ezetimibe (Zetia®), which can reduce LDL by approximately 20 % with 10 mg dose [86, 87]. Laboratory research suggests ezetimibe favorably impacts prostate tissue and reduces prostate enlargement [88]. Ezetimibe is also commonly added to statin therapy or other lipid lowering agents to achieve synergistic impacts and more favorably reduce LDL [86, 87]. Thus, it should not be surprising that beta-sitosterol by itself or with other lipid lowering medications could reduce non-cancerous prostate enlargement (BPH) symptoms. For example, despite some data to suggest no impact of statins on established BPH over a short period of time [89, 90], other epidemiologic and past laboratory studies suggest potentially favorable impacts on BPH prevention and progression with cholesterol lowering prescribed medications [91–94]. What does this have to do with supplements in general? No problem, we will arrive at this point very soon.

There were two critical and similar reviews that were published in 1999 that has allowed beta-sitosterol supplements to become a potential option for BPH [95, 96]. It is interesting that since this time period no other definitive clinical trials (positive or negative) have been published. The first systematic review was by Wilt et al. and appeared in BJU international that identified studies from 1966 to 1998 [95]. A total of four clinical trials that included 519 men met the inclusion criteria [97–100]. All

four trials were randomized, double-blind, placebo-controlled that included men with mild to moderate symptomatic BPH, and the intervention was given from 4 to 26 weeks. Beta-sitosterol significantly improved symptom scores and flow measures compared to placebo. Beta-sitosterol had no impact on prostate size. Gastrointestinal side effects were the most common side effects and occurred in 1.6 % of men on beta-sitosterol compared to 0 % on placebo. Erectile dysfunction was reported in approximately 0.5 % of men on beta-sitosterol and none on placebo. The authors of this systematic review concluded that beta-sitosterol "improves urological symptoms and flow measures," but that more long-terms studies and standardization of beta-sitosterol preparations were needed. The beta-sitosterol utilized in these studies were known by the names "Harzol," "Azuprostat," or "WA184" (standardized like drugs in other countries), usually derived from South African star grass (*Hypoxis rooperi* or from species of Picea or Pinus). Studies used primarily purified extracts and three studies used "nonglucosidic B-sitosterol" again from 60 to 195 mg/day (two of these studies used Azuprostat, 65 mg TID or 195 mg/day with a 70 % beta-sitosterol content). The preparation generally contained 50 % or higher amounts of B-sitosterol.

The second review was published in 2000 and consisted of similar authors compared to the first review [96], except there may be the potential for beta-sitosterol to reduce getting up at night (nocturia) approximately one less time. The positive results observed in these trials compare with results from pharmaceutical agents. Although beta-sitosterol was considered the active ingredient in these clinical trials this has not been definitively proven but it is reasonable to conclude that it is the most likely or primary efficacious ingredient.

The clinical question is why not just utilize beta-sitosterol as a stand-alone cost-effective single ingredient pill as a patient or recommend it as a clinician? Beta-sitosterol is a heart healthy low-cost ingredient. However, the dosage recommended in cholesterol treatment guidelines is 2000–3000 mg a day to reduce LDL by 6–15 %, and in fact in these National Cholesterol Education Panel recommendations it states that the following: "Plant stanol/sterol esters (2 g/day) are a therapeutic option to enhance LDL cholesterol lowering" [101]. This should be kept in mind when consulting with patients about beta-sitosterol because it is important to be able to discuss the efficacious dosages from the older 1990 prostate studies (20–65 mg TID) compared to the evidence-based hearth healthy guidelines of just plant stanol/sterols to reduce LDL cholesterol (2000–3000 mg/day). Regardless, using just beta-sitosterols or plant sterols by themselves make clinical sense right, but perhaps does not make cents but dollars.

Currently there appears to be multiple costly prostate healthy products that patients are paying as much as 30–50 dollars or more per 1–2 months that appear to have diverse and numerous ingredients but promote their product utilizing the research mentioned earlier. This was not the research on their product but the research someone else conducted. This has ethical issues in some cases because it is my perception and reality that the patients believe the product being sold to them at a high price was the exact product utilized in the research! However, again this is not the case and more importantly they are a variety of other ingredients in these products

that combined have never been tested in any clinical trial or any single rigorous clinical trial. For example, imagine if I sold you aspirin and then I sold you aspirin with ten other ingredients in the same pill and utilized the research on aspirin itself to sell the more expensive 10-item pill! Oh, and I also added a celebrity endorsement to promote the product with real verve. And this is exactly what has been done by some (small number but vociferous and profitable) companies in the supplement business, but one would hope that patients and clinicians would be wise enough to simply just recommend low-cost aspirin? Yet this is not the case in my opinion because they are not aware of what is happening in terms of the "bait and switch here." Thus, in this example I would simply just recommend beta-sitosterol from food or the lower priced single ingredient or primarily generic "plant sterol" supplement pill compared to any other product, and this would save the patient a large sum of money and would follow the research and it would appear to be the most ethical route. These tactics are not utilized only in prostate health products but throughout the supplement spectrum by a select number of companies so just being aware of this one teachable example, which can pave the way for future objectivity, success, and cost-savings for your patients. As I was writing this chapter coincidentally I observed multiple other celebrity endorsed weight loss and other products that are costly and utilize one ingredient or several from some other groups research and surround that ingredient with others that do not contain arguably any reliable clinical research (the beat goes on unless it is stopped at the grass roots or patients and health care professional level).

Plant sterols are an interesting option and they arguably will continue to garner positive data. For example, the early research in breast cancer suggests that this and other compounds in this class are heart healthy and breast healthy [102]. And lowering cholesterol by blocking the uptake of cholesterol from food is now again a legitimate pharmaceutical option (again ezetimibe or Zetia), especially after the recent conclusion of the IMPROVE-IT clinical trial of over 18,000 patients in a randomized, double-blind that included a placebo and statin arm versus statin and ezetimibe [103], and has preliminary anticancer effects via favorable lipid changes or a reduction in inflammation [104]. Please see Chap. 4 for more on this and other lipid lowering products (such as PCSK9 inhibitors) that will be utilized in clinical trials with cancer patients in the future.

• Remember, the primary goal with patients should be pill-free or the minimum number of pills needed (MNPN) and NOT to encourage a self-medication personality.

The concept or belief that a pill is needed regardless of evidence or safety should be antiquated, but it is not. Patients should be instructed that based on an extensive evaluation of benefit-versus-risk a pill (supplement or prescription) should be considered. Ingesting countless pills, without evidence for this practice, I have found no different from an addict self-medicating for the pleasure derived from his or her drug of choice. The plethora of other negative outcomes with self-medication practices apart from dependence and abuse abound including: incorrect use, delay in care, adverse reactions, drug interactions, masking of another physical or mental health issue … [105]. When talking to patients about prescriptions or supplements I believe the initial mantra should be "less is more" and patients appear to appreciate

that philosophy because it saves money and sets a philosophy from baseline that you are objective when it comes to pill ingestion (aka "not in the back pocket of the pharmaceutical or supplement industry").

• There is nothing "natural" about taking pills if you are otherwise healthy unless the benefit exceeds risk (rare), and there is nothing healthy about the natural versus synthetic debate.

Arsenic, tobacco, mercury, … are all natural but I do not recommend them. Pills contain all kinds of obscure compounds such as fillers and binders and compounds that are not natural at all and the body must metabolize and excrete them. And the longest-lived populations in the world from Andorra to Mediterranean to Singapore are not massive pill consumers (quite the contrary) [1]. There is also nothing natural about indoor pipes, heating and cooling systems, airplanes, highways …, but I am grateful they exist. The "natural" is better debate is one that I find is often used to create some kind of debate advantage that is usually tied into something financial or profitable in the industry. I often explain to the public and patients that I have no idea if something natural is better, worse or the same for you unless it is tested. For example, I have heard for years that natural vitamin E supplements are better compared to synthetic but in reality in major clinical trials the benefit and toxicity have been similar or with slight differences neither advantageous or disadvantageous. In fact, it could be argued that from eye disease to other medical conditions such as Alzheimer disease that synthetic vitamin E actually has slightly better efficacy data now [13, 14, 20–22], but in reality I treat them the same. It could also be argued that Centrum Silver is the most tested synthetic multivitamin in the history of medicine from the 11-year and over 14,000 individuals tested versus placebo in the Physicians Health Study II. Regardless of the modest reduction in cancer and cataracts the percentage of patients experiencing or reporting rash with the placebo or multivitamin was 27–29 %. In other words, ingesting any pill including a placebo has the potential to create some minor to major side effects. There is nothing "natural" about taking a pill unless one actually needs a pill.

• "Tachyphylaxis" can occur with any pill including dietary supplements, as well as toxicity when higher dosages are utilized and/or saturation kinetics finally comes into play. The antiquated terms "water-soluble" and "fat-soluble" vitamins because they are all dangerous in excess.

Many, if not most drugs have patients that experience "tachyphylaxis" (Greek, meaning "rapid" and "protection") or desensitization to a medication after it has been utilized for a short or long period of time. For example, histamine 2-receptor antagonists, antidepressants, statins, nitrates, and most classes of drugs have some patients that experience this phenomenon [106–109]. Yet there is little to no research on tachyphylaxis with dietary supplements. However, it is evident that in multiple past studies utilizing a well-known supplement a form of tachyphylaxis can easily occur, for example when larger doses of L-arginine are administered in patients with essential hypertension to increase nitric oxide levels [110]. It is also known that saturation kinetics does not allow some supplements to exceed a certain concentration without excessive displacement in the urine or other physiologic spaces or as another metabolic by-product. This is another form of tolerance, but whether or not

tachyphylaxis is encouraged under these circumstances is not well known and does not matter simply because toxicity eventually surfaces because of this phenomenon. Ingesting too much of a compound eventually causes saturation of the blood or tissue and the rest of the compound is discarded or increases to unhealthy levels [25]. For example, overexposure to calcium and vitamin C supplements could increase the risk of kidney stones [111, 112]. Selenium can get deposited in soft tissues and increase the risk of nail or hair loss, and perhaps even diabetes, skin cancer recurrence, and other cancers in excessive amounts [1, 25]. Thus, the concept of tachyphylaxis and/or saturation kinetics needs to be explained to patients as another reason why a supplement should not be ingested without extensive analysis of the benefit-to-risk scenario. Folic acid has a metabolic by-product known as "UMFA" or unmetabolized serum folic acid that could be a future concern in those that ingest mega-quantities of this dietary supplement. Vitamin A can cause excessive damage to the liver in large amounts. Vitamin B6 can cause a sensory neuropathy at excessive intakes. And the list goes on and on …. The idea that "water-soluble" vitamins like the B-vitamins or vitamin C are harmless in excess if you take excess amounts that just get excreted in urine is obviously an antiquated thought process and designation, as is "fat-soluble" essentially (although fat in diet may increase their absorption). In other words, all of these compounds or supplements display toxicity in excess and this has already been known for some supplements and for the rest it is starting to reveal itself via good research.

• Pill esophagitis? Ulcers? Kidney stones made of sand (silicon dioxide) oh my? The ongoing list of side effects from dietary supplements or pills. Another reason that pill ingestion is not "natural" unless needed.

Pills come with unique side effects, and although life saving in many cases, another reason not to ingest a pill unless needed is due to "pill esophagitis." This is known in the pharmaceutical industry for example and often it is due to patients not drinking enough water or standing up when ingesting a pill [113]. The symptoms of pill esophagitis include difficulty swallowing, pain on swallowing, and retrosternal pain. Yet dietary supplements can also cause pill esophagitis and esophageal ulcers [114], so the concern or at least recognition over this side effect in the supplement industry should immediately match that of the pharmaceutical industry. Increasing awareness of dietary supplement side effects allows for the identification of pill side effects unique to the industry itself, especially when compounds such as "silicon dioxide" (aka "sand") are utilized in some products to a large extent (improve flow or anti-caking agent). Recently, recognition of an increased risk of 100 % silicate based kidney stones can occur in products that contain ample amounts of this compound [115]. And this is just one of many compounds uniquely utilized in pills, especially supplements that were believed to be inert in humans.

• Reducing fluoride in water and why it is symbolic for the current status of diet and supplements and why nutritional education needs to shift from a primarily deficiency to sufficiency. Further proof that "less is more" in the twenty-first century compared to 1700s or 1800s, and medical education needs to reflect this shift, or the "over-antioxidation of the US (and other) population" and living in one of many "first world" countries.

Grand Rapids, Michigan became the world's first city to add fluoride to its drinking water in 1945 and within 6 years of this landmark change a study showed dramatic reductions in tooth decay among children living in this area [116]. Next, the US surgeon general and others began to endorse it. Fast forward to now, and approximately 75 % of Americans receive fluoridated water. However, recently federal officials (aka Department of Health and Human Services) released a statement that they are lowering the recommended amount of fluoride in drinking water because some kids are getting too much, which could cause white splotches on their teeth (also known as "fluorosis"). This overexposure to fluoride appears to be permanent in many cases unless of course an individual receives some kind of tooth whitening procedure to correct it. In fact, in one study 40 % of adolescents had tooth spottiness or streaking. Thus, this recent announcement to lower fluoride is a smart move. Since 1962, the government has recommended a range of 0.7 mg/L for warmer areas where individuals consume more water to 1.2 mg in cooler areas. Now, the new government standard is simply 0.7 everywhere. Not dramatic, but a small significant step in the right direction. The CDC's advice for small children is to not use fluoride toothpaste for children under 2 unless recommended by a dentist and use only a pea-sized amount of toothpaste for children 2–6 and avoid fluoride mouthwash.

And regardless of what side of the fence you are when it comes to fluoridating water, the bigger implications of this latest government recommendation has even far broader implications when it comes to future nutrition and supplement recommendations! What? What is Dr. Moyad talking about? How is that related to the whole fluoride controversy—seems like an obvious non-sequitur Moyad, right? Nope!

Several years ago during my lectures I decided to review clinical studies with health care professionals that showed why getting more of something that is perceived to be healthy, if you are already healthy, has in general never been shown to be better. And the reason I added this to my teachings and regular lectures is due to the disturbing trend I began to see in countless situations, where a plethora of compounds were being added to the food or beverage supply in large amounts from so many directions including fluoride. You see, one of the biggest frustrations I was experiencing was antiquated nutritional lectures being given to health care professionals as if we were living in the year 1750 and mentioning for example that if you do not get enough vitamin C you can get scurvy. If you do not get enough vitamin B6, you can get nerve damage, not enough beta-carotene or vitamin A then night blindness, or if you do not get enough niacin you can get the disease "pellagra" [25]! Our clinics are not satiated by these medical conditions anymore.

Today the issue is not getting too little vitamin C, but some individuals are getting too much supplemental vitamin C, which is increasing their risk of kidney stones [25]. Too much supplemental B6 actually can increase the risk of nerve damage, too much supplemental beta-carotene in former and current smokers could increase the risk of lung cancer, too much supplemental vitamin A can increase the risk of liver toxicity, and consuming too much supplemental niacin is now linked to liver toxicity and potentially heart unhealthy changes. Physicians in the USA hardly ever see these nutritional deficiency diseases anymore unless they volunteer in third

world countries. In fact, most of the nutritional deficiencies I see today are from the overuse of many medications, which is now "first world" country. For example, chronic use of acid reflux drugs can result in a deficiency of vitamin B12 and/or magnesium, which the FDA recognizes along with multiple other issues [117]. My point is that nutritional education needs to change to spend more time addressing what I call in medical publications the "over-antioxidation of our population" or "the over-antioxidation of the US population" [118].

We now live in a time where nutrition and supplements are a billion dollar industry where folks compete to add the latest and greatest nutrient to the food supply, which in some cases can result in an overexposure to many things. For example, selenium deficiency use to be a serious problem in some countries, and it is still can rarely cause a serious medical condition known as "Keshan disease" but today an overexposure of selenium is more common and could lead to problems [12, 25]. I remember only a few years ago attending multiple medical lectures where Keshan disease was mentioned as a reason for some individuals to supplement with selenium?!

In one of the largest dietary supplement studies ever completed in the world (SELECT Trial) in healthy individuals, researchers recently found the potential for an increased aggressive prostate cancer risk in men getting large amounts of selenium from food and then taking a higher dose of selenium as a supplement [43]. In other words, if you were already receiving sufficient selenium from the diet and then you added more in terms of a supplement (200 μg a day), then more was not better. However, it was not that long ago selenium was difficult to find in our food supply but in the 1990s when preliminary research showed a potential anticancer and overall health benefit of selenium it took only a few years before it started getting added to many nutritional products from protein powders to almost every basic multivitamin. So, by the time this landmark SELECT study started the minimal deficiency once seen in the USA with selenium was no longer an issue, and sufficiency or overexposure quickly became the problem [25]. There is also the concern that an overexposure to selenium can increase the risk of skin cancer returning after treatment. This is also somewhat similar to the story with calcium supplements in this country. Some US restaurants have now enriched their breads with calcium, and calcium is fortified in many foods and beverages from numerous almond milks that contain over 450 mg of calcium in just 8 ounces, to some multivitamins replete with calcium. Now, in most major clinical trials women are getting enough calcium from food and beverages to match or exceed the RDA so that by the time a clinical trial of calcium supplements and bone health is initiated, many of the participants are replete with calcium before the study even starts. This was observed not long ago in one of the largest clinical trials in the world to prevent bone loss and fractures known as "WHI" or the Women's Health Initiative [119]. The end result … more kidney stones in the group taking calcium and recent concerns that more calcium is not better for women and men. Calcium and vitamin D deficiency used to be such a problem in the USA that the disease rickets (a bad bone disease) occurred, but now this has become rare, and it was only a few decades ago that not getting enough calcium caused an increase risk of kidney stones [25].

Now, think about the number 1 cause of acute liver failure in the USA. It is due to overexposure to the over-the-counter pain reliever acetaminophen, generally (not always) in combination with alcohol. However, acetaminophen has been around a long time and so has alcohol, so why only more recently did this become a problem? In my opinion it is due to the overexposure of a drug that use to be just sold as a pain reliever and during my lifetime it got added to almost everything you can imagine, from as many as 50 % of the cold and flu therapies, to many of other targets discomfort relievers [25]. We woke up one day and it was everywhere and it is now so easy to be overexposed to this drug. Acetaminophen is a good drug but the overexposure to it has led to devastating consequences.

And fluoride use to be fairly difficult to ingest in the USA and during my lifetime it got added to almost all the dental products such as toothpaste and mouthwashes and the drinking water supply [116]. Thus, the call for the reduction of fluoride by the US government (a first in over 50 years) in my opinion is a harbinger of things to come where sudden overexposure to certain compounds and ingredients and eventually the risk will exceed the benefit, and more government or simply personalized regulation will reduce the overexposure of what not to long ago was a "deficiency." It is not 1700 or 1850 and part of our challenge is accepting the benefits and limitations of past dietary and medical advice, and how it really pertains to the modern world. We need to be vigilant and be willing to admit when we have reached the point where more does not mean better, and at least with fluoride that moment has arrived. The question now is "What is next?"

Is there really anything the US population and other industrialized countries have an overt "deficiency" of today that might still exist 50 years from now in the population? There are a small number of subtle exceptions or true subtle "deficiencies" today and for objectivity and completeness of this discussion they are mentioned in the next section.

• The only true long-term and extreme deficiencies that most patients are dealing with are dietary limitations for chronic disease prevention, for example fiber and/or especially potassium, which are basically part of the foundation of a heart healthy diet and lifestyle program. Otherwise, getting too much of a good thing is the norm.

This will be reviewed in the next chapter, especially fiber but these two "deficiencies" I often lecture on are simply part of eating more heart healthy and primarily pertain to chronic disease prevention.

Low potassium is a problem for arguably 98–99 % of the population. Why? Few people realize that the suggested intake or arguably the recommended daily allowance (RDA) or recommended daily intake for adults is 4700 mg/day (only 1–2 % of the po**p**ulation) [1]. This is how much is needed to keep the body functioning normally in terms of disease prevention, for example stroke and hypertension, kidney stones … [120]. Say you eat a banana every day, but that only gives you 450 mg or less so where are you going to get another 4000+ mg during your day? Another 8+ or so bananas daily?

How about taking a simple potassium dietary supplement? However, you can only purchase tablets with 99 mg or less in them [1]; otherwise should everyone be

on potassium prescription drugs? Plain yogurt, beans, fish, fruits, veggies, and even coconut water can contain almost as much potassium as a banana or more. So, the key to ingesting more potassium is simply eating a heart healthy diet! How about spinach? One cup has almost twice the amount of potassium compared to a banana and so does one cup of avocado.

In fact, there is new strong evidence to suggest that it is not excessive sodium alone increasing the risk of hypertension, but excessive sodium and sugar, with a reduced potassium intake [1]. It is the potassium that counteracts the effects of sodium and the reduced sugar reducing weight/waist and lowering blood pressure (foods high in sodium and sugar tend to be low in potassium and high potassium foods are low in sodium and sugar). In the most recent study from the CDC (Center for Disease Control in Atlanta, GA) of over 10,000 participants, researchers found the average American intake of sodium was 3659 mg/day and for potassium it was only 2745 mg/day [120]. So, the real message should be increase potassium intake from heart healthy foods and this will naturally cause you to lower your sodium (and sugar) intake.

The World Health Organization advocated for a sodium-to-potassium ratio of 1 or less [121], but in reality some of the best dietary studies to lower blood pressure (for example DASH = Dietary Approaches to Stop Hypertension) the target was 0.6 sodium-to-potassium ratio [122]! It is also interesting recent research is demonstrating not only blood pressure reductions with an increased consumption of potassium from food, but also a reduction in other medical conditions such as kidney stones, and perhaps in other situations from my personal experience in following some patients. For example, cancer medications being utilized in prostate cancer and being tested in breast cancer (such as abiraterone) that lower potassium in many patients could potentially ameliorate this side effect at greater rate if educated on how to get ample potassium in their diets. My favorite list of banana-competing sources of potassium, apart from just asking patients to generally eat more fruits and vegetables and beans and seeds, is the following [25]:

- Avocado
- Spinach
- Plain yogurt
- Coconut water (after an extensive workout)
- Lentils
- Carrot juice (6 ounces contains over 500 mg of potassium and only about 70 calories)
- Soybeans (half-cup contains almost 500 mg of potassium)
- Fish (Alaskan Salmon, Halibut, Tuna, …)
- Sweet potato
- Prunes or an orange

An ample discussion on fiber will occur in the next chapter, but the vast majority of the population cannot achieve 20–30 g/day. Arguably, this is due to the reliance of fiber from non-dietary sources such as pills and powders [1], and arguably the reason normal potassium ingestion is also difficult to achieve is the reliance on pills

and powders or fortification to usually close this gap, but again this does not exist or is not permitted. Thus, once again dependence primarily on dietary sources.

• "Inflammation," "Free Radicals," "Boost the Immune System," and other buzzwords help sales but not objective education of patients and health care professionals. Remember the hygiene-hypothesis?

If a product claims to reduce inflammation it tends to appear to be a legitimate pathway and solution (I cannot help but use this term at times). However, upon further investigation like most things in life there are two sides to every story. Inflammation in healthy individuals is a necessary evolutionary process to signal the body to produce more protective compounds and items such as mitochondria [1, 25]. Thus, it appears that in some individuals suppressing inflammation does not allow the body to adapt to stress and actually could reduce the body's ability to handle extrinsic and intrinsic damaging compounds. It is for this reason recent research in athletes suggests a reduction in mega-doses of supplements in order to enhance exercise performance.

It is now appreciated that the generation of "free radicals" are critical signaling compounds that aid in promoting adaptive changes to exercise training such as intrinsic antioxidant defense system increases, insulin sensitivity, glucose uptake, mitochondrial mass or number increases, and growth factors involved in tissue repair (IL-6 …) [123–128]. Recent research and discovery of "inflammasomes," which are multi-protein oligomers of the cell, that appear to function as a critical intracellular sensors and responders (maturation of inflammatory cytokines …) to oxidative stress are now considered a part of the innate immune system [128]. Ongoing research in this area is needed to determine which supplements enhances or suppresses the role of this part of the immune system. Regardless, less appears to be more again.

I remember when it was critical to be clean (aka "hygienic") and ensure a lack of exposure to pathogens when growing up and currently the hygiene hypothesis is challenging this concept [129, 130]. Allowing the body to deal with germs or infectious agents to help the immune system demarcate self versus true extrinsic threats could be one pathway to reducing the ongoing increase in autoimmune disease and allergies (including some food-based sensitivities). I find this argument similar and as compelling to the potential reduction of athletic performance and fitness with mega-doses of antioxidants, and again just because a buzzword appears to make sense the clinician needs to explain to the patient while it is not always logical. Inflammation and the creation of free radicals are part of a necessary trigger for the body to adapt to stress and heighten defense and even endurance mechanisms. Patients should be told that it is more chronic or unmitigated stress or inflammation that is the real issue and not temporary or acute inflammation or stress.

Another example of this marketing phenomenon is products that promise to "boost your immune system." In reality patients should be told that better immune surveillance is what is really required because when boosting the immune system the result is also allergies and autoimmune disease. In cancer treatment, drugs that boost the immune system represent a breakthrough for melanoma and other disease, but it comes with the limitation of autoimmune (attacking of self) side effects,

which can be quite serious [131]. Thus, these drugs of course are only reserved for those cancer patients where benefit can exceed risk. Therefore, if otherwise healthy or free from cancer why would I, or a patient want to ingest a supplement that claims to "boost the immune system." No thanks.

• "When you have a hammer everything looks like a nail," but "when you have a mouth everything looks like a supplement." What is the difference between some conventional doctors that push a plethora of prescriptions versus a naturopathic doctor that pushes a plethora of dietary supplements? A good review with a patient with or at high-risk of a medical condition covers lifestyle changes and supplements (to take or not) and prescriptions (to take or not). The goal again is less pills, or lower dosages of the existing medications.

I have reviewed this elsewhere in this book, but I believe this point needs reiteration because I find that it is becoming very relevant. I find it frustrating when a patient constantly seeks the attention of a medical doctor only to walk away with more and more prescription medications as the only solution to an isolated or related problem. Today, almost every issue in medicine has a lifestyle option (or not) or a supplement option (or not), or a prescription option (or not). In other words, it is just as critical to feel comfortable NOT recommending something as it is to recommending something. Exercise to reduce muscle/joint pain from aromatase inhibitors, weight loss for the reduction of acid reflux with the lowest dose of a proton pump inhibitor, acupuncture for hot flashes and not just progesterone [1, 25] …. The list is endless. However, when only a pill is presented it tends to set up a toxic, "one size certainly fits all," solution/dependence for patients. Occasionally I get frustrated with some conventional doctors that hand out scripts like candy to patients and suddenly 5–10 drugs later the patient becomes completely dependent on them, and polypharmacy and all its inherent issues abounds. However, I also become occasionally frustrated with naturopathic doctors that push supplements and sell them out of their office like candy. It is comical when I hear surgeons suffering from that old adage "when you have a hammer everything looks like a nail," but I find this no different than anyone else in medicine that wants to push a product out of their office or within their possession. So, I like to say "when you have a mouth everything looks like a supplement!" I meet breast and other cancer patients that visit with some naturopathic doctors and walk out purchasing or being recommended 5–10 different supplements when they have never even used one in the past. I find this so concerning because it simply reinforces the behavior of dependence on pills when in some cases many of these pills were never needed. *In reality, whether a good medical doctor or osteopathic or naturopathic or physician assistant or nurse practitioner or nutritionist or nurse or whatever … I think we should share the common mantra that pill dependence, when not absolutely needed, is not good for patients, and not the reason we first entered into the medical profession.*

• "Us" versus "Them"—Okay perhaps in politics but completely toxic in medicine!

It is never my intention to have anyone perceive that I am personally endorsing or advertising a specific brand whether it is from a pharmaceutical or nutraceutical company. My only goal is to provide an audience with many things to consider

when choosing any pill. One of the most critical factors has to be the human or clinical evidence that a product or procedure currently has compared to others. For example, the supplement that has the longest and most rigorous multivitamin clinical trial compared to a placebo is Centrum Silver [132]. There is simply no other multivitamin that has this amount of human evidence. Let me play devil's advocate here—if the Centrum trial would have failed, then their product and business would not have survived. This was an incredibly risky venture, as is the case with any supplement or drug that decides to actually test their product in a human research setting. This is also the reason some supplement companies never really want to test or invest in research.

My goal is to never engage in an "us" versus "them" scenario because in my opinion it is so toxic and unhealthy in so many areas from politics to television news to pharmaceutical versus nutraceutical companies. I am grateful for many pharmaceutical companies and the researchers behind them that have changed the course of AIDS or breast cancer or hepatitis C … for many of my friends and family (not just patients). In fact, there are also some friends and family members that were not able to live a long life simply because a game changing drug for their disease (including breast cancer and Hepatitis C in the case of my family) was invented just a few years after they died. However, I have also been very vocal about other pharmaceutical companies that have provided no purpose to the overall health and well-being of individuals, and I will continue to be critical of them (spinning over and over different forms of a drug that was about to become generic).

Supplements are no different over my 25 years of experience—we have very good and very bad supplement companies. We have some that simply gauge the public and are dangerous and others that provide benefits. It is messy out there at times (especially now) and it takes a lot of information (evidence, cost, quality control, safety, …) for someone to personally decide what they want or not to consume. I mention in my books, and in my articles and all my lectures, all the different factors someone should consider as if I am advising my own wife and kids. If you decide not to purchase Centrum or any other brand I think this is fabulous. Do what you are comfortable with after all the evidence is in. I will continue to push to extract the most information on these pills to help provide some guidance. Of course I would like to see all companies become more transparent with their consumers including Centrum or any other company. I also would like to see more supplement clinical trials that include women and minorities, which is a major past and current problem. I would like to see companies think twice before giving or offering kids supplements with no research, such as many gummi (primarily added sugar) variety brands. I would like to see more companies utilize less toxic ingredients but at the same time others need to quit hiding behind a "natural is better" label and really invest and test their specific product in a clinical research setting. Natural is better when proven to be better especially when it comes to taking a pill. Arsenic and tobacco again are natural but I do not recommend them. I cannot objectively educate future health care professionals on the positives of lifestyle and supplements without research. My list is endless for what I want to see change ASAP (more on that at a later time).

In the meantime, I can promise you that I will never take a side in a discussion simply because I have to pick a side and ignore the other important qualities offered in the argument. Health care professionals, patients and just consumers should try not to fall the "us" versus "them" debate from "big pharma versus supplements" to "medical doctors versus naturopaths" to "holistic/alternative versus conventional" … no one wins except the side that wants you to believe that you have to take their side in order to be right and profitable. Again, I will never take a side in a discussion simply because I have to pick a side and ignore the other important qualities offered in the argument.

This is a debate I clearly mention to my audience that I will promise to never engage in but will instead function like an old reliable news anchor that reports on the existing or past evidence or lack thereof. And I think this is exactly why many of us wanted to go into medicine—to be the trusted objective non-influenced advisor to the patients.

• If I am not supposed to get overly excited if a supplement company claims (as mentioned in your rule number 1) they follow the FDA cGMP (current good manufacturing practices) how do I know I have a quality product? Look for a seal of approval on the company website, or even better on the product itself that is legitimate (NSF, USP, NPA, …). The top choice is arguably NSF (once every 6 months of auditing), but USP, NPA, and Informed Choice are also credible.

In 2007, current Good Manufacturing Practices (cGMP) were established for dietary supplements sold in the USA, which means the FDA now has the authority to enforce and ensure that companies meet current requirements for the identity, strength, quality, and purity of their products [133]. And many companies like to claim that they follow the cGMP, but in reality again you have no idea if this is true unless someone actually tests this claim. Some companies claim to follow cGMP but we really do not know unless some outside party tests them or they get caught for doing something wrong by the FDA. So, do not rely on this self-advertisement to ensure that your herbal products are clean and contain what they report on the label. The FDA does not have the person power to enforce this ruling on a large scale, which is why following other steps will be helpful.

Imagine an independent and private third party testing group that most professional athletic organizations like the NFL, Major League Baseball (MLB), PGA, LPGA, NHL, and even Olympic athletes use to guarantee that the supplements (sport supplements in this case) they consume are clean and have exactly what they report on the label! Well, that company exists and it is known as NSF [25, 134]! It is in my opinion the best quality control insurance that exists right now for herbal supplements and supplements overall. In fact, it is also the only quality control company that actually does ON-SITE auditing or checking of a facility EVERY 6 MONTHS! That is simply outstanding quality control. So, whether the supplement provider is in China or India or Brazil or the USA they are there on-site every 6 months!

Why doesn't everyone just sign up with NSF? Good question. It costs money that many companies simply do not want to spend and every 6 months is really daunting

for many companies. Yet in my opinion the cost is minimal because the risk in terms of potential insurance costs and litigation are large. Ideally, a perfect herbal or supplement has an NSF label (NSF or NSF Certified for Sport®) on the bottle itself, which means that individual product was tested versus an NSF label on the website, which is still of high quality and provides or identifies the facility that the supplement was produced follows the FDA rules on quality control. Again, ideally a supplement should have an NSF label on the bottle or container and the silver medal (almost as good) is an NSF label on the website (to help ensure cGMP). The company also tests for all sorts of bad things such as herbicides, pesticides, and heavy metals. And it also tests athletic or sports nutritional products for countless athletes and organizations around the world, and this program is known as "NSF certified for sport" (mentioned earlier).

Athletic or sports nutritional products have a history of contamination or quality control issues, so actually two quality control companies have stepped in to ensure compliance with the FDA and clean products. The first one was mentioned previously and this is NSF, but more specifically when the company or product states "certified for sport" by NSF this equates to outstanding quality control for that athletic enhancement product [134]. In addition, another group known as "informed choice" is another quality assurance program for sports nutrition products [135]. "Informed choice®" is a label with a check mark on it that identifies a product that has been tested especially for banded substances and helps to ensure good quality control in the sports nutritional area.

Another very good independent quality control group is USP and if the website or bottle contains the label then usually what is reported on the label is actually in the bottle [136]. When looking at the auditing or on-site monitoring accomplished by this group it appears to be longer than 6 months and seems to be on average every year or two which, is why I do not rank them number 1. Regardless, they are excellent. Again, the catch (similar to NSF) is that many companies or herbal products do not have a USP label. Additionally, The Natural Products Association or NPA label is another good group that appears to audit every year or more and when a company carries the NPA (Natural Products Association) label they are also appear to be following FDA quality control rules (yet audit every year or two) [137].

I am often asked the meaning of NSF or USP and things can be found in the history of these organizations, which were not originally designed to ensure quality control for dietary supplements, which is why the companies like to be known by their abbreviated name rather than their antiquated original name (NSF = National Sanitation Foundation and USP = United States Pharmacopeial Convention or United States Pharmacopeia).

• Herbal supplements are a whole new and old wild animal, so make sure you treat them that way! Always look for some quality control seal/proof AND the standardized ingredient in the herbal that was found to be effective in the phase-3-like clinical trial for the medical condition it might reduce or resolve.

I usually have little to worry about when it comes to basic vitamins and minerals in supplements like vitamin D or A or C or magnesium. The amount listed on the label is usually accurate so I am not obsessed with finding an NSF or USP label for

example but that would a nice bonus. However, the real concern over quality control lately has been herbal products so if you think you might be purchasing one soon demand some level of quality control testing. In other words, look for a seal of approval as mentioned earlier and look on the website for some other types of quality control testing. I am often really surprised by large supplement companies that do not mention they are NSF certified until page 4 or 10 of their website. This should be on the first page!

Also, it is important to understand that almost every herbal product that has ever demonstrated a benefit from American ginseng to reduce cancer related fatigue (CRF) to ginger to reduce chemotherapy nausea have an active ingredient that was standardized in the more rigorous and definitive trial that demonstrated a benefit [1, 25]. So, look for the active ingredient on the website and label. For example, in many of the cancer-related fatigue (CRF) reducing studies of American ginseng the active ingredients were standardized to 3–5 % ginsenosides (the active ingredients, and the supplement was obtained from the Ginseng Board of Wisconsin) at a dosage of 1000–2000 mg/day for 8 weeks [138, 139], and it now appears this may be one of the only pill options for CRF and the only one that has similar side effects to a placebo [140]. Additionally, *Panax ginseng* (Asian ginseng) also has novel preliminary evidence (800 mg/day—7 % or greater ginsenosides) [141]. Ginger (*Z. officinale*) supplements at 500–1000 mg for chemotherapy-induced nausea (started 3 days before start of chemotherapy and for a total of 6 days) were also standardized (purified liquid extract of ginger root "with concentrated 8.5 mg of combined gingerols, zingerone, and shogoal content, equivalent to 250 mg of ginger root, in extra virgin olive oil …") [142]. Interestingly, the ginger was manufactured by Aphios Corporation in Woburn, MA, which is now testing their product (called Zindol®) in a phase III clinical trial and should be lauded for this wonderful dedication to research [143]! Again, the difference between a drug and supplement is perception and not reality, but the ginger product itself can be purchased right now as a dietary supplement (Zindol® DS) [144]. *In addition, it is critical to mention that the majority of the patients in all of these previously mentioned herbal studies were being treated for breast cancer* [138–142].

• Several other outstanding quality control sites and/or publications on herbal/supplements reviewing quality and/or efficacy are the following:

- **Center for Science in the Public Interest (CSPI or www.cspinet.org),**
- **Consumerlab.com,**
- **ConsumerReports.org,**
- **The "Natural Medicines Comprehensive Database" (www.naturaldatabase.com).**

CSPI is a very reputable group that reports on the evidence as well as periodic quality control testing of supplements. Overall, I find that they are objective and well-researched group and the staff that reports on dietary supplements is excellent. Since they follow quality control intermittently it is not the ideal place to get regular information but since they have regular evidence-based reviews of herbal products for medical conditions overall it is a good source. And their overall focus on nutritional information is really interesting. They have a newsletter that is low cost.

Consumerlab.com is a website that commissions independent testing on all types of dietary supplement brands so you know exactly what you are or are not getting in them. It was this site that informed me about many multivitamins and which ones passed their test. You probably have to pay a small fee to obtain the latest and greatest quality control information, but for those in need of the latest testing and who passed or not—it is usually there.

Consumer reports? Yes, the same independent and noncommercial group that tests everything from blood pressure monitors to cars and vacuum cleaners also regularly follows stories or issues with dietary supplements. Overall they are objective and interesting and tend to require a certain level of evidence to endorse any product. I do not always agree with their take on the clinical research (as with many other groups) but when it comes to protecting the safety of the public I agree with them. They may require a small fee for their newsletter or more extensive website access but it is worth it.

The Natural Medicines Comprehensive Database is essentially a group of health care professionals that claim they are a source of "unbiased, scientific clinical information on Complementary, Alternative, and Integrative Therapies" and in my opinion this is accurate. Thus, they really do not have a profound role in quality control testing but their regular information of clinical efficacy for supplements is very good. The cost of their information can be a little pricey but is worth it. There are few places on earth that one can find such good information on everything from drug and supplement interactions to clinical efficacy of supplements (apart from this and other Moyad texts …). Pharmacists are a large part of the writing and staff of this group, which again should provide some assurance that especially for drug and supplement interactions the information is up to date and excellent.

• Pharmaceutical brand supplements have a lot to lose if they are wrong (Note: this does not mean I endorse any of these brands or want you to take one, but it is a simple tip for guidance).

When a pharmaceutical company begins to market and sell supplements such as Pfizer (Centrum®) or Bayer (One-A-Day®) or Abbott Labs … they generally have very good quality control and overall their prices are competitive (aka low cost or cheap like me). Another reason I like some of them is personally I believe they have a lot to lose if they are wrong. In other words, bad products on the supplement side could be a disaster in terms of public relations and profit on the drug side. So, in general I find that these companies fly straight because they cannot afford to fly any other way.

Now here is the catch! I wrote this exact same tip on a popular website and about 10 % of those that read this tip were very upset. They thought I was endorsing "big pharma" and suggesting that the only products you should buy when it comes to supplements are pharmaceutical supplements?! This is never the intention, but instead I wanted readers to know that they could rely on these brands in terms of the accuracy of what is on their label is almost always in the bottle (for example this is exactly what consumerlab.com has found since 2007). In addition, I was upset that individuals somehow think that pharmaceutical supplements are all bad! Again, it is never my intention to have anyone perceive that I am personally endorsing or advertising a specific brand whether it is from a pharmaceutical or nutraceutical company.

My only goal is to provide the audience with many things to consider when choosing any pill. One of the most critical factors has to be the human or clinical evidence that a product or procedure currently has compared to others

Again, I would like to see more companies utilize less toxic ingredients but at the same time others need to quit hiding behind that "natural is better" label again, and really invest and test their specific product in a clinical research setting. Again, natural is better when proven to be better especially when it comes to taking a pill. Pharmaceutical brands have a history of containing exactly what they claim on the ingredient label and they should be complemented for this fact (see the next chapter—multivitamins section).

• Multivitamin with herbal ingredients? No thanks!

The largest and best objective multivitamin clinical trials like the Physicians Health Study II (PHSII) never used any herbal products in their multivitamin and they have the longest and best clinical study ever conducted in this area, and they still showed a benefit (slight reduction in risk of cancer and cataracts) [132]. The only other major phase-3-like multivitamin randomized trial that included healthy women and men (called "SU.VI.MAX" or The Supplementation en Vitamines et Mineraux Antioxydants) also did not use and herbals in their formulation [145]. In other words, I see no reason to purchase a multivitamin with any herbal ingredients on the label because you might as well mimic what worked best in the largest clinical trial of a multivitamin (Centrum Silver® or SU.VI.MAX but both were just one pill a day).

• Only purchase a single ingredient supplement most of the time except in rare situations (like a multivitamin or when a clinical trial specifies/utilizes more than one ingredient, which rare). Dilution = Pollution? Don't be a clinical trial of 1! Proof and reward should be in the research and again in standardization of the active ingredient!

Most well done clinical studies of supplements to help almost any condition usually used a single standardized ingredient. For example, melatonin use for jet lag, or insomnia (single ingredient) or even SAM-e supplements for mental health improvement or osteoarthritis (usually 1 ingredient) [1, 25]. Where consumers get in trouble is when they start to buy products with multiple ingredients in them that were never used in the largest and best studies. This process not only dilutes the active ingredient rendering it less effective, but also pollutes the product and can make it tougher on your liver to metabolize. Again, think about this for a second, you would never buy a bottle of aspirin that also contained multiple herbs and vitamins and compounds in the aspirin because it would not only make aspirin itself less effective, but increases the risk of further toxicity because now you are a clinical trial of one! Aspirin was only studied in most major clinical trials as a single ingredient and not combined with multiple other products.

There are exceptions such as macular degeneration (mentioned earlier) where several ingredients were used together (500 mg vitamin C, 400 IU vitamin E, 10 mg lutein, 2 mg zeaxanthin, 25–80 mg zinc, and 2 mg copper) but in those situations it is clear what was used in the clinical trial (called AREDS2 for macular degeneration) and you should only use those ingredients [20–22]. Another example is glucosamine

sulfate (1500 mg daily) and chondroitin sulfate (800 mg daily) used together in notable clinical trials such as LEGS study [146]. So, do your research and again only buy or recommend what was used in the most impressive clinical trial and copycat that scenario (not different from a drug trial).

I am asked often asked what kind of saw palmetto I recommend for prostate issues and I tell audiences that since two very large clinical trials (called "STEP" and "CAMUS") both showed that saw palmetto works about as well as a placebo [31, 32], so I do not recommend it. However, butterbur extract for migraine prevention was given a "Level A" (one of the highest and means it is "effective") by a subcommittee of the American Academy of Neurology and the American Headache Society in 2012 in the medical journal "Neurology," which is highly reputable [72]. However, what they failed to emphasize was the product called "petadolex" (mentioned earlier) was the supplement (actually a drug in other countries) utilized in the best clinical studies. In other words, if I were going to recommend or use butterbur then petadolex (petadolex.com) would be my initial choice. For example, when the Mayo clinic and 40 other medical centers did a very large clinical trial of American ginseng to reduce fatigue from cancer treatment they found 2000 mg worked significantly better than placebo after 8 weeks (mentioned earlier) [138, 139]. However, what fails to be mentioned in other publications is that the Ginseng Board of ginseng (www.ginsengboard.com) provided the product and this is exactly what I recommended to patients with cancer inquiring about which ginseng to utilize for their fatigue. In other words, I reward and trust the products that have gone through the most human research on efficacy and safety. So, the next time you hear about a positive or negative herbal supplement study just look at the medical paper on line and check the materials and methods section to see exactly what commercial product was used.

• Always reevaluate your situation and do not be afraid to be a part-time guinea pig (if benefit >>> risk). The A, B, C's of whether a pill is working and if you really need it (the impact on heart health and other parameters)! Look for non-pill pill-like options (the new calcium supplement)?!

I often tell patients to only take the supplements that you and the doctor you trust (and a pharmacist …) think you need. Revisit your list every single 6-months to a year. Now, this sounds simplistic but I meet people daily that don't know why they are taking many of their supplements, and they have no idea if they are experiencing any benefit. In other words, I hear words like it has "antiaging" effects or "prevents free radicals" but this means nothing unless you feel or see some benefit. Would you follow this same approach with a drug? No. Most supplement pills have very low levels of heavy metals or other pollutants that are not a concern daily but when taken over years this amounts to a great deal of exposure and no one knows the implications.

Apart from a multivitamin, which helps a little (not much but a little) it is my opinion that this idea that supplements subtly change your life is primarily an advertising or marketing ploy. There are realities that I believe folks should contemplate. For example, many healthy individuals do not qualify for pills—not just supplements, but also drugs. I think we should embrace and celebrate a person when they

are so healthy they need little to no pills. And I am convinced future generations will feel this way. Still, I apply A, B, and C rules (three of them) to determine if patients or individuals need a pill or supplement.

A. Subjective Test (aka guinea pig approach)

If you ever wonder whether or not a supplement is helping (which I am asked this question all the time) you need to embrace the Dr. Moyad guinea pig approach—stop the product for 1 month and tell me if you feel any better, or worse, or the same? For example how has anything you feel changed including your mood. This works very well. I often hear from folks that they actually feel better or no different and then they simply stop the pill and save a lot of time and money. There are also moments where someone says they feel worse or more fatigued and they get ill more often, especially after they stopped their supplement. Well, this is a good indication that you may need your pill.

B. Objective Test (aka laboratory or numbers approach)

Is the supplement you are taking changing any single parameter that suggests you are becoming more healthy? I like to first look at cardiovascular disease (CVD) parameters because CVD has been the number 1 cause of death in women and men for 114 of the last 115 years [25]. In fact, I do not like to take or recommend any pill unless I know what its impact is on heart health. "First do no harm" right?! So, is the pill you are taking dropping your cholesterol, blood pressure, blood sugar, or helping you lose weight? In other words, what is it objectively doing for you? If the answer is nothing then I would become a little skeptical. If it is increasing some number that is unhealthy such as your liver enzymes then this is another bad sign. What numbers are changing for the bad or good with this pill? Working with a good doctor is critical to getting number 2 answered. A doctor or pharmacist or another health care practitioner that applies broad strokes to supplements (all bad or all good for example) make me nervous. Patients should find one with an open and objective mind.

Ideally I want a pill to change both A and B above but if it can still change A or B then this increases the chances that what you are taking is actually helping you. People need to do this more often with their drugs or supplements. However, always remember rule number C.

C. Lifestyle Test (to reduce or determine pill count/dosage)

Is there a lifestyle change that can substitute for this pill or at least reduce the dosage?

I find that many people who are taking great care of their bodies and minds also take some of the largest number of supplements and this is what the research also shows [1, 25]. However, it is almost a form of self-medication and giving credit where the credit is not due. In other words, they claim all these benefits from taking these pills but they do not realize how much of what they are doing personally is simply making them feel and be healthier (not the pills).

Look at athletic supplements mentioned earlier and how research is now showing that mega-doses of supplements may actually be hindering the benefits of exercise by not allowing oxidative stress to help signal the body that it needs more mitochondria or cellular changes that in the long-term would build better fitness or endurance.

Additionally, we have too many individuals hooked on pills because many do not realize that moderate lifestyle changes could get them off these pills or reduce their dosage to a more safe range if they make these changes [1, 12, 25]. Higher or mega-dosages of drugs or supplements make no sense because ultimately there is some ugly price to pay. Look at cholesterol lowering drugs and the number of folks that rely on the maximum dosage to keep their cholesterol down. Now, you start to dramatically increase the risk of never imagined before side effects like type 2 diabetes, serious muscle discomfort …. Look at vitamin C-mega doses (1000 mg+) can dramatically increase oxalate levels in the urine and increase the risk of kidney stones [25]. Applying moderate lifestyle changes first and foremost allows you to determine how much of a drug or supplement you truly need or maybe you do not need it at all. Give yourself the chance to figure out what you can do on your own before turning toward pills as a solution. When you take better care of yourself this is the ultimate truth detector test of what your body really needs or not in terms of pills. And if you can replace a pill with a food or beverage of your liking then this is always an option (8 ounces of almond milk = 455 mg of calcium or protein in food/powder instead of pills).

• Do patients really need comprehensive testing via blood or genetics to determine their nutritional deficiencies if they are otherwise healthy? No. And get ready to buy a pill! Remember genes can also be changed or altered in some situations like "jeans."

Comprehensive nutritional testing have not been comprehensively tested (ironic right?) to see if they change hard (not soft) clinical endpoints that matter, for example stroke or heart attack or cancer or whatever. In other words, just because a company says you need to increase your intake of X or Y does not mean you need to do this. Blood testing on nutrients is interesting but well within its infancy still so that we do not know what disease they do or do not predict. Look what has happened lately with the FDA and some home genetic testing companies. The FDA did a good job of exposing the fact that some of these tests would tell your chance of getting a disease but in reality did not have that kind of research to really predict this [147], so you end up creating a number of people that just live with a lot of unnecessary anxiety. Patients should be told that in some cases even when a genetic test demonstrates some risk, lifestyle changes can alter risk or even prevent that gene from being ultimately expressed (just because you have a gene does not mean you will express the clinical endpoint of that gene).

Another example of over testing the population for nutrient issues should be exemplified in the "homocysteine" blood test used by some companies and practitioners to generally screen asymptomatic healthy individuals. If the test was slightly abnormal many folks were placed on high doses of B-vitamins. However, no one had tested what happens when you bring that test level down on these high dosages. Now, decades later countless clinical trials later and arguably hundreds of millions of taxpayer dollars, and little to no benefit has been found in using this test to screen the general population [148]. It still has some merit in a minority of high-risk individuals but in the majority of folks they were found to be worthless.

Many nutritional blood tests also simply change dramatically in your favor with differing factors weight loss such as vitamin D [25]. And again many tests have not been validated in terms of the best assay and accuracy or correlation with end points (like vitamin D). And just because a blood test is low or high does not necessarily mirror the amount in your body tissues or vice versa. In other words, part of good testing is figuring out what type of test is really needed and what precise sample is needed for optimal testing—whole blood, red blood cells, plasma, tissue, lymphocytes … and this takes time and money and lots of research.

We live in an age of over testing but in supplements there is also huge profit tied to nutritional testing because what is the first thing I see patients receive when some blood test is low? A recommendation to buy a high priced supplement from the same office that provided the blood testing! That is a clear conflict of interest. Again, "when you have a hammer everything looks like a nail." However, when you sell supplements especially out of your office "everything looks like a mouth." Subconsciously or consciously it is easy to require a patient to take a supplement when behind the scenes you profit from recommending it. This is no better or worse than the old days of doctors being placed on advisory boards for pharmaceutical companies or having paid trips if they prescribed a drug more or willing to prescribe more of a drug from the company that is paying for their medical advisory trip in the Bahamas.

• What is my best advice for determining what supplements an otherwise healthy person could need? Supplements are primarily for medical conditions and targeted dieting once again to the rescue.

There are a few simple tips [25]:

- Get comfortable with your family disease tree. What were individuals in my family diagnosed with and suffer from and why? What did they die from and why? Thus, it allows you to determine what you may be at high-risk for and why you have what you have, or may be diagnosed with in the future. So, if you are starting to suffer from migraines and there is a family history of migraines you may want to be aggressive in taking something to prevent migraines. And this leads to the next point ….
- Try to put as much effort as is practical and realistic in becoming more heart and mentally healthy to determine if you need a pill for the major issues. This was mentioned many times before but also applies here. Diet, exercise …. Are you capable of achieving optimal cholesterol, blood pressure, blood sugar, and weight on your own. How about your mental health? If not you may need some pill support because these are the big preventive numbers that really make or break whether or not you are predicted to live a longer and better life. I find it interesting again that in the longest lived populations in the world such as Andorra [25], which is number 1 (I have been there also) in global population longevity, it is actually unusual to take any pills or supplements unless you have been diagnosed with a medical condition. Hmmm, interesting.
- Think of taking a supplement for a condition or to reduce the risk of recurrence of that condition and not for primary prevention (except perhaps for a multivitamin)

unless you have already been diagnosed and treated for a condition. And think of taking a pill to reduce side effects of some conventional medical treatments (ginseng and cancer fatigue …). If you have been diagnosed with Celiac or bone loss or any other conditions then it makes sense to review what supplements have worked or is needed and which are worthless.
– If you are taking any prescription medications ask yourself and the doctor you trust if a supplement is needed to reduce any "quiet" side effects the drug is causing such as lowering vitamin B12 (with acid reflux drugs, metformin …) [1]. Many of the so-called "deficiencies" I see today again occur from other medications.
– If someone tells you that you have to take a pill or supplement, is there also a way you can just get it with targeted dieting. Look at calcium in food, mentioned earlier and almond milk (or cashew milk …) or look at protein pills and now protein powders have in many cases 25 g of protein in 100 or so calories with no sugar and excellent taste and these pills are not needed anymore.

The beauty of most supplements is not for preventing countless diseases but in treating diseases or side effects suffered from the treatment of a disease. Unfortunately the perception is the opposite of what I just mentioned.

• What does the medical research suggest about the form of the supplement that should be ingested? Tablets? Capsules? Liquids? What should patients know about this and the best time of the day or situation to ingest a supplement for maximum efficacy? How about the half-life of supplements in the body? Following the path of compliance and flexibility and with aging metabolism, intestine, kidney, liver … changes (we also age on the inside). Never forget "20 %"? Children, adolescents, and supplements?

The answer is similar to the drug world, where compliance is the biggest issue and everything else is a distant second. Research shows us that pill ingestion does not ever become routine and this has been my clinical experience. After a few years many begin to get bored or simply forget to take their drugs regularly, even if they are life saving in some cases [149]. This "non-adherence" as it is called is intentional in some cases, unintentional in others, neglectful in other cases by caregivers, and other possibilities abound. Yet it is a reality. In the famous Women's Health Initiative (WHI)—the largest clinical trial of calcium and vitamin D in the world to prevent bone loss and hip fractures published almost 10 years ago many people still believe the supplements did not work! And they used very cheap brands of calcium and vitamin D. However, a secondary look at the same trial actually showed for the women that took their supplements most days of the month (80 % of the time), they did work in slowing bone loss and preventing hip fractures by almost 30 % [119]!

Thus, the form (calcium carbonate) that was used in the phase-3 like study (one of my criteria) is important but compliance is just as important [1, 25]. Still, every year you have to ask yourself how much of this nutrient is now in foods and do I even need the pill anymore. Again, look at calcium supplements and a decade ago it made sense to take a supplement. However, 10 years later there are countless well fortified with calcium foods and beverages. Many almond, cashew, and hemp milks

including the leading brands have 455–500 mg of calcium in just 8 ounces. So, you could just drink two cups a day and no longer need calcium supplements! ND, most multivitamins now carry larger amounts and numerous beverages (including milk substitutes) are now fortified so taking an individual vitamin D supplement is rarely necessary. The bottom line is that if you need a pill or supplement, you find the form or type used in the clinical study that was most definitive or the one that has the highest probability of working and then ingest it normally in the form (liquid, capsule, powder, …) that allows for the best individual compliance. It's all about the compliance!

Most of the time when asupplement says ingest "with a meal" it is to reduce gastrointestinal side effects and improve compliance and memory (remembering that you need to take a pill being tied or associated with meals) [1]. And in some other cases you get slightly better absorption with a meal but there are many exceptions. Iron supplements work better in terms of absorption without a meal, as do osteoporosis drugs. However, it seems that iron absorption is adequate enough if used right after a meal, and it can reduce many of the gastrointestinal side effects [150]. In fact, ingesting iron with some acidic foods and vitamin C (food and/or supplement) or using a non-enteric coated brand also increases absorption [151].

I find that most of this research in drugs and supplements was based on lowering side effects with a meal compared to make or break clinical changes or endpoints. I find that too many people get caught in the minutiae or specifics of how to take it and this just increases their anxiety and reduces the focus on what really matters—again regular compliance.

Absorption is often used as a way to sell a more expensive non-researched compound to a customer but I rarely am attracted by this approach. Again, just because you might absorb better does not mean you will be better until it is tested to prove this fact. It turns out that some low cost supplements (used in most supplement major clinical trials by the way) mentioned in this book absorb just fine when measuring blood levels.

There is an old saying about absorption I have been using for over 25 years, and that is "if you can hit a baseball 500 feet in Detroit Tiger Stadium then it is called a home run, but if you can hit a baseball 500 miles into Canada from Tiger stadium then this is so impressive that I am sure you will make more money in endorsement deals but it still counts as a home run!" In other words the body works by a threshold effect so that you do not need massive absorption for an impact, but just some absorption. It is kind of like asking me is it better to run 5 miles a day or 5.2 miles a day. Both are fine.

Still, I know there are some individuals that think the best time to take a certain pill is on a full moon in October after midnight, but again the research overall does not support this behavior. I tell patients that you should generally try and take your supplements right before or during or right after a meal (if you able) to lower side effects, and in some cases and it may or may not increase absorption. Groundbreaking drugs, such as metformin, were found to have reduced absorption with food, but this increased compliance (lowered gastrointestinal complications), which resulted in lowering the risk of type-2 diabetes and/or still providing adequate weight loss

[152]. So, taking a product with meals improves compliance and still gives clinical results even if food in some cases moderately reduces the absorption of the product. Patients appear to be often told to take their statin in the evening before bed because cholesterol production via the liver is highest at this time, but in the largest clinical trials this was not how they were generally utilized, and they still favorably changed clinical end points [153]. Still, the reality or bottom line is that a person should take a pill primarily at the time of day when they can best remember to take it.

The half-life of many supplements is not known, because research has not been adequate in this area. I mentioned earlier the WHI trial and we learned that you needed to take your calcium 6–7 days a week (80 % of the time) for the best results [119]. We know with red yeast rice for cholesterol lowering the half-life of the active ingredient is only a few hours, so you need to take it daily to keep your cholesterol lowering effects [25]. It should also be utilized with a meal if possible because the active ingredient is a lovastatin drug mimic, which does absorb better with food (this rarely or ever is mentioned in the medical literature).

It is a shame because in the drug world we can help people by knowing all the drug pharmacology, so I know if I recommend the cholesterol lowering drug rosuvastatin (Crestor®) that the drug half-life is long enough that ingesting the drug once a week still reduces cholesterol moderately well [154]. I know that taking alendronate (Fosamax) for osteoporosis or fracture prevention can be stopped after 5–10 years ("drug holiday"), which still allows for adequate bone protection in most individuals because the half-life of the drug itself is in years, and there are clinical studies that proved this [155, 156]! We just do not have this data with supplements, and all one can do is mimic the method from the clinical study that peaked your interest in utilizing or recommending it. As a broad rule of them, the majority of positive dietary supplement trials have used something you should take daily. Whenever the half-life of a supplement appears to increase that product ultimately turns into a drug (like melatonin in Europe) [68].

Finally, it needs to be remembered that aging is associated with gradual but tangible changes internally and not just externally [25]. Intestinal absorption decreases, liver metabolism is not as adequate and the kidney is not similar to the 16-year-old individual. Thus, pill consumption and analysis of needs or not should become even more critical with age. *In the most recent years of analysis, arguably due to greater awareness and monitoring, approximately 20 % of the serious hepatotoxic (liver failure, need for transplant, or death) events from pills occurred with dietary supplements (1 out 5)* [157]*, which is the largest that I am aware of in US history. The average age of the person experiencing such an event was a 40-year-old healthy female ingesting a "fly by night" product (weight loss …). Every day countless men and women take a dietary supplement that has never been adequately tested for safety and efficacy and are essentially agreeing to be a clinical trial of 1!*

The earlier an adult or child is sent this message the better, which is why I often tell parents to try and not have your kids solve a perceived non-issue with a supplement or drug. In my experience, the teenager that embraces the 1–2 supplements today is the 30-year-old that ingests 5 of them and the 50-year-old that ingests 8 of them …. I find it interesting that one of the biggest predictors of childhood or adolescent pill

consumption is if a parent(s) is an advocate of supplements/pills and/or the child or adolescent has a higher household income and more optimal health [158–160]. This is in many cases precisely the group that does not need them as a preventive option (adult data is not much different).

• You cannot trust health TV shows? Maybe you cannot just trust what TV shows claim about dietary supplements?

A recent study of the "Dr Oz" show and "The Doctors" television shows found that often their advice is not accurate and conflict of interest is revealed less than 1 % of the time [161]! The conclusion of this large research study was the following:

> Recommendations made on medical talk shows often lack adequate information on specific benefits or the magnitude of the effects of these benefits. Approximately half of the recommendations have either no evidence or are contradicted by the best available evidence. Potential conflicts of interest are rarely addressed. The public should be skeptical about recommendations made on medical talk shows.

I was a featured guest on Dr. Oz and it was a lifestyle piece and it was a wonderful moment. In general TV health shows have provided some valuable advice especially in regard to practical or lifestyle changes. However, apparently these shows have also had some negative moments. Researchers randomly selected 40 episodes and reviewed 80 recommendations total from both shows [161]. Less than half the time there was evidence to support a claim and over 50 % of the time there was no evidence or contradictory evidence, and this was for the Dr. Oz show and The Doctors demonstrated slightly better results. And again, less than 1 % of the recommendations from these shows included information on conflicts of interest.

When these shows begin to especially recommend dietary supplements they ran into some trouble. I think this can be cleaned up but will it keep their audience? In other words, I believe there are many people that want to believe in magic potions and miracle weight loss products and quick fix it situations. In fact, when any media source from a magazine to the nightly news appears to endorse a dietary supplement it tends to feed the self-medication or pill solution appetite and psyche. However, when a health show no longer promotes countless quick fix products or ideas then what happens to the ratings. And part of what is also driving this criticism or cacophony to end these shows is that I believe there are a plethora of jealous health care professionals that would like to have their own TV show.

Regardless, these TV shows need to do a better job of referring to well-done research especially in the area of dietary supplements, and if you think about it for a second, when it comes to surgery or taking pills how can you decide what is right for you in a several minute segment? I like Doctor Oz and The Doctors just like I like some reality TV shows but I am not about to imbibe specialized advice from them or refer consumers to them as their primary resource, but rather a piece of their potential large health puzzle that contains a variety of pieces. The glass is half-full here but patients should be told if deciding or thinking about taking a supplement because of a short endorsement like TV segment then this is precisely why you need to be careful, because supplements like drug, need a detailed benefit-to-risk assessment before

utilizing them. Over 25+ years I cannot name a single supplements whose hype was matched by the eventual research (not acai berry, green tea, lycopene, magnesium, shark cartilage, vitamin C, D, E, K, zinc, …).

• Any other advice? Doctors know more than they think about supplements. Family disease trees for better communication and supplements for medical conditions. Recommending one brand of supplements? Why the future looks great! Ground-to-Gut or Dirt-to-Duodenum!

Circle of Trust

This might sound simplistic but I tell patients and health care professionals they need to assemble a team that can be trusted in regard to supplements. Doctors get criticized a lot for not knowing about supplements (almost cliché) but many of them know everything else about the patient (arguably more than anyone apart from the patient herself or himself) in terms of their health and they should defend that position. Just because they don't have specialized knowledge in this area does not make them invalid. Arguably, the health food store expert or another interesting source of information for some patients does not have the head-to-toe medical information that the health care professional harbors, so it is critical that they know supplement intake. The medical literature is now replete with good and bad supplement information in medical journals so the average supplement knowledge of many physicians has increased substantially. Objective pharmacists are arguably the best source for drug–herb interactions and objective nutritionists know about which foods might substitute for a pill and an objective naturopath could provide the latest information on a particular herbal and the beat goes on and on. Assemble a team you can trust.

Additionally, I often encourage clinicians to review a patient's family disease tree and this allows for an objective discussion of what, if any, supplements are needed for an otherwise moderately healthy individual. If the family disease tree suggests heart disease or cancer or Alzheimer disease or autoimmune disease is prevalent in a particular family then the heart health lifestyle approach in the next chapter has ample information for most patients. Otherwise, if there is macular degeneration or migraines then one can discuss those particular supplements if needed in the future. All of this provides a healthy and transparent bidirectional dialogue between the patient and the physician and in my experience reduces the risk of a patient becoming mesmerized by the latest and greatest pill advertised on the television. Also, it keeps the focus of pill use (supplement or drug) on medical conditions or high-risk medical situations and not for antiaging or esoteric and obscure prevention purposes.

Recommend A Brand or Line of Supplements? No thanks. Just Reward the Research

I favor no brands and this is my job. I have to go into any situation with objectivity and the "please prove it to me approach." So, my first job is to reward the research by explaining to patients and the public the product that was used in the most impressive clinical trial that shows a benefit or harm. Next, for each and every condition I need to know quality control and safety data for the product and study. And finally are there are products with the same or potentially cheaper and safer ingredients? I tend

to find that companies that lead with their own research and boast about their quality control are the ones that grab my attention. I treat every situation separately as a new story and rather than subscribing to a brand, I subscribe to the supplement that shined or not for the individual condition [25]. Petadolex or generic riboflavin for migraine prevention [72, 162], red yeast rice for cholesterol lowering from Sylvan Bioproducts, Kittanning, Pennsylvania was used in several good trials and was tested and free of a contaminant called "citrinin" that could be found in some red yeast rice supplement [163, 164]. SAM-e from Pharmavite used in a fabulous preliminary clinical trial from Massachusetts General/Harvard in patients that were not responding to their conventional antidepressant drugs [165, 166], but keep in mind that SAM-e is considered a drug in many other countries [25]. How about the probiotic product "Align" (Bifidobacterium infantis 35624 from Procter & Gamble) used in moderately impressive several clinical trials of IBS and should be discussed with patients as an option [167, 168]. And the best goes on and on …. Health care professionals could never endorse one pharmaceutical company and only their drugs as the best option for countless medical conditions because the research has never supported this activity, and so why would it be any different in the dietary supplement world.

Dirt-to-Duodenum and Ground-to-Guts?

Currently an individual can get an herbal from the dirt/ground in China and then have it arrived to a center in Brazil, which then combines that herbal with other ingredients from three other countries so by the time it hits the duodenum/gut the patient is getting raw and processed materials from around the world with no certification or process to trace these components throughout all the steps or stops it takes in the process. Imagine if a contaminant is found, then what lots or boxes need to be stopped or not shipped? This scenario is not uncommon because personally I recently witnessed a recall of supplements potentially contaminated with the antibiotic "chloramphenicol" from India. There were at least 25 companies that would have received this supplement from this supplier/manufacturer if this error were not detected in the supplements (voluntary recall) [169, 170]. Chloramphenicol can rarely cause bone marrow suppression or aplastic anemia in otherwise healthy individuals. The mistake was caught and product or lots in question recalled (it was fortunate the problem was discovered early in the process).

The past may be partially prologue. In the early 1990s, an epidemic of rapidly progressive interstitial renal fibrosis and renal failure occurred in young female patients in Belgium taking a weight loss supplement with Chinese herbs [171, 172]. The cause of this problem was aristolochic acid (AA) and the condition it caused is now known as aristolochic acid nephropathy or AAN. Over 100 patients were impacted during this time. An investigation revealed that one component in the weight loss regimen (*Stephania tetrandra*) was replaced by *Aristolochia fangchi*. Other case series have occurred all over the world (Australia, China, Europe, Japan, Korea, Taiwan, …). And the only risk factor identified for this renal disease is cumulative AA exposure or dose. Currently, it is also known that AA is associated with an increased risk of urothelial cancer (upper urinary tract and bladder). This association is independent of even arsenic exposure (another bladder carcinogen).

The mechanism of action suggests extensive DNA damage when exposed to this compound. In the USA, the FDA issued an alert in 2001 on AA and the seizure of any product with AA is in place.

And when my career started as a student in the late 1980s/early 1990s while at the College of Public Health at the University of South Florida, the L-tryptophan dietary supplement outbreak or eosinophilia–myalgia syndrome (EMS) occurred among some users of this product. More than 1500 cases were documented and over 30 deaths (6-month period) [173], and the State of Florida had one of the top three (along with California and New York) occurrences of cases. My job while in school was to interview these patients and their current symptoms. Ultimately, one of the most famous cases of supplement contamination was traced back to a company in Japan, which was a supplier to American supplement manufacturers. The ban on L-tryptophan was removed in 2005 and there are still some concerns about this product but how can this kind of chaos be prevented?

How can all of these past issues be prevented with current technology? In the future, I believe most supplement companies will need to subscribe to an independent third party quality control group to survive and thrive, such as NSF and others mentioned in this chapter. Additionally, at the time of this writing and for transparency sake, I own stock in the Park City Group (PCYG) because food and supplement companies that use their service are forced to comply with standards and transparency from dirt-to-duodenum and ground-to-guts [174]. In other words, it forces all of the groups up and down the supply chain to follow the rules (via software monitoring batch by batch and company by company) and monitor each and every player in the game! In other words, this and other software companies will be arriving soon that will allow a consumer to feel more comfortable about the source of their pills from ground-to-guts or dirt-to-duodenum.

There are also companies that are looking at better bar coding so that in the future you can scan the product and see where all the parts of your supplement came from and what is in it. For example, a company called "DNA TREK" currently allows customers to "trace fresh produce, protein and processed foods back to their source in minutes," or from "fork to farm traceability" [175]. A product is sprayed directly onto food products and only one billionth of a gram is adequate to trace the product back through the entire food chain process. This type of similar technology is being developed in the dietary supplement world. So, the glass is half-full but it is a little dirty, and by following some of these rules in the future, which I am confident will occur, the glass will be very clean!

Conclusion

Table 2.1 is a brief summary of the observations and advice proffered in this chapter.

Dietary supplements are a full-time job today as opposed to 25 years ago or should be a full-time job. The reason I see a lot of doctors get into trouble trying to

Table 2.1 Recommendations and observations proffered over a 25+ dietary supplement career

Dr. Moyad and his 25+ observations over 25+ years in the dietary supplement world	Dr. Moyad commentary
1. The difference between an effective drug and supplement is perception and not reality	Some of the most effective supplements sold in the USA are drugs in other countries (SAM-e for depression and osteoarthritis, melatonin for insomnia, …)
2. Supplements are not allowed to "diagnose, treat, cure, or prevent any disease"? Instead they are usually allowed structure and function claims like "supports" or "maintains" or "promotes _____ health"? For example, "bone," "digestive," "immune" health	This is precisely how they are used by clinicians today—to prevent or actually treat numerous medical conditions from chronic non-bacterial prostatitis to migraine prevention to neural tube defect prevention, to statin intolerance …. Some supplements using structure and function claims are of course hinting at a drug-like benefit (wink-wink)
3. There are almost countless examples of dietary supplements that are utilized like drugs by health care professionals, and there are examples of supplements that should not be used by health care professionals	– Alzheimer Disease (2000 IU from TEAM-AD VA Cooperative Trial) – Age-Related Macular Degeneration (AMD) and AREDS1 and AREDS2 Trials – Antiaging and the failure of significantly consistent results with resveratrol – BPH and the failure of Saw palmetto in US Trials (STEP and CAMUS) and the need for more research with the European drug-like product Permixon® – Breast and Prostate Cancer and the failure of multiple supplements, especially the potential increased risk of prostate cancer (Vitamin E-400 IU) and aggressive prostate cancer with a supplement (200 μg selenium) in healthy individuals – Dry Eye and/or high triglycerides and the benefit of omega-3 supplements – Erectile Dysfunction and the benefit of L-citrulline supplements – High cholesterol or statin intolerance and the benefit with red yeast rice – Low testosterone and the lack of effective supplements – Insomnia and melatonin including prolonged release (PR) melatonin – Migraine prevention and butterbur extract (also used for seasonal allergies) or riboflavin – Parkinson Disease and the clinical research ongoing with inosine (also with MS or ALS research) – UTI and the potential benefit over cranberry supplements (with a high concentration of proanthocyanidins) over juice and to prevent antibiotic resistance

4. Most dietary supplements starts as generics and then some become proprietary or patented versus pharmaceuticals where most start out with a patent and then eventually become generic	– Beware of many supplements just throwing together a proprietary blend of compounds and using someone else's research along with a celebrity or "expert" to promote their product that they actually have not adequately tested. And look for drug copycats in some of these products like "salicin" used in pain relieving supplements at a high price, which is metabolically altered basically into the same compound or active metabolite of low-cost aspirin
5. The primary goal with patients should be no or a minimum number of pills (supplement or prescription) and never to encourage self-medication	– Lifestyle changes are powerful and provide key information in making t the decision of whether or not a pill is needed and/or the lowest dose needed when otherwise taking care of you or being followed by a medical professional
6. There is nothing "natural" about taking pills and there is nothing healthy about the natural versus synthetic debate	– Pill use is minimal in the areas of the world with the longest life expectancy except when needed for a medical condition – And most of what surrounds humans and what we utilize is also "not natural" unless we need them—cars, highways, cooling, heating, plumbing, toilets, airplanes AED device, … – Natural is better than synthetic when proven to be better. For example, natural vitamin E supplements have data that is no better clinically versus synthetic in major clinical trials (a synthetic vitamin E increased the risk of prostate cancer SELECT trial) and a natural vitamin E may have increased the risk of cardiovascular complications (HOPE TOO) in diabetics and those with vascular disease. A natural vitamin E supplement appears to help kids and adults with NAFLD/NASH (PIVENS and TONIC Trials) and a synthetic vitamin E appears to have helped Alzheimer patients (TEAM-AD VA Cooperative trial)
7. All pills have the potential for "tachyphylaxis" and "saturation kinetics," which is also why we need to always review benefit-versus-risk	– Desensitization to medications is known to occur with a variety of drugs over time and in some cases even higher dosages are needed for an impact and this encourages pill addiction. Some supplements for example arginine and others may also cause this in some individuals – Ingesting too much of a compound eventually causes saturation of the blood or tissue and the rest of the compound is discarded or increases to unhealthy levels. For example, vitamin C in excess increases the risk of kidney stones and selenium can get deposited in soft tissues and increase the risk of nail or hair loss, and perhaps even diabetes, skin cancer recurrence and other cancers in excessive amounts

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Table 2.1 (continued)

Dr. Moyad and his 25+ observations over 25+ years in the dietary supplement world	Dr. Moyad commentary
8. Increased awareness has increased the risk of novel prescription pill like side effects in supplements such as pill esophagitis, esophageal ulcers, silicon-based kidney stones …	– Pill esophagitis and esophageal ulcers are known to rarely occur in the drug world but it also can occur now in the supplement world. In addition, novel side effects from the pill itself such as silicon-based kidney stones from the excess of silicon dioxide (aka "sand") used in some supplements is a concern. Another reason pill consumption is not "natural" and should only be used when benefit>>>risk
9. Fluoride levels in drinking water are symbolic for the need to realize that we are experiencing overexposure to a variety of ingredients with recent societal advancements including the "over-antioxidation of the population" in some cases Medical education needs to shift from discussing antiquated disease deficiencies from the lack of a nutrient (Keshan disease from selenium deficiency for example or vitamin C and scurvy …) to modern day overexposure to certain nutrients	– The recent Department of Health and Human Services request to lower fluoride levels in drinking water was smart because over the past decade fluorosis was increasing from overexposure to fluoride not just from water, but also in toothpastes and mouthwashes. The cumulative exposure over time was becoming concerning and this is symbolic for the nutrition world – The ongoing additions of nutrients to food are reducing the need for some pills, for example calcium exposure in some beverages (almond milk = 455 mg per 8-ounce serving in some products). Increased exposure to pills and food sources of the same nutrient could be hazardous such as selenium (SELECT Trial) and an increased risk of cancer, calcium supplement excess and kidney stones or constipation … – Medical education needs to shift from not just emphasizing third world nutrient or antiquated needs (vitamin C to prevent scurvy), but to also reflect modern day or "first world" overexposure (excess vitamin C creates increased oxalate levels in urine and risk of kidney stones) – Acetaminophen became the number 1 cause of acute liver failure when this compound began to be found not just in pain pills but half of the cold and flu remedies …

10. The only consistent or true deficiencies are related to chronic disease prevention or cardiovascular disease (stroke, hypertension, …) and these are potassium (RDA basically 4700 mg/day—only 1–2 % of the population complies with this intake and the average intake is 2500–2700 mg) and fiber (average intake 10–15 g and intake should be at least 20–30 g)	– Fiber and potassium are difficult to achieve goal because heart healthy foods contain them (we do not consume enough) and because we have relied on pills and powder that can never meet the needs in the case of fiber and potassium (potassium supplement pills are only allowed to have 99 mg or less in them and some fiber pills are needed in mega-quantities for only a 3–5 g intake) – Many deficiencies are actually created by the use of pills and lifestyle today, such as increased zinc supplement intake and copper deficiency, or acid reflux and B12 and magnesium deficiencies. Increased weight/waist gain increases the risk of being diagnosed with a vitamin D deficiency
11. Buzzwords like “inflammation,” “free radicals,” “boosts the immune system” help sales of pills but not objective education of patients and health care professionals. Remember the hygiene-hypothesis?	– Temporary inflammation, or even the generation of free radicals, is a critical signaling in the human body, which is needed to improve exercise performance and overall bodily function. Suppressing of these signals with the use of pills comes at a price. This is also what is observed in the drug world and may be the reason for increased diabetes risk in some high-dose statin users – Allergies and autoimmune disease are caused by “boosted immune systems” but detrimental to health. Optimal immune surveillance is really what is needed and many can achieve this effect without pill unless critically needed for example in melanoma treatment – Hygiene-hypothesis states that the lack of allowing exposure to pathogens or a somewhat unclean environment raises the risk of allergies and autoimmune disease. Thus, trying to prevent every acute illness with pills when not really needed could be detrimental in teaching the body how to respond adequately to these insults
12. “When you have a hammer everything looks like a nail, but when you have a mouth everything looks like a supplement”	– Surgeons are subject to jaded commentary on desiring to do surgery to fix something. However, this can actually occur in any field of medicine including supplements – There is no difference between a conventional doctor that pushes a drug out of conflict of interest and a naturopath or conventional doctor that pushes a supplement, because of conflict of interest. The goal with patients again is minimal pill reliance and independence and not complete dependence on you and the products you (the health care professional) proffers

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Table 2.1 (continued)

Dr. Moyad and his 25+ observations over 25+ years in the dietary supplement world	Dr. Moyad commentary
13. "US" versus "Them" maybe okay in politics but it is completely toxic in medicine	– Medicine is evidence-based and whether it is a supplement or a drug it should be utilized or avoided as needed. However, the terms "big pharma" is used by some major advocates of alternative medicine, and "snake oil" by some in conventional medicine. This serves no purpose but to polarize consumers and patients in one direction that supports these radical agendas. The art and practice of medicine essentially follows evidence and when there is a lack of evidence making sure this is transparent to patients because in the end it is arguably their choice to be treated. I am grateful to some drug companies and not so much for others, and this is also true of supplement companies (grateful for some and can't stand others)
14. FDA cGMP sounds good but needs help. Look for NSF ideally, or USP, or Informed Choice, or NPA … contrary to popular belief there is a lot of support to help you decide supplements with quality and those without quality or efficacy. NSF is arguably my favorite because NFL, MLB, NHL, PGA/LPGA, Olympic athletes and most major athletic organizations use them to keep athletes clean and it has worked well	– In 2007, the FDA cGMP rules helped to moderately clean up the industry but this ruling is similar to requiring a 55 MPH speed limit on the highway with few highway patrol officers. The need for third party oversight or proof of cGMP is critical. Look for NSF labels (on website or on bottle and they audit companies anywhere in the world every 6 months), but also USP and NPA are adequate as well, and "Informed Choice" for sports supplements (and NSF Certified for Sport). Now some of these companies like NSF are also offering gluten free certification and other benefits
15. Herbal supplements are a whole new and old wild animal, so make sure you treat them that way! Always look for some quality control seal/proof AND the standardized ingredient in the herbal that was found to be effective in the phase-3-like clinical trial for the medical condition it might reduce or resolve	– I am not as concerned about labeling issues on simple ingredients like vitamins and minerals as I am on herbals, because of the potential for contamination and the need to demonstrate an active standardized ingredient among the other herbal compounds in the pill. For this reason, I only recommend the herbal used in the definitive clinical trial for example ginseng from the Ginseng Board of Wisconsin when used in the Mayo Clinic reduction in fatigue trial (cancer-related fatigue or CRF). And I look for some definitive quality control measure or seal

16. Several other quality control sites and/or publications on herbal/supplements follow quality and/or efficacy and include some the following: – Center for Science in the Public Interest (CSPI or www.cspinet.org) – Consumerlab.com – ConsumerReports.org – The "Natural Medicines Comprehensive Database" (www.naturaldatabase.com)	Other sources of information on dietary and supplement efficacy and quality are good including Center for Science in the Public interest (CSPI), consmerlab.com, consumer reports, and the "Natural Medicines Comprehensive Database." All of them come with some small to moderate fee but are worth it if you are taking supplements or thinking about using them or even recommending them
17. Pharmaceutical brand supplements have a lot to lose if they are wrong (Note: this does not mean I endorse any of these brands or want you to take one but it is a simple tip for comparison guidance, for example how does your multivitamin compare to Centrum Silver in price, research, quality, …). Quality control is rarely an issue—aka what it says on the label is in the bottle with pharma brands	– Pharmaceutical brand supplements known for their drugs (Bayer, Pfizer) have excellent quality control and also many are cost-competitive. The largest multivitamin trial in the world utilized a pharmaceutical brand (Centrum Silver® in the PHS2 trial). They need to continue to provide cleaner products but some of these options are at least partially evidence based (Centrum, or Align®-B. infantis 35624 by Procter & Gamble …)
18. Multivitamin with herbal ingredients? No thanks!	The two largest multivitamin trials in the world were SU.VI.MAX (five ingredients) and PHS2 (or PHSII-30 ingredients) and both products used a limited or low number of ingredients and dosages (both were one pill a day) and did not include any herbal products. And the risk of adding an herbal to a multivitamin is not worth it and it is not even evidence based now or anytime soon
19. Only purchase a single ingredient supplement most of the time except in rare situations (like a multivitamin or when trial specifies/utilizes more than one ingredient, which is rare). Dilution = Pollution? Don't be a clinical trial of 1! Proof and reward should be in the research and again in standardization of the active ingredient!	– Most supplements for medical conditions consist of one ingredient or one standardized ingredient with a few exceptions (multivitamin, macular degeneration, …). Multiple ingredients without evidence of efficacy and safety potentially dilute and pollutes the active ingredient and increases the risk of toxicity – For example, you would never buy an aspirin pill with ten ingredients in it for pain relief or heart protection or when given to someone having a heart attack. Melatonin and insomnia, and SAM-e and depression, or American ginseng standardized to 3–5 % ginsenoside … all have that one compound that was the result of a benefit usually in a clinical trial

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Dr. Moyad and his 25+ observations over 25+ years in the dietary supplement world	Dr. Moyad commentary
20. Always reevaluate your situation and do not be afraid to be a part-time guinea pig (if benefit>risk). The A, B, C's of whether a pill is working and if you really need it! Look for non-pill pill-like options (the new calcium supplement)?!	We should embrace and celebrate a person when they are so healthy or getting healthier they need little to no pills or lower dosages. Still, I apply A, B and C rules (three of them) to determine if patients or individuals need a pill or supplement *A. Subjective Test (aka guinea pig approach)* Stop the product for 1 month at least and tell me if you feel any better, or worse, or the same? *B. Objective Test (aka laboratory or numbers approach)* Is the supplement you are taking changing any single important parameter that suggests you are becoming more healthy? Cholesterol, blood pressure, blood sugar, weight, … *C. Lifestyle Test (to reduce or determine pill count/dosage)* Is there a lifestyle change that can get me off this pill or at least reduce the dosage?
21. Do patients really need comprehensive testing via blood or genetics to determine their nutritional deficiencies if they are otherwise healthy? No. And get ready to buy a pill! Remember genes can also be changed in some situations like "jeans"	– The FDA did a good job of exposing the fact that some genetic tests would tell you your chance of getting a disease but in reality did not have that kind of research to really predict this, so you end up creating a number of people that just live with a lot of unnecessary anxiety. Patients should be told that in some cases even when a genetic test demonstrates some risk, lifestyle changes can alter risk or even prevent that gene from being ultimately expressed (just because you have a gene does not mean you will express the clinical endpoint of that gene) – Another example of over testing the population for nutrient issues should be exemplified in the "homocysteine" blood test used by many companies to generally screen asymptomatic healthy individuals and place some patients on high-dose B-vitamins – Some nutritional blood tests also simply change dramatically in your favor with lifestyle changes such as weight loss such as vitamin D. And many nutritional tests or specific assay have simply not been validated with any hard clinical endpoints (vitamin D …) – What is the first thing I see patients get when some blood comprehensive nutrient panel demonstrates that something is low? A recommendation to buy a high priced supplement from the same office that provided the blood testing or an office that recommends a supplement and gets paid on the back end without being transparent of that fact! That is a clear conflict of interest. When you sell supplements especially out of your office "everything looks like a mouth"

22. What then is my best advice for determining what supplements an otherwise healthy person could need? Supplements are primarily for medical conditions and targeted dieting once again to the rescue	Supplements mirror drugs in that they can be life altering or life wrecking in the wrong person. Supplements should be primarily used for high-risk medical conditions or medical conditions themselves – Currently in cancer supplements look like a good option to reduce some side effects of treatment and not for treatment itself (ginseng for cancer-related fatigue, ginger for chemotherapy-induced nausea, melatonin for insomnia, protein powder for weight loss or gain …) – Targeted dieting involves getting rid of a pill because of sufficient targeting of foods/beverages high in the nutrient of interest (calcium from foods and beverages and no longer in need of the supplement is easier than ever and so is vitamin D …)
23. When does the medical research suggest about the form of the supplement that should be ingested? Tablets? Capsules? Liquids? What should patients know about this and the best time of the day or situation to ingest a supplement for maximum efficacy? How about the half-life of supplements in the body? Following the path of compliance and flexibility and with ongoing aging metabolism, intestine, kidney, liver, … changes (we also age on the inside). Never forget "20 %"? Children, adolescents and supplements?	– The answer is similar to the drug world, where compliance is the biggest issue and everything else is a distant second – In the famous Women's Health Initiative (WHI)—the largest clinical trial of calcium and vitamin D in the world to prevent bone loss and hip fractures published a decade ago many people still believe the supplements did not work! However, a secondary look at the same trial actually showed for the women that took their supplements most days of the month (80 % of the time) they did work in slowing bone loss and preventing hip fractures by almost 30 % – Most of the time when a supplement says ingest "with a meal" it is to reduce gastrointestinal side effects and improve compliance and memory – My old saying about absorption I have been using for over 25 year, and that is "if you can hit a baseball 500 feet in Detroit Tiger Stadium then it is called a home run but if you can hit a baseball 500 miles into Canada from Tiger stadium then this is so impressive that I am sure you will make a lot of money in endorsement deals but it still counts as a home run!" Absorption is oversold – Groundbreaking drugs, such as metformin, were found to have reduced absorption with food, but this increased compliance (lowered gastrointestinal complications), which resulted in lowering the risk of type-2 diabetes or still providing adequate weight loss. Iron supplements appear to operate this way – 20 % of serious hepatotoxic events in the USA last year occurred with supplements and in generally healthy people. So, again take a supplement that has been tested if you qualify. Do not be a clinical trial of one! – The healthy kids of today that take pills are the adults of tomorrow that ingest more pills. And the parents that take pills usually are the kids that take pills

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Table 2.1 (continued)

Dr. Moyad and his 25+ observations over 25+ years in the dietary supplement world	Dr. Moyad commentary
24. You cannot trust health TV shows? Maybe you cannot just trust what TV shows claim about dietary supplements?	– A recent study of the Dr. Oz show and The Doctors television shows found that often their advice is not accurate and conflict of interest is revealed less than 1 % of the time – These shows do offer some very good advice especially on lifestyle and diet but appear to run into trouble when recommending supplements. Regardless, no pill should be suddenly ingested because of a short segment on a TV show. Instead use TV advice as part of the larger discussion of the health of the overall patient (one piece of the larger health puzzle)
25. Any other advice? Doctors know more than they think about supplements. Family disease trees for better communication and supplements for medical conditions. Recommending one brand of supplements? Why the future looks great! Ground-to-Gut or Dirt-to-Duodenum!	– Doctors know more than they think about supplements – Recommending a supplement line exclusively is like recommending one pharmaceutical line of drugs exclusively?! Let the evidence lead to the specific supplement brand recommendation (hey, like with drugs). I recommend Petadolex for migraine prevention, Pharmavite for SAM-e, Align for some IBS, Sylvan Bioproducts for red yeast rice … and the beat goes on! – Dirt-to-Duodenum and Ground-to-Guts is what new software and third party seals will allow in the future. Supplement companies should be required to sign up with one of these companies in order to sell their products. And it reduces their insurance costs and litigation – The future looks bright because transparency software and testing I believe will become a part of the supplement business (it is now in many cases—moving into food safety and next into supplements)

interpret the supplement research is they think they can dabble in this field and provide all the answers but the days of dabbling are over. It is time to respect that fact that over 5000 articles in diet and supplements are published yearly and this requires your full (not part-time) attention. Imagine if I dabbled in orthopedic surgery or dermatology … would one really then wonder why things could go very wrong and inaccuracies would abound?!

Still, the advice proffered in this chapter has provided a foundation for teaching and instructing and helping consumers and patients around the world. The field of dietary supplements appears bright because the sheer amount of clinical research has increased exponentially, and determining what is working and what is worthless gets easier year-to-year. On the other hand, it is a business and the good side of that business is more options for patients and the nefarious sides is also more trickery for some patients that I observe get financially abused and become no more salubrious or hurt. Yet it starts with the clinician because I have always argued that wherever I have traveled in the world patients want to hear these answers to their questions from you (the clinician), and if you are not able to objectively answer them, then going to less credible sources down the street will become the norm.

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