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Drugs versus Nutritional Fundamentals: Blurring the Line Between Treatment and Prevention

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The identity gap between drugs and natural food–based products has been narrowing. Until recently, functional foods and the natural health products have been considered to act in a health prevention capacity, while drugs are seen more utilized in the process of treatment of disease. However, recently lines have blurred across these definitions, with a case in point being plant sterols and statins, both of which have been shown efficacious in acting on an identical endpoint, i.e. LDL-cholesterol levels, in the treatment of hypercholesterolemia. And this is not surprising, as both stem from a common ancestor, the fungi on foods such as purple rice. Indeed, increasing numbers of natural health products including omega-3 FA and CoQ_{10} have crossed the floor to be embraced as prescription pharmaceuticals. Such discrepancies illustrate the challenges in distinguishing between categories of products used to improve health by preventative approaches versus mitigate disease states through treatment modalities. Thus, the objective of this review is to explore the gaps in distinguishing drugs from functional foods and natural health products ,as well as identify challenges for the future for these industries.

The notion of using diet in disease treatment has been around some time. Long before the advent of modern medicine, Hippocrates coined the phrase "let food be thy medicine". Many scores of years later, researchers and the medical community have caught on, creating a functional food and natural health product industry grossing hundreds of billions of dollars per year. This industry has not only successfully incorporated recognized bioactives into new functional products, but also generated a public where the average consumer presently understands that food labels reading "omega-3" or "high fibre" are healthy ingredients... and reaches out to purchase them in the form of value-added foods and or supplements for premium prices. The idea of consumers identifying healthy bioactives such as "omega-3" on food labels empowers them to pay for such products, and thereby reduce disease incidence rates and health-care costs, without the need to rely solely on drug therapy.

And for good reason. Similar to the manner it does in the pharmaceutical domain, research clearly demonstrates that functional foods and natural health products possess physiological and molecular targets that modulate clinical endpoints associated with chronic disease. But despite current research demonstrating that such products combined with pharmaceuticals can benefit patients better than pharmacomonotherapy, information regarding the efficacy of functional food– and natural product–based therapies is rarely appropriately communicated to health-care practitioners and implemented into disease-treatment regimens. On occasion, efforts are made to

educate mainstream medical practitioners that certain foods and natural products can go beyond prevention, but extend into the realm of treatment.

For instance, former doctoral student Chris Marinangeli and I published a paper in the Annals of Medicine (2010) alerting the medical community that science has now developed in support of the health attributes of food and natural-based products to the extent that we can come close to defining these ingredients as medicines. Three key points emerged from our publication. First, the point was made that, similar to pharmaceutical agents, functional foods and natural products affect physiological and molecular bioprocesses which modulate clinical endpoints associated with chronic disease. Moreover, despite current research demonstrating that these products, combined with pharmaceuticals, can benefit patients better than does pharmacomonotherapy, functional food–and natural product–based therapies are unfortunately presently deemphasized as risk factors for chronic disease accumulate over time. Indeed, in some instances natural products are deliberately undermined. The Wikipedia page for plant sterols, as an example, has been for some years regularly altered by unidentified editors who claim that plant sterol usage results in higher circulating plant sterol levels and thus, by association, increased risk of heart disease. Such a position provides a highly imbalanced perspective, given that 200 clinical trials exist which attest to the safety and efficacy of plant sterol utilization. Some sinister force appears to be at work in this instance.

Second, in the context of metabolic syndrome, a multifaceted disease state, which is a focus of the Marinangeli and Jones article, natural products including marine-derived omega-3 fatty acids, plant sterols, fibre, and tomato extract have been shown to target metabolic processes associated with atherogenic dyslipidemia, hypercholesterolemia, insulin resistance, vascular dysfunction, and hypertension. Such targets are as much therapeutic as they are prophylactic; thus, these agents can be considered as much as drugs as they are natural products.

Third, the article asserts that food and natural products should be emphasized throughout all stages of treatment as adjuncts to pharmacotherapy, not just at initial stages as is currently recommended (see Figure 1, below). For such a shift in therapeutic approach to occur, however, new developments in natural product research must be communicated to health-care practitioners through mainstream

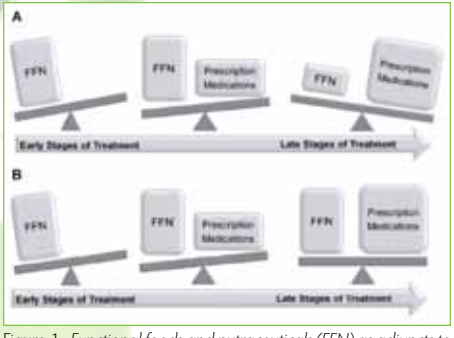

Figure 1 - *Functional foods and nutraceuticals (FFN) as adjuncts to pharmacotherapy for the treatment of hyperlipidemia. Part A is a visual depiction of how current clinical guidelines de-emphasize the use of FFNs as treatments for hyperlipidemia progress. Part B incorporates the notion that FFN should be emphasized during all stages of treatment for hyperlipidemia.*

channels and implemented into officially sanctioned clinical guidelines, such that they may be utilized by modern medicine as a valuable part of the toolbox for combating disease. To some extent, inroads along these lines have been occurring as in the case of endorsement of plant sterol use in the management of hyperlipidemia by the American Heart Association and the European Atherosclerosis Society. Nonetheless, given the current drug-based mindset which preoccupies much of mainstream medicine, substantial hurdles remain to be overcome to achieve an optimal level of communication of the benefits of natural health products to physicians.

So what factors are important to continue to develop and promote the natural product industry to assure optimal uptake of products by health-care professionals? Paramount is the question of credibility. For the industry to continue gaining momentum, scientific substantiation of products using correctly designed and implemented experimentation is essential. Fortunately, increasingly standardized approaches for conducting randomized controlled trials have been set in place to improve that level of substantiation. Whether the recent move by the US FDA to regulate food trials using the same regulations as drug trials will dampen the appetite for human testing with natural products requires time to determine and assess.

It will also be important to continue to explore categories of natural products that move closer into the gap between natural and pharmaceutical definitions. For instance, combining two natural molecules such as ascorbic acid and resveratrol is chemically simple, but from a regulatory standpoint, more of a challenge in defining whether the product becomes classified as a drug, or simply a pair of natural products bonded together to improve efficacy or bioavailability. These issues will need to be addressed in order to enable forward and positive migration of the field.

Lastly, the eventual success of the industry will rely on optimization of roles and linkages between essential stakeholders. This again ultimately relies on trust between partners. Food and supplement companies that manufacture and distribute functional foods and natural products, and provide funding for clinical trials, need to demonstrate that functional food and natural products are efficacious and safe. Scientists and health-care practitioners including naturopathic doctors, in addition to facilitating preclinical and clinical trials that prove product safety and efficacy, must act as key opinion leaders to ensure sound, objective science regarding efficacious food and natural product is communicated to the public. Similarly, regulators and governmental authorities must introduce and enforce laws that make certain the public are not misled by products that are unsafe and/or fail to elicit health benefits. Finally, consumers, the ultimate end-users of natural products, are ultimately the drivers of functional food and natural health product development, research, and production, have to reach out and financially backstop this industry. Without these drivers, the entire industry would lose momentum.

In summary, despite continued growth of

the natural product industry, the lack of harmonization between jurisdictions for approving food- and natural product–based health claims, blurred lines regarding the classification of novel and/or synthetic products as foods or pharmaceuticals, and challenges for developing dietary requirements reflecting therapeutic dosages of nutrients, all continue to represent issues that need to be addressed in order to support a vibrant and productive functional foods and natural product industry. Natural products of the future will continue to engender success and uptake by the medical community, as both agents for treatment and prevention, as long as these fundamental challenges are successfully addressed.

Reference

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The Efficacy of Melatonin in the Treatment of Endometriosis

Tori Hudson, ND

A randomized, double-blind, two-group parallel clinical trial conducted in Brazil compared the effects of melatonin with a placebo on endometriosis-associated pelvic pain, brain-derived neurotrophic factor level, and sleep quality. Forty women were randomized into melatonin 10 mg/d (n = 20) or placebo (n = 20) groups for eight weeks.

Forty women with chronic pelvic pain, who were between 18 and 45 y.o., were recruited from gynecology outpatient clinics. Chronic pelvic pain was defined as a moderate-to-severe pain lasting for more than six months and eliciting pain scores of at least 4 or greater on a 10-point pain scale that required regular analgesic use. All patients had a diagnosis of endometriosis as confirmed on laparoscopy, and the study included patients with any stage from 1 to 4. Three patients in the melatonin group and one in the placebo group withdrew due to treatment inefficacy.

The primary outcome of the trial was pain, as assessed by pain-score diaries within the last 24 hours, painful menstrual periods, or dyspareunia as well as the amount of analgesics used each week throughout the treatment period and the level of brain-derived neurotrophic factor (BDNF). Secondary outcomes were pain during urination or defecation, and sleep quality.

Results

The melatonin group had significantly lower pain visual analogue scale (VAS) scores than the placebo-treated group, with a mean pain reduction of 39.3% in the melatonin group vs. the placebo group. The melatonin group also had significantly lower pain scored during menstruation, with mean reduction in analgesic use of 42.2% in the placebo group and 22.9% of patients in the melatonin group. The placebo group was 80% more likely to require additional

analgesics than the melatonin group. In the placebo group, acetaminophen was used by 66.7%, NSAIDs by 60%, and codeine or tramadol by 60%. In the melatonin group, 33.3% used acetaminophen, 40% used tramadol or codeine, and 35% used NSAIDs.

The adjusted mean BDNF level for the placebo group was 25.64 vs. 20.46 for the melatonin group, with a mean difference of 5.94, which is significant, and the authors concluded that the effect of treatment on the BDNF level is not dependent on the pain level. This suggests that melatonin has a direct effect on pain pathways or on the levels of chemicals that are signals for pain. Patients in the melatonin group had better sleep quality than the placebo group, and melatonin produced a mean improvement of 42% in how patients felt upon waking in the morning.

Commentary

This study demonstrated that melatonin at 10 mg/d reduces endometriosis-associated chronic pelvic pain, including a reduction in pelvic pain, dysmenorrhea, dyspareunia, dysuria, and dyschezia (pain during defecation) that is statistically and clinically significant. This reduction in pelvic pain due to melatonin was of a magnitude > 35% overall, as well as an 80% reduction in analgesic use.

This study is consistent with evidence from animal studies in which melatonin caused regression and atrophy of endometriotic lesions. The current study also corroborates other randomized clinical trials on melatonin and pain in treating fibromyalgia and acute postoperative pain.

The mechanisms of action may include the antinociceptive effect on melatonin involving the activation of supraspinal sites and the inhibition of spinal windup. Other experimental evidence suggests that the analgesic effects of melatonin are mediated by opioids and GABA, and anti-inflammatory effects by inhibiting the release of cytokines. The effect of melatonin on chronic endometriosis-associated pelvic pain may also be explained by its effect on diverse hormonal pathways.

Melatonin is well tolerated by most patients, and appears to represent an effective option for pain symptoms related to endometriosis. A 2013 observational study on *N*-acetylcysteine also resulted in significant pain reduction and ovarian cyst size reduction associated with endometriosis. I consider these two nutrients as mainstays in our treatment strategies for endometriosis.

Reference

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Impact of Vitamin D_3 Dietary Supplement Matrix on Clinical Response

M. Traub, J.S. Finnell, A. Bhandiwad, E. Oberg, L. Suhaila, and R. Bradley

Background: There are no comparative effectiveness trials of vitamin D_3 (D_3) dietary supplements for the repletion of serum 25-hydroxycholecalciferol (25-OHD) in a routine clinical setting.

Objective: To compare changes in 25-OHD concentration in adults following treatment with three active D_3 dietary supplements with different delivery matrices.

Design: Multi-site, single masked, randomized, comparative effectiveness trial.

Setting: Two clinical sites in Seattle, WA and Kona, HI.

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Patients/Intervention: 66 healthy adults with (25(OH)D) < 33 ng/ml were randomly assigned to take one of three D_3 supplements, i.e. a chewable tablet (TAB), an oil-based drop (DROP), or an encapsulated powder (CAP), at a label-claimed dose of 10,000 IU/day. Actual D_3 content was assessed by a third party, and the results adjusted based on the actual D_3 content administered.

Measurements: The primary, secondary, and tertiary outcome measures were between group change in serum 25-OHD; between group difference in proportion of participants reaching 25-OHD ≥ 30 ng/ml; between group change in serum 1, 25-dihydroxycholecalciferol. We then re-analyzed the primary outcome based on the third party–measured D_3 content of each supplement.

Results: In two of the three products tested, the measured vitamin D_3 content varied considerably from the label-claimed dose. Differences in 25(OH)D/mcg D_3 administered were significantly different between groups (p = 0.04; n = 55). Pairwise comparisons demonstrated DROP resulted in a greater increase than TAB (p < 0.05), but not than CAP. TAB was not different from CAP. The proportions reaching sufficiency were 100% (TAB and CAP) and 80% (DROP) (p = 0.03 between groups, n = 55). 1,25-dihydroxycholecalciferol did not change significantly in any group.

Limitations: Results may not be generalizable to all clinical populations, different supplement batches, or other D_3 supplements.

Conclusions: Dietary supplements at doses of 10,000 IU/day for 12 weeks were safe and effective, though variable, for increasing serum 25-OHD concentration in a routine clinical population. Oil-emulsified vitamin D_3 supplements resulted in a greater mean change in serum 25(OH)D concentration, but fewer patients reaching vitamin D sufficiency, than chewable or encapsulated supplements.

Commentary: This study began as an attempt to test a manufacturer's claim that their oil-based vitamin D_3 supplement was superior to an encapsulated D_3. The manufacturer was a supporter of a naturopathic residency program. The

program director saw an opportunity to give back to the manufacturer and to involve his resident in a clinical research project. What originally seemed to be a straightforward comparative effectiveness trial eventually morphed into a complicated multi-year project.

An unexpected outcome of this study was the finding that the label claims of the products tested varied widely. Our third-party analysis ranged from 105 to 227% of the expected dose of 2,000 IU. This was consistent with the findings of LeBlanc, et al., who observed notable variability in the quality of D_3 dietary supplements.[1] We concur with the conclusion of LeBlanc, et al., that this D_3 concentration variability "threatens the validity of vitamin D trials." To best interpret vitamin D clinical trials, we recommend that all vitamin D dietary supplements be tested by a third-party analytical lab, at the beginning and end of the intervention period of the trial. We also recommend trial results be adjusted to report the actual dose(s) administered in the trial, and the actual dose(s) be considered in all relevant analyses.

The U.S. Food and Drug Administration (U.S. FDA) does provide regulatory guidance for the D_3 content in dietary supplements (21 CFR 101.9), which states that the content be at least equal to and not exceed 20% of the label claim, or that the content falls within the variability of the accepted analytical method and current good manufacturing practices (cGMP).[2] The U.S. Pharmacopoeial Convention National Formulary (USP-NF) criteria, allowing 90% to 165% of label claim in D_3 dietary supplements, are often used to meet the U.S. FDA cGMP guidelines to ensure potency at the product expiry date.[3]

References

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2. FDA US. *Code of Federal Regulations,* Title 21, Volume 2, Part 101.9, 2012.

3. United States Pharmacopeial Convention. *USP 35-NF 30: Dietary Supplements Compendium.* Rockville, MD: United States Pharmacopeial Convention; 2012.

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