Chiropractic and Naturopathic Medicine for the Promotion of Optimal Health and Alleviation of Pain and Inflammation

A Detailed Review of Current “Daily Use” Research with Implications for Clinical Practice and Healthcare Policy

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Objective:
This article has four major objectives: 1) to discuss modern chiropractic and naturopathic primary care and wellness promotion within the American healthcare context, 2) to review new research on the physiology and biochemistry of the inflammatory cascade with an emphasis on safe and effective nutritional and botanical interventions appropriate for clinical use, 3) to present an integrated model wherein spinal manipulation and nutritional interventions are hypothesized to break the self-perpetuating cycle of immunogenic and neurogenic inflammation, and 4) to correlate current research and documentation with logical implications for clinical practice and healthcare policy.

Data Sources:
Several hundred sources of information were identified, the vast majority from peer-reviewed biomedical journals as identified via numerous Medline searches. Authoritative textbooks by research scholars are also cited, as are published texts and periodicals documenting historical fact. To the extent possible, emphasis is placed on controlled clinical trials, especially those that allow comparison between pharmaceutical vs. natural treatments and/or those that provide data regarding efficacy, safety, adverse effects, and cost-effectiveness.

Results:
The scientific rationale and clinical basis for the nutritional, non-pharmacologic treatment of many common painful inflammatory disorders is well established in the peer-reviewed biomedical research. Many natural treatments (ie, spinal manipulation, interventional nutrition, and botanical medicines) appear superior to pharmacologic drugs in terms of efficacy, cost, safety, and overall health promotion. Whereas most pharmacologic treatments for pain and inflammation carry numerous adverse effects and thus contribute directly to increases in patient suffering and healthcare expenses, several of the nutritional and botanical interventions described in this comprehensive review appear relatively devoid of adverse effects and have been shown in long-term follow-up studies to favorably modify the course of disease and in several instances to reduce overall mortality and healthcare expenses.

Conclusions:
Given the superior cost-effectiveness, relative lack of adverse effects, and additional “side-benefits” of natural treatments used by chiropractic/naturopathic physicians, the chiropractic/naturopathic management of outpatient musculoskeletal pain with comprehensive treatment plans that integrate carefully selected nutritional and botanical interventions as described in this review appears clinically, financially, and ethically superior to those interventions commonly employed by allopathic medical physicians. Research has shown that many of the drug and surgical interventions (over)utilized by medical physicians for the treatment of musculoskeletal pain are dangerous, expensive, and/or ineffective. The recent rofecoxib/Vioxx catastrophe demonstrates that neither FDA approval nor routine allopathic utilization of a drug sanctifies its efficacy and safety. Scope of practice laws and healthcare/insurance policies should be protected and amended to ensure that ailing patients have access to science-based natural healthcare interventions. This review will provide chiropractic/naturopathic physicians with clinically useful information to help their patients attain improved health and well-being. Increased professional involvement by all chiropractic and naturopathic physicians combined with ever-growing public support should be immediately leveraged to effect widespread healthcare reform in favor of natural medicine. Given that 493 American patients die as a direct consequence—“side effect”—of allopathic medical interventions on a daily basis, decreasing reliance on medical treatments by increasing access to chiropractic and naturopathic physicians should be treated as a public health priority. Political action and collaboration between the chiropractic and naturopathic professions will be required to obtain: 1) national licensure for naturopathic physicians who have graduated from residential 4-6 year doctorate programs, 2) limited prescriptive authority for chiropractic physicians at least for the purpose of legally discontinuing and thereby protecting their patients from pharmaceutical drugs known to significantly increase the risk of injury and death, 3) the nation-wide passage and enforcement of "every category of provider laws" to empower the public with financial access to and insurance coverage for nondrug nonsurgical healthcare providers.
Introduction
As primary care providers with specialized training in musculoskeletal medicine, chiropractic physicians typically play a dual role in clinical practice on a daily basis, generally striving to simultaneously accomplish two related goals in each patient: 1) promoting overall wellness and professionally-supervised patient-implemented preventive healthcare, and 2) alleviating acute and chronic musculoskeletal pain. Both of these goals are important given the tremendous financial and social impact of musculoskeletal pain and the progressive deterioration of Americans' health. At any given time, nearly thirty percent of the American population suffers from musculoskeletal pain, joint swelling, or limitation of movement, and approximately 1 of every 7 (14% of total) visits to a primary healthcare provider is for the treatment of musculoskeletal pain or dysfunction. Resulting in more than $100 billion in US healthcare costs each year, back pain is the most prevalent medical problem in the US, is the leading cause of long-term disability, and is the second leading cause of restricted activity and the use of prescription and non-prescription drugs. The preventive healthcare and wellness promotion advocated and implemented by chiropractic and naturopathic physicians is now more important than ever since the health of the American population is consistently and progressively declining: obesity and diabetes are “ever-growing” epidemics among children and adults, infant mortality has recently increased for the first time in 40 years, and self-reported health status and health-related quality of life among adults are declining. In the 25 years between 1975 and 2000, the incidence of cancer increased significantly, and the number of people diagnosed with cancer is expected to double in the next several decades. Despite these negative health trends, America spends more on healthcare than does any other nation—an unprecedented $1.55 trillion, which is roughly 15% of the US gross domestic product. From the perspective of cost-effectiveness, the healthcare system in America, currently dominated and “lead” by the allopathic medical community, delivers a very poor return on investment, and it appears that assertive wellness promotion and increased utilization of chiropractic and naturopathic healthcare may provide improved outcomes and decreased overall healthcare costs.

American citizens, families, businesses, and communities are burdened by expensive medical management, assessments, and interventions. Indeed, compared to those in other nations, impressive discrepancies exist between healthcare investments and outcomes in America, and the generalization that Americans patients spend more money for worse health outcomes has been termed “the American paradox” by the current author. Compared to citizens of other nations, Americans spend more on medical care and receive more drugs and medical procedures, yet paradoxically we experience the overall worst health outcomes among citizens of industrialized nations. In 2000, the Director of World Health Organization’s Global Program on Evidence for Health Policy, Christopher Murray MD PhD, concluded, “Basically, you die earlier and spend more time disabled if you’re an American rather than a member of most other advanced countries.” According to the 1999 review by Anderson and Poullier, the average annual income for allopathic medical physicians in America (at approximately $200,000 per year) is disproportionately higher than the income for physicians in other countries (approximately $100,000 per year), especially considering the superior health outcomes that are commonplace in other nations that spend much less per capita. Recent data has shown that one in seven households—almost 20 million American families—faces significant financial hardships due to medical bills, and of these almost
two-thirds (about 13 million families) report difficulty paying for other basic necessities—rent, mortgage payments, transportation or food—as a result of medical debt. The toll of medical coverage is a heavy burden for American small businesses, too; in 2003 health care costs rose about 15% for businesses with fewer than 200 workers vs. 13.5% for those with 500 or more, and many small employers cited increases of 20% or more, leading USA Today to conclude, “That’s made [medical/healthcare] insurance the No. 1 small business problem.” Among Medicare recipients, more than one in seven (14%) report financial difficulties that result from medical bills. In response to the rhetorical question “What do we get for our money?” Money Magazine published in 2003 that, “For a start, we get lots of technology. Though the U.S. has slightly fewer doctors per capita than the typical developed nation, we have almost twice as many MRI machines and perform vastly more angioplasties. We also get an extraordinarily rich health-care industry: Last year, for example, shareholders in the drugmaker Pfizer saw after-tax earnings of $9.2 billion, reflecting a net profit margin of 28 percent…” A 2004 article in the Washington Post summarized, “Although they spend more on health care than patients in any other industrialized nation, Americans receive the right treatment less than 60 percent of the time, resulting in unnecessary pain, expense and even death…” This discrepancy between exorbitant costs and inferior results suggests the need to reconsider the paradigms and policies that shape American healthcare, especially if underutilized options exist for immediate implementation that can effect widespread health improvements at comparatively reduced costs.

Americans also suffer an astoundingly high level of iatrogenic (doctor-induced) morbidity and mortality in the process of receiving medical care. Drug interactions, drug “side effects”, prescription errors, unnecessary surgeries, nosocomial infections, and “hospital errors” are a leading cause of death in America. The number of deaths due to “medication errors” more than doubled from 1983 to 1993. Lazarou et al published a landmark report in JAMA in 1998 showing that hospital-supervised administration of drugs leads to adverse effects in more than 2.2 million American patients and directly results in more than 100,000 deaths, thus “making these reactions between the fourth and sixth leading cause of death.” An article by Starfield published in JAMA in 2000 documented that allopathic medicine is the third leading cause of death in America after heart disease and cancer; this article can be paraphrased as stating, “iatrogenic causes” result in “225,000 deaths per year” constituting “the third leading cause of death in the United States.” Other estimates have been more conservative, such as the 1997 review by Holland and Degury in American Family Physician, wherein the authors note, “Recent estimates suggest that each year more than 1 million patients are injured while in the hospital and approximately 180,000 die because of these injuries. Furthermore, drug-related morbidity and mortality are common and are estimated to cost more than $136 billion a year.” Thus, according to these authoritative reviews, we can reasonably conclude that not less than 110,000 and up to 225,000 American patients are killed every year by adverse drug effects, hospital errors, and other “side-effects” of allopathic medicine. Placing this into a public health context, we see that more people die every year from iatrogenic disease than from cerebrovascular disease (168,000), diabetes (69,000), influenza or pneumonia (65,000). If it were not for the politics involved—that is, if allopathic iatrogenesis were an infectious disease rather than a consequence of professional error—major public health campaigns would be directed to alert the public about risk-reduction measures for this underappreciated major cause of death. Likewise, medical organizations such as the American Medical Association would fight vehemently for improved patient care, rather than focusing on limiting malpractice liability for allopathic doctors sued for harm or negligence.

Numerous adverse effects are produced as a direct result of medical/pharmaceutical management of benign musculoskeletal pain. According to a 1998 review by Singh, “Conservative calculations estimate that

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23) The results of the study demonstrate that, over the past four decades, the United States has been spending more and accomplishing less when compared with other industrialized nations.” Shi L. Health care spending, delivery, and outcome in developed countries: a cross-national comparison. Am J Med Qual. 1997;12(2):33-93.
approximately 107,000 patients are hospitalized annually for nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone. The figures for all NSAID users would be overwhelming, yet the scope of this problem is generally under-appreciated.” More recently following the withdrawal of the arthritis drug rofecoxib (Vioxx) in late September 2004, Topol30 extrapolated that as many as 160,000 adverse cardiovascular events (including stroke, myocardial infarction, and death) may have resulted from the collusion of Merck’s intentional failure to withdraw what was known for years to be a dangerous drug, the FDA’s failure to enforce regulatory standards to protect the public, and the overutilization of Vioxx by the medical profession, which was well informed of the lethal nature of Vioxx for several years31 before Merck’s confessionary and belated withdrawal of the drug. Soon thereafter, several other so-called “anti-inflammatory drugs” such as valdecoxib (Bextra),32 celecoxib (Celebrex),33 and naproxen (Aleve)34 were likewise associated with excess cardiovascular injury and death. Although the advertising-induced feeding frenzy on Celebrex made it the most successful drug launch in US history with more than 7.4 million prescriptions written within its first 6 months35, within 2 years of its release evidence linking the drug to increased cardiovascular events (including death) was accumulating36, and the drug has since been linked to a wide range of adverse effects such as membranous glomerulopathy and acute interstitial nephritis,37 acute cholestatic hepatitis,38 and toxic epidermal necrolysis.39,40 Current guidelines hold that patients must be informed of the excess cardiovascular risk associated with this drug and that its use should be limited to the lowest dose for the shortest time possible (weeks).41 When compared with placebo in cardiac surgery patients, Bextra/valdecoxib is associated with a 3-fold to 4-fold increased risk of heart attack, stroke, and death42, and recently 7 million arthritis patients, many of whom were already at high risk for cardiovascular disease, were being treated with this drug.43 Use of Bextra was also strongly associated with toxic epidermal necrolysis, a potentially fatal condition.44 Due primarily to the adverse cardiovascular effects,45 in the interest of protecting the public from additional adverse effects and unnecessary deaths, in April 2005 the FDA ordered that Bextra/valdecoxib be taken off the market in the US46 and Health Candada followed suit by removing the drug from Canadian markets.47 It is inexcusable that these drugs were so highly utilized (due to aggressive marketing) despite evidence of relative analgesic inefficacy (not better than earlier NSAIDs like aspirin), exorbitant costs (US $90-180 per month48) and clear evidence of danger (e.g., cardiovascular death) by two well-identified mechanisms: inhibiting the formation of vasodilating and anti-aggregatory prostacyclin, and shunting arachidonate toward leukotriene formation by blocking cyclooxygenase.

Allopathic medical education has recently been described as “woefully inadequate” in preparing medical doctors for the medical treatment of musculoskeletal conditions,49 and these deficits stem from the paucity of didactic and clinical training provided to medical students in musculoskeletal diagnosis and treatment. In their 2004 review published in Physician and Sportsmedicine, Joy and Van Hala50 describe the formal training of a sample of 85 recent medical graduates, “…the average time spent in rotations or courses devoted to orthopedics during medical school was only 2 weeks. One third of these examinees graduated without any formal training in orthopedics. As would be expected, these data suggest that limited educational experience contributes to poor

33) “Patients in the clinical trial taking 400 mg of Celebrex twice daily had a 3.4-times greater risk of CV events compared to placebo. For patients in the trial taking 200 mg of Celebrex twice daily, the risk was 2.5 times greater. The average duration of treatment in the trial was 33 months.” FDA Statement on the Halting of a Clinical Trial of the Cox-2 Inhibitor Celebrex. http://www.fda.gov/bbs/topics/NEWS/2004/NEW01144.html Available on January 4, 2005
40) Friedman B, Ortiz HK, Still JM, Law E. Toxic epidermal necrolysis due to administration of celecoxib (Celebrex). South Med J 2002;95(10):1213-4
41) “Celecoxib should be used in the lowest effective doses for short periods (weeks) only. A risk-benefit discussion is necessary for those requiring the drug for a longer period.” Cotter J, Wodotkin E. New restrictions on celecoxib (Celebrex) use and the withdrawal of valdecoxib (Bextra). CMAJ. 2005 May 10;172(10):1296. Epub 2005 Apr 15. Access September 28, 2005
46) “On April 7, the Food and Drug Administration requested that Pfizer suspend sales of BEXTRA in the United States. As a result, BEXTRA will no longer be available to patients in the United States... In light of the FDA’s position that there is an increased cardiovascular risk for all prescription non-steroidal anti-inflammatory arthritis medicines, as well as the increased rate of rare, serious skin reactions with BEXTRA, the FDA has requested that sales of BEXTRA be suspended.” http://www.bextra.com. Accessed September 28, 2005
47) Sibbald B. Pfizer withdraws valdecoxib (Bextra) at Health Canada’s request. CMAJ. 2005 May 10;172(10):1296. Epub 2005 Apr 7 http://www.cmaj.ca/cgi/content/full/172/10/1296 Accessed September 28, 2005
performance.” In 1998, Friedman and Bernstein\(^{51}\) published a landmark study in *Journal of Bone and Joint Surgery* wherein they administered a validated musculoskeletal competency examination to 85 recent medical graduates who had begun their hospital residency; 82% of these medical doctors failed to demonstrate basic competency on the examination, leading the authors to conclude, “We therefore believe that medical school preparation in musculoskeletal medicine is inadequate.” They repeated their study in 2002, and this time the examination questions, which had previously been validated by orthopedic specialists, were validated by directors of internal medicine departments; their conclusions stated, “According to the standard suggested by the program directors of internal medicine residency departments, a large majority of the examinees once again failed to demonstrate basic competency in musculoskeletal medicine on the examination. It is therefore reasonable to conclude that medical school preparation in musculoskeletal medicine is inadequate.”\(^{52}\) In February 2005, Matzkin et al\(^{53}\) administered a standardized test of musculoskeletal competency to 334 medical students, residents, and staff physicians; the conclusion from their study reads as follows: “Seventy-nine percent of the participants failed the basic musculoskeletal cognitive examination. This suggests that training in musculoskeletal medicine is inadequate in both medical school and nonorthopaedic residency training programs.” Again in August 2005, Schmale\(^{54}\) from the University of Washington showed that when a standardized musculoskeletal examination was administered “…less than 50% of fourth-year students showed competency. Students who completed a musculoskeletal clinical elective scored higher and were more competent (78%) than students who did not take an elective. These results suggested that the curricular approach toward teaching musculoskeletal medicine at this medical school was insufficient...” These results are particularly alarming because the University of Washington consistently ranks as the best medical school in America.\(^{55}\) If medical schools across the nation are failing to prepare doctors to evaluate and thus treat patients with musculoskeletal complaints, then would this not present a danger to the public health? What might be the consequences of such widespread professional ineptness? Insufficient training in musculoskeletal management might be expected to produce negative clinical consequences and an increased reliance on stereotypic and simplistic (rather than personalized and comprehensive) treatments such as the overutilization of so-called “anti-inflammatory” drugs. Furthermore, such a high level of incompetence among recently graduated medical doctors in basic musculoskeletal assessment may represent a public health risk to patients seeking care. The overutilization of surgical treatments for musculoskeletal disorders also places an unjustified burden on the nation’s healthcare system; for example, arthroscopic knee surgery is performed on at least 225,000 middle-age and older Americans each year at a cost of several billion dollars to Medicare, the Department of Veterans Affairs and private insurers\(^{56}\) yet the results are no better than those obtained from placebo.\(^{57}\) In their 2003 review of the literature on this topic, Bernstein and Quach\(^{58}\) concluded, “Arthroscopy for degenerative conditions of the knee is among the most commonly employed orthopedic procedures, but its effectiveness (like the effectiveness of many surgical operations) has never been proven in prospective trials.”

In contrast, chiropractic and naturopathic physicians receive extensive training in the management of outpatient musculoskeletal disorders during their course of graduate healthcare training, which typically lasts from 4-6 years. Although some differences exist between the naturopathic and chiropractic professions in terms of philosophy and clinical interventions, physicians in these professions share almost identical clinical goals: to help patients become as healthy as possible without the use of drugs and surgery via the implementation of comprehensive treatment plans that emphasize safe and effective natural interventions such as personalized diets, therapeutic exercise, nutritional supplementation, and preventive, holistic healthcare.\(^{59}\) Following the basic science courses which are similar in medical, osteopathic, naturopathic, and chiropractic schools,\(^{60}\) doctorate students in the health sciences learn different clinical therapeutics. Allopathic students learn to use drugs and surgery as their main interventional tools. Osteopathic students learn the use of drugs, surgery, and manual physical manipulation. Naturopathic students receive training in manual physical manipulation (including drugs and surgery as their main interventional tools); therapeutic diets, clinical and interventional nutrition, botanical medicines, and...
lifestyle counseling, environmental medicine, and other modalities, and licensed naturopathic physicians commonly practice as generalists and family doctors. 61,62,63,64 Chiropractic students learn clinical nutrition, and receive extensive training in manual physical manipulation and physical rehabilitation and therapeutic exercise. In accord with this comprehensive training in musculoskeletal management, numerous sources of evidence demonstrate that chiropractic management is much safer and less expensive than allopathic medical treatment, particularly for treatment of low-back pain. In their extensive review of the literature, Manga et al65 published in 1993 that chiropractic management of low-back pain is superior to allopathic medical management in terms of greater safety, greater effectiveness, and reduced cost; they concluded, “There is an overwhelming body of evidence indicating that chiropractic management of low-back pain is more cost-effective than medical management.” And “There would be highly significant cost savings if more management of LBP [low-back pain] was transferred from medical physicians to chiropractors.” In a randomized trial involving 741 patients, Meade et al66 showed, “Chiropractic treatment was more effective than hospital outpatient management, mainly for patients with chronic or severe back pain… The benefit of chiropractic treatment became more evident throughout the follow up period. Secondary outcome measures also showed that chiropractic was more beneficial.” A 3-year follow-up study by these same authors67 in 1995 showed, “At three years the results confirm the findings of an earlier report that when chiropractic or hospital therapists treat patients with low-back pain as they would in day to day practice those treated by chiropractic derive more benefit and long term satisfaction than those treated by hospitals.” Most recently, in 2004 Legorreta et al68 reported that the availability of chiropractic care was associated with significant cost savings among 700,000 patients with chiropractic coverage compared to 1 million patients whose insurance coverage was limited to allopathic medical treatments. Simple extrapolation of the average savings per patient in this study ($208 annual savings associated with chiropractic coverage) to the US population (295 million citizens in 200579) suggests that, if fully implemented in a nation-wide basis, America could save $61,360,000,000 (more than $61 billion per year) in healthcare annual expenses by ensuring chiropractic for all citizens in contrast to failing to provide such coverage; obviously extrapolations such as this should consider other variables, such as the relatively higher prevalence of injury and death among patients treated with drugs and surgery. 80,81 A literature review by Dabbs and Lauretti72 showed that spinal manipulation is safer than the use of NSAIDs in the treatment of neck pain. Contrasting the rates of manipulation-associated cerebrovascular accidents to the dangers of medical and surgical treatments for spinal disorders, Rosner73 noted, “These rates are 400 times lower than the death rates observed from gastrointestinal bleeding due to the use of nonsteroidal anti-inflammatory drugs and 700 times lower than the overall mortality rate for spinal surgery.” Similarly, in his review of the literature comparing the safety of chiropractic manipulation in patients with low-back pain associated with lumbar disc herniation, Oliphant74 showed that, “The apparent safety of spinal manipulation, especially when compared with other [medically] accepted treatments for [lumbar disk herniation], should stimulate its use in the conservative treatment plan of [lumbar disk herniation].” Increasingly aware of the negative effects of pharmaceutical management of musculoskeletal pain, patients and healthcare providers alike are looking to natural treatments and chiropractic healthcare,75,76 with the hopes of avoiding the risks of iatrogenic disease, such as drug-induced renal failure77,78, hepatotoxicity79,80,
gastrointestinal ulceration and hemorrhage, osteonecrosis, joint degeneration, hypertension, myocardial infarction, and premature death are associated with the non-steroidal anti-inflammatory drugs ("NSAIDs"), non-NSAID analogues such as acetaminophen, and the relatively new selective cyclooxygenase-2 inhibitors (cox-2 inhibitors, or "coxibs"). It is tragically paradoxical that many of the pharmaceutical drugs used for the suppression of arthritis symptoms and advertised as "arthritis relief" actually exacerbate joint destruction and chronic inflammation by interfering with the biosynthesis of the glycosaminoglycans that are essential components of joint cartilage while also promoting destruction of subchondral bone. This places chiropractic physicians in an ethical dilemma when helping patients who have been prescribed potentially dangerous medications by their medical doctors. On the one hand, chiropractic physicians are aware of the research showing that, for example, coxibs provide little clinical benefit while promoting increased cardiovascular mortality and other potentially lethal adverse effects. On the other hand, if a chiropractic physician advises discontinuation of the medication, he or she may be reprimanded for "practicing medicine." It appears that chiropractic physicians will need to obtain limited prescription rights for the sake of helping protect their patients from iatrogenic and drug-induced disease. Given that chiropractic physicians are already duly trained in basic and clinical sciences sufficient for primary care, post-graduate certification courses in pharmacology would be sufficient if additional training is deemed necessary to obtain these prescription rights.

Despite the long-standing historical precedent in which human disease was treated by natural means (i.e., diet modification, botanical medicines, physical modalities) for the majority of human existence, the current healthcare paradigm in America and other Western/industrialized nations is such that treatment with drugs and surgery is labeled "conventional" while natural treatment as with nutritional, botanical, and physical interventions is now described "alternative" and "unconventional." This unfortunate inversion of terms causes confusion among doctors and patients alike while it connotes scientific superiority and cultural sanctification of pharmaceutical and surgical interventions, including those that are dangerous, ineffective, and unduly expensive. Furthermore, the ongoing impact of the slanderous campaign by the American Medical Association (AMA) and other organizations against non-medical healthcare professionals—particularly chiropractic physicians—and inaccurate medical "research" and publications which continue to intentionally denigrate chiropractic and naturopathic medicine in the eyes of the public and other healthcare professionals form additional barriers which subtly yet effectively disenfranchise chiropractic physicians.
In order to document and solidify a large body of interconnected research that has day-to-day relevance for chiropractic and naturopathic physicians, this review will provide an update on the ongoing progress that increasingly supports if not favors the use of natural therapeutics in the management of patients with disorders associated with chronic pain and inflammation. Chiropractic and naturopathic physicians should appreciate the benefits and limitations of natural treatments, as well as nutrient-drug interactions (if any) that may arise in patients using both drug and non-drug treatments. In addition to reviewing the biochemistry of inflammation and eicosanoid metabolism, this article reviews the most commonly used and well-researched nutritional and botanical interventions for the treatment of pain and inflammation, namely “essential fatty acids”, vitamin D, glucosamine and chondroitin sulfate, niacinamide, proteolytic enzymes, Devil’s Claw (Harpagophytum procumbens), Cat’s Claw (Uncaria spp), Willow bark (Salix spp), Boswellia (Boswellia serrata), and ginger (Zingiber officinale). This review will provide chiropractic and naturopathic physicians with clinically useful information to help their patients attain improved health and well-being. Osteoarthritis and chronic low-back pain, the two most prevalent musculoskeletal afflictions, will serve as prototypes for this discussion.

The Biochemistry of Inflammation: From NF-kappaB to Eicosanoids

Numerous influences and pathways are involved in the processes of inflammation. Clinicians are tasked with appreciating these contributions while maintaining a conceptual overview that facilitates effective clinical intervention. As the processes of inflammation have been elucidated with increasing clarity and precision in the past several years, most clinicians will benefit from a brief review of the current understanding of inflammation. Simplistic, linear models of inflammatory processes must be discarded in favor of conceptualizations that incorporate the biochemical, nutritional/botanical, neurogenic inflammation, and psychogenic contributions to inflammation modulation.

The process of inflammation may be said to begin with the translation of an environmental trigger into a biochemical signal that initiates the inflammatory pathway. As discussed in more detail in the paragraphs that follow, environmental triggers can include injury, radiation, infection, oxidative stress, and certain foods, particularly those high in fat and those with a high glycemic index (ie, “simple sugars”). Regardless of the original locus or etiology, each of these stimuli may lead to activation of the NF-kappaB cascade, which is a major pathway for the amplification of inflammatory processes. A ubiquitous nuclear transcription factor that promotes the activation of genes that encode for inflammatory mediators and enzymes, NF-kappaB can be thought of as the major intracellular “amplifier” which ultimately increases the production of the direct mediators of inflammation such as cytokines, prostaglandins, leukotrienes, nitric oxide and other reactive oxygen species (“free radicals”). Preparation for the process of inflammation begins when two subunit proteins—p50 and p65—merge in the cytoplasm to form NF-kappaB, which is kept in an inactive state by inhibitor kappaB (I kB). When triggered by any of the common stimuli listed above,IkB is phosphorylated and destroyed by inhibitor kappaB kinase (IKK). The destruction of IkB allows NF-kappaB to move into the nucleus of the cell where it activates genes encoding for inflammatory responses. These genes then elaborate their inflammatory products such as interleukin-1 (IL-1), IL-6, tumor necrosis factor, and the proinflammatory


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destructive enzymes including nitric oxide synthase, lipoxygenase, cyclooxygenase, and matrix metalloproteinases including collagenase and gelatinase, which destroy connective tissue. Nitric oxide synthase catalyzes the formation of nitric oxide (NO), which plays an important role in the development of peripheral osteoarthritis\(^\text{111}\) and spinal disc degeneration\(^\text{112}\) via oxidative destruction of articular tissues. Cyclooxygenase transforms arachidonic acid into prostaglandins and thromboxanes, which recruit leukocytes to the area of inflammation, exacerbate edema, sensitize peripheral neurons to increased pain perception, and ultimately facilitate the liberation of proteinases, such as matrix metalloproteinases (MMP) which destroy joint structures. Present in several isoforms, the lipoxygenase enzyme acts on arachidonic acid to produce leukotrienes that also increase inflammation, joint destruction, and production of MMP. Overall, this same inflammatory response plays a part in the genesis and perpetuation of numerous inflammatory disorders, such as osteoarthritis, cancer, rheumatoid arthritis and other autoimmune diseases, and numerous conditions associated with pain and inflammation. This process of NF-kappaB activation and modulation of genetic expression is illustrated in Figures 1 and 2.


Figure 1. The creation and activation of NF-kappaB—a crucial step in the amplification of proinflammatory gene expression. Adapted from Vasquez A. Integrative Orthopedics. Natural Health Consulting Corp. (OptimalHealthResearch.com): 2004

NF-kappaB is made from two subunit proteins: p65 and p50.

In the cytosol, NF-kappaB is made "inactive" by inhibitor KappaB.

Exposure to 'stressful stimuli' such as LPS or oxidative stress, activates "inhibitory kappaB kinase", which phosphorylates IkB for destruction.

Once IkB is destroyed, then NF-kappaB is free to bind with DNA.

NF-kappaB enters the nucleus and binds with DNA to activate genes which encode for the increased production of inflammatory mediators.

Increased production of inflammatory mediators - such as cytokines, prostaglandins, leukotrienes - promotes cellular dysfunction and tissue destruction.
Activation of NF-kappaB results in the upregulation of genes which encode for the production of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6 as well as enzymes with generally proinflammatory effects such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and the lipoxygenases (LIPOX). IL-6 stimulates production of C-reactive protein (CRP), which is a sensitive serum marker of inflammation (such as in osteoarthritis and rheumatoid arthritis) and which is associated with an increased risk of cardiovascular disease, progressively deteriorating health and “rapid biological aging” in men and women.\(^\text{113,114}\) INOS increases production of the free radical nitric oxide which is elevated in degenerating spinal discs\(^\text{115}\) and peripheral joints\(^\text{116}\) and which contributes directly to joint destruction via destructive oxidation of articular tissues.\(^\text{117}\) COX-2 is responsible for the conversion of arachidonic acid to prostaglandins, several of which increase the perception of pain by sensitizing peripheral nociceptors\(^\text{118}\) in addition to having a central hyperalgesic effect\(^\text{119}\) and promoting the destruction of articular structures by increasing production of proteolytic enzymes, variously named collagenases, gelatinases, and matrix metalloproteinases.\(^\text{120}\) Similarly, LIPOX catalyzes the conversion of arachidonate to the leukotrienes, which, promote swelling, inflammation, chemotaxis, and tissue destruction via release of increased quantities of proteolytic enzymes. In their anti-inflammatory roles, LIPOX and COX also act on gamma-linolenic acid for the production of the anti-inflammatory 15-HETrE and prostaglandin E-1, respectively, as well as on the omega-3 fatty acids EPA and DHA for the production of anti-inflammatory prostaglandins, leukotrienes, docosatrienes, and resolvins as discussed in the sections that follow. Our discussion of the mechanisms of anti-inflammatory nutritional interventions must also include mention of the phytonutraceutical activation of peroxisome proliferator-activated receptors (PPARs), since fatty acids and selected botanical medicines exert their actions at least in part by activation of PPAR-alpha and PPAR-gamma, which then mediate health-promoting and anti-inflammatory effects that are clinically significant. As fatty acid receptors that influence genetic expression via

\(^{113}\) Kushner I. C-reactive protein elevation can be caused by conditions other than inflammation and may reflect biologic aging. Cleve Clin J Med. 2001 Jun;68(8):535-7


suppression of NF-kappaB activation as well as via NF-kappaB-independent pathways, PPARs when activated in moderation induce numerous beneficial physiologic responses, including direct and indirect anti-inflammatory, anti-cancer, and cardioprotective effects.\textsuperscript{121,122,123} The biochemical flowchart beginning with the dietary intake of fatty acids and ending in the catalyzed production of lipoxygenases and prostaglandins is provided in Figure 3 for omega-3 fatty acids and in Figure 4 for omega-6 fatty acids.

**Figure 3: Metabolism of omega-3 fatty acids and related eicosanoids** From Vasquez A. *Integrative Orthopedics: Natural Health Consulting Corp. (OptimalHealthResearch.com): 2004*

The process of inflammation is not unalterable, nor must pharmaceutical drugs always be employed to modify its course. Numerous dietary, nutritional, and botanical medicines can favorably influence this pathway and the resultant clinical sequelae. Unlike pharmaceutical drugs which are generally designed to target a specific, isolated event along the cascade (as seen with selective COX-2 inhibitors), natural therapeutics generally intervene at numerous junctures, thus allowing for safe yet powerful clinical benefit, generally with nonexistent or negligible adverse effects. Now that readers have a conceptual overview of the inflammatory process, understanding the mechanisms of action for each of the clinical therapeutics listed below will be greatly facilitated.

**Nutrition Against Disease: Interventional Nutrition for the Natural Alleviation of Inflammation and Promotion of Optimal Health**

An altruistic interest in our patients’ care and adherence to scientific principles converge to direct us against the use of popular symptom-suppressing and anti-inflammatory chemical drugs which all-too-often accelerate joint destruction and premature mortality, and instead choose a more rational and holistic approach that improves long-term health outcomes. It is important to note that inflammation is a systemic, body-wide phenomenon which is more appropriately and effectively ameliorated by whole-body improvements than it is to single-intervention therapies that target isolated enzymes and biochemical processes.

The pro-inflammatory nature of the standard American diet: The typical American/Western diet is proinflammatory in nature and contributes directly to the initiation and exacerbation of chronic inflammation and disorders such as joint destruction, diabetes mellitus, cardiovascular disease, and cancer. The chiropractic physician Dr. David Seaman deserves recognition and accolades for his 2002 review of the literature published wherein he proposed the proinflammatory nature of the standard Western diet—typified by the common American diet with an abundance of omega-6 and trans fatty acids, simple sugars and starches, and nutritionally-depleted convenience foods and a serious deficiency of vitamins, minerals, omega-3 fatty acids, and phytonutrients. The concepts that Dr. Seaman promoted as a hypothesis a mere 3 years ago have by this time been scientifically validated in clinical trials in humans. While it has long been documented that increased consumption of refined grains and carbohydrates correlated with the rapid and population-wide onset of “diseases of Western civilization” such as diabetes, arthritis, cardiovascular disease, cancer, and neuropsychiatric illness, we are only now beginning to understand the biochemical and physiologic mechanisms by which dietary components influence physiologic function and, ultimately, health and disease.

Consumption of refined “simple” carbohydrates such as sugar, white bread, pastry, candy, and fruit juice generally leads to a rapid increase in blood glucose followed by an accompanying increase in insulin. While it is well known that elevation in blood glucose following consumption of sugar or fruit juice results in oxidative stress and to suppression of immune function (inhibition of neutrophil-mediated bacterial phagocytosis) for several hours, only recently has glucose consumption (75 grams; 300 calories) been shown to directly promote inflammation and to increase expression of chondrolytic enzymes such as MMP-2 and MMP-9, higher levels of which correlate with and appear to contribute to the progression of joint destruction. Wheat consumption

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124) "Al...consumptions comparable to those...in the synovial fluid of patients treated with the drug, several NSAIDs suppress proteoglycan synthesis... These NSAID-related effects on chondrocyte metabolism... are much more profound in osteoarthritic cartilage than in normal cartilage, due to enhanced uptake of NSAIDs by the osteoarthritic cartilage." Brandt KD. Effects of nonsteroidal anti-inflammatory drugs on chondrocyte metabolism in vitro and in vivo. Am J Med. 1987 Nov 20; 83(5A): 29-34

125) "The results from VIGOR showed that the relative risk of developing a confirmed adjudicated thrombotic cardiovascular event (myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, and transient ischemic attacks) with rofecoxib treatment compared with naproxen was 2.38." McAlister D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286(8):954-9


133) Cordain L. The Paleo Diet: Lose Weight and Get Healthy by Eating the Food You Were Designed to Eat. Indianapolis: John Wiley and Sons, 2002

134) Paye WA. Nutrition and Physical Degeneration: A Comparison of Primitive and Modern Diets and Their Effects. Santa Monica; Price-Pottenger Nutrition Foundation: 1945


has been shown to trigger migraine headaches\textsuperscript{140} in certain patients, and in recent experimental studies the wheat protein gliadin was shown to induce a pro-inflammatory effect via activation of NF-kappaB.\textsuperscript{141,142} Cow’s milk can contribute to adverse effects that can include migraine headache\textsuperscript{143}, otitis media\textsuperscript{144}, and joint inflammation\textsuperscript{145,146}, and it is a rich source of emulsified arachidonic acid which is the precursor to prostaglandins and leukotrienes and their pain-enhancing and joint-destroying properties via prostaglandin-E2 (PG-E2), PG-I2 and PG-F2\alpha, leukotriene-B4, and 5-HETE as illustrated in Figure 4. Rich sources of arachidonic acid such as cow’s milk, beef, liver, pork, and other grain-fed land animal meats add fuel to the inflammatory fire by providing the biochemical precursor (arachidonic acid) which is necessary for the production of prostaglandins, thromboxanes, and leukotrienes that promote and perpetuate processes such as atherosclerosis\textsuperscript{147}, cancer\textsuperscript{148}, arthritis and joint destruction.\textsuperscript{149} To demonstrate the pro-inflammatory effect of a typical Western meal, Aljada et al\textsuperscript{150} administered a single meal of egg and sausage muffin sandwiches with 2 hash browns and documented a postprandial increase of 150\% for NF-kappaB (from \textasciitilde 190 to \textasciitilde 510 AUC) which lasted for approximately 2 hours and was associated with increases in oxidative stress and the inflammatory marker CRP. Thus, data are consistent with the general conclusion that typical Western dietary components including refined carbohydrates, cow’s milk, wheat, and arachidonate-rich animal products will promote pain, free-radical damage, immunosuppression, inflammation, and numerous diseases via molecular, immunologic, and biochemical mechanisms. By extension, treatment of “inflammatory diseases” without addressing the proinflammatory nature of the patient’s diet becomes questionable; anti-inflammatory efficacy almost always improved following dietary improvements as described here.

**The Supplemented Paleo-Mediterranean Diet:** The health-promoting diet of choice for the majority of people is a diet based on abundant consumption of fruits, vegetables, seeds, nuts, omega-3 and monounsaturated fatty acids, lean meats and fish. This diet prohibits and obviates overconsumption of chemical preservatives, artificial sweeteners, and carbohydrate-dominant foods such as candies, pastries, breads, potatoes, grains, and other foods with a high glycemic load and high glycaemic index. This “Paleo-Mediterranean Diet” is a combination of the “Paleolithic” or “Paleo diet” and the well-known “Mediterranean diet”, both of which are well described in peer-reviewed journals and the lay press. The Mediterranean diet is characterized by increased proportions of legumes, nuts, seeds, whole grain products, fruits, vegetables (including potatoes), fish and lean meats, and monounsaturated and n-3 fatty acids.\textsuperscript{151} Consumption of this diet is consistently associated with improvements in insulin sensitivity and reductions in cardiovascular disease, diabetes, cancer, and all-cause mortality.\textsuperscript{152} The Paleolithic diet detailed by collaborators Eaton\textsuperscript{153}, O’Keefe\textsuperscript{154}, and Cordain\textsuperscript{155} is similar to the Mediterranean diet except for stronger emphasis on fruits and vegetables (preferably raw or minimally cooked), omega-3-rich lean meats, and reduced consumption of starchy foods such as potatoes and grains, the latter of which were not staples in the human diet until the last few thousand years. Emphasizing the olive oil and red wine of the Mediterranean diet and the absence of grains and potatoes per the Paleo diet appears to be the way to get the best of both dietary worlds; the remaining diet is characterized by fresh whole fruits, vegetables, nuts (especially almonds), seeds, olive oil, lean meats rich in n-3 fatty acids, and red wine in moderation. In sum, this dietary plan along with the inclusion of garlic and dark chocolate (a rich source of cardioprotective,
Biochemical justification for this type of diet is ample and is well supported by numerous long-term studies in humans wherein both Mediterranean and Paleolithic diets result in dramatic reductions in disease-specific and all-cause mortality. Diets rich in fruits and vegetables are sources of more than 5,000 phytochemicals, many of which have antioxidant, anti-inflammatory, and anti-cancer properties. Oleic acid, squalene, and phenolics in olive oil and phenolics and resveratrol in red wine have antioxidant, anti-inflammatory, and anti-cancer properties and also protect against cardiovascular disease. N-3 fatty acids have numerous health benefits via multiple mechanisms as described in the sections that follow. Increased intake of dietary fiber from fruits and vegetable favorably modifies gut flora, promotes xenobiotic elimination (via flora modification, laxation, and overall reductions in enterohepatic recirculation), and is associated with reductions in morbidity and mortality. Such a “Paleolithic diet” can also lead to urinary alkalinization (average urine pH of ≥ 7.5 according to Sebastian et al) which increases renal retention of minerals for improved musculoskeletal health and which increases urinary elimination of many xenobiotics and nephrotoxins for a tremendous reduction in serum levels and thus adverse effects from chemical exposure or drug overdose. Furthermore, therapeutic alkalinization was recently shown in an open trial with 82 patients to reduce symptoms and disability associated with low-back pain and to increase intracellular magnesium concentrations by 11%. Ample intake of amino acids via dietary proteins supports phase-2 detoxification (amino acid and sulfate conjugation) for proper xenobiotic elimination, provides amino acid precursors for neurotransmitter synthesis and maintenance of mood, memory, and cognitive performance, and prevents the immunosuppression and decrements in musculoskeletal status caused by low-protein diets.

Described here for the first time, the “supplemented Paleo-Mediterranean diet” provides patients the best of current knowledge in nutrition by relying on a foundational diet plan of fresh nuts, seeds, fruits, vegetables, fish, and lean meats which is adorned with olive oil for its squalene, phenolic antioxidant/anti-inflammatory and health benefits from fruits and vegetable favorably modifies gut flora, promotes xenobiotic elimination, and which increases urinary elimination of many xenobiotics and nephrotoxins for a tremendous reduction in serum levels and thus adverse effects from chemical exposure or drug overdose. Inclusive of medical foods such as red wine, garlic, and dark chocolate which may synergize to effect at least a 76% reduction in cardiovascular disease, this diet is supplemented with additional doses of vitamins, minerals, and fatty acids for reasons described in the sections that follow.

**Multivitamin/multimineral supplementation (excluding iron and excess vitamin A and including additional vitamin D):** Leading pioneers in the science of nutritional medicine include the late Roger Williams, whose classic texts *Biochemical Individuality* in 1956 and *Nutrition Against Disease* in 1971 established

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163. Liu RH. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. Am J Clin Nutr 2003; 78(Suppl):S175-S205
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178. Franco OH, Boneva L, de Cate L, Peeters A, Steyler EW, MacKenzie JP. The PolyPharmac: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. BMJ 2004;329(7465):1447-50
the scientific and conceptual rationale for the use of interventional nutrition for the preservation of health and in the treatment of human disease, and Linus Pauling, whose concept of using the ‘‘right molecules’’ such as vitamins, minerals, and other dietary factors opened the field of ‘‘orthomolecular medicine.’’ More recently, Robert Heaney183 advanced our understanding of the adverse effects of chronic subclinical nutritional deficiencies with the phrase ‘‘long-latency deficiency diseases,’’ and Bruce Ames has helped us appreciate the importance and biochemical/physiologic mechanisms of optimal vitamin supplementation184 and high-dose vitamin supplementation185, respectively. Although practitioners of natural healthcare have long advocated the use of supplemental vitamins and minerals, the value of this health-promoting practice has only recently been conceded by allopathic groups such as the Harvard Medical School and the American Medical Association186 who stated in 2002 that, ‘‘Most people do not consume an optimal amount of all vitamins by diet alone’’ and ‘‘...it appears prudent for all adults to take vitamin supplements.’’ Vitamin and mineral supplementation helps compensate for inadequacies of foods grown in depleted soils or by non-organic techniques187,188, and to ensure adequate nutritional intake during times of dietary indiscretion (reduced intake) or illness (increased utilization or excretion). Since vitamins commonly function as enzyme cofactors, their daily consumption is required to maintain enzymatic activities, and their provision in supraphysiologic quantities can be used to overcome genotypic defects and facilitate activity in variant (ie, ‘‘slow’’ or ‘‘defective’’) enzymes.189 Vitamin E supplementation must be in the form of mixed tocopherols and include a high (~40%) percentage of gamma-tocopherol190 to avoid the purported adverse effects of alpha-tocopherol when used alone191, and vitamin E appears to improve the action of insulin192 and to ameliorate neurodegenerative disorders193, osteoarthris194,195, inflammation in diabetics196, and may provide protection against the effects of urban pollution.197 Excess vitamin A clearly carries a risk of hepatotoxicity198 and is controversially associated with an increased risk for birth defects when consumed in doses greater than 10,000 IU per day by pregnant women. The most notable exception to the generally health-promoting benefits of mineral supplementation is iron, which should not be administered to those who are not iron deficient due to its oxidative and oncogenic properties.199 Indeed, iron overload is quite common in the general population200 and particularly among patients with musculoskeletal pain201,202,203 and is causatively associated with numerous maladies including cardiovascular disease204,205, cancer206,207, diabetes mellitus208,209, hypogonadism and infertility210, thyroid disorders210, infectious disease211, and spinal and peripheral arthropathy.212,213,214,215

Vitamin D deserves special attention in the discussion of vitamins, particularly in light of the recent upsurge in research documenting its manifold health benefits216,217 and the importance of obtaining and maintaining optimal serum
levels. Although cholecalciferol is a prehormone naturally produced in the skin by chemical reactions induced by exposure to sunlight (UVB radiation), it is also found in small amounts in a few foods and is therefore also referred to as "vitamin D." Insufficient dietary sources of vitamin D along with insufficient sun exposure have created an epidemic of vitamin D deficiency in America and other industrialized nations, which contributes to the development of mental depression, diabetes mellitus, and other conditions.

Vitamin D deficiency is common in many of these and other illnesses. Doctors can easily assess vitamin D status with measurement of serum 25-OH-vitamin D, and we recently proposed that serum levels of 40 - 65 ng/mL (100 - 160 nmol/L) as shown in Figure 5 from Vasquez et al. would provide optimal protection from the many diseases associated with vitamin D deficiency while minimizing risk for adverse effects. Chiropractic and naturopathic physicians are aware that vitamin D deficiency is common in patients with generalized musculoskeletal pain and low-back pain, that vitamin D has anti-inflammatory benefits, and that treatment with vitamin D can safely lead to dramatic reductions in musculoskeletal pain in a large percentage of patients.

Figure 5. Proposed normal and optimal ranges for serum 25(OH)D levels based on current research. From Vasquez A, Integrative Orthopedics. (OptimalHealthResearch.com): 2004

<table>
<thead>
<tr>
<th>Excess vitamin D</th>
<th>&gt; 80 ng/mL (200 nmol/L)</th>
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<tr>
<td>Proposed optimal range</td>
<td>40 - 65 ng/mL (100 - 160 nmol/L)</td>
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<tr>
<td>Insufficiency range</td>
<td>&lt; 20 - 40 ng/mL (50 - 100 nmol/L)</td>
</tr>
<tr>
<td>Deficiency</td>
<td>&lt; 20 ng/mL (50 nmol/L)</td>
</tr>
</tbody>
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227) Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. Recent Results Cancer Res. 2003;164:371-7
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233) Thys-Jacobs S. Vitamin D and calcium in menstrual migraine. Headache. 1994 Oct;24(9):544-6
244) Masood H, Naranj AP, Bhat IA, Shah GN. Persistent limb pain and raised serum alkaline phosphatase in Kashmiri patients with subclinical hypovitaminosis D. Indian J Physiol Pharmacol. 1989;33:259-61
Generally speaking, vitamin/mineral supplementation has been shown in clinical trials to improve nutritional status and reduce the risk for chronic diseases, improve mood, enhance wellbeing, potentiate antidepressant drug treatment, alleviate migraine headaches (when used with diet improvement and fatty acids), improve immune function and infectious disease outcomes in the elderly (especially diabetics), reduce morbidity and mortality in patients with HIV infection, alleviate premenstrual syndrome, ameliorate bipolar disorder, reduce violence and antisocial behavior in children and incarcerated young adults (when used with essential fatty acids), improve scores of intelligence in children, and to benefit children with attention deficit and hyperactivity disorder. Vitamin supplementation has anti-inflammatory benefits as evidenced by significant reduction in CRP in a double-blind placebo-controlled trial. In an increasingly toxic world, wherein the average American shows a body burden of more than a dozen different pesticides and where toxic metal accumulation is commonplace, vitamin and mineral supplementation becomes even more necessary to help protect against oxidative damage caused by pollution and heavy metals, and to support the nutrient-dependent detoxification reactions that are required for the proper elimination of xenobiotics.

Of course, dietary modification and nutritional supplementation needs to be tailored to the needs, goals, health status, and pharmacotherapy (if any) of each individual patient; however, the recommendations included in this article will be safe and beneficial for the vast majority of patients. An overview of vitamin and mineral supplementation is provided in Appendix A.

“Essential fatty acids”: To the extent that most fatty acids are neither produced de novo nor produced in sufficient amounts for the attainment of optimal health, nearly all of the dietary fatty acids discussed here can be considered “essential” insofar as they must be supplied from diet or supplementation. Strictly speaking, the term “essential fatty acids” (EFA) refers only to n-3 alpha-linolenic acid and n-6 linoleic acid, both of which are the “first in line” in their respective n-3 and n-6 categories.

Fatty acids obtained from diet, and endogenous production effect powerful biological actions via numerous mechanisms such as 1) altering cell membrane/receptor function, 2) modulating gene transcription, 3) modulating hormone production and reception, and 4) shifting eicosanoid metabolism from proinflammatory to anti-inflammatory.

References:

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280) Menzel DB. Nutritional needs in environmental intoxication: vitamin E and air pollution, an example. Environ Health Perspect. 1997;105:281-91
281) Menzel DB. Nutritional needs in environmental intoxication: vitamin E and air pollution, an example. Environ Health Perspect. 1997;105:281-91
relatively less inflammatory and perhaps “anti-inflammatory.” Three major groups of unsaturated fatty acids are present in the human diet—n-3 (ALA, EPA, DHA), n-6 (linoleic acid, GLA, arachidonic acid), and n-9 (oleic acid). Based on a survey of the literature including recent reviews by Vasquez and Larsson et al, we may reasonably conclude that the fatty acids with the most clinically significant health-promoting benefits are the n-3 fatty acids ALA, EPA, and DHA, the n-6 fatty acid GLA, and the n-9 fatty acid oleic acid, as summarized in the sections that follow. The n-6 fatty acids linoleic acid and arachidonic acid show proinflammatory, hyperalgesic, atherosclerotic, and oncogenic properties via numerous mechanisms and should be minimized in the diet of most patients.287,288,289

alpha-linolenic acid (ALA): ALA is an essential fatty acid as it is the “first in line” in the family of omega-3 polyunsaturated fatty acids (PUFA). Sources include flaxseed oil (57% ALA), canola oil (9% ALA), soy oil, breast milk, English/black walnuts, soybeans, pine nuts, green vegetables, and beans. Conversion of ALA to the more biologically active EPA and DHA does not reliably or efficiently occur in humans.290 Milk, English/black walnuts, soybeans, pine nuts, green vegetables, and beans. Conversion of ALA to the more biologically active EPA and DHA does not reliably or efficiently occur in humans.290 No increase in DHA has been consistently observed in humans after supplementation of ALA292; in fact, supplementation with flax seed oil has actually been shown to reduce DHA levels in humans.293 Although ALA can reduce blood pressure and cardiovascular mortality,294 it does not reduce serum lipids as do EPA and DHA. In a study of men with metabolic syndrome, ALA was shown to have anti-inflammatory benefits independent of its conversion to EPA or DHA.295 The mechanism of action appears to be downregulation of NF-KappaB (the main “amplifier” for the expression of proinflammatory gene products296) rather than the direct modulation of eicosanoid biosynthesis. One study using flaxseed oil as a source of ALA to treat rheumatoid arthritis found no clinical or biochemical benefit (i.e., no change in Hgb, CRP, ESR)297; however, the poor results of this study may have been due to the inferior quality of the flaxseed oil product that was used which only supplied 32% ALA compared with the much higher concentration of 57% found in most products. Moderate intakes of ALA from flaxseed oil profoundly reduce production of proinflammatory prostaglandins (e.g., PG-E2, measured by urinary excretion) by 52% to 85% in humans298 which is superior to the 42% reduction induced by rofecoxib (the drug “Vioxx”).299 In summary, increased intake of ALA appears to provide cardioprotective300 and anti-inflammatory benefit31,302, and ALA can help reduce the frequency and severity of migraine headaches when used as part of a comprehensive natural treatment plan that includes diet change and nutritional supplementation.303

Eicosapentaenoic acid: EPA, 20:5n3: EPA is essentially absent in vegan diets since the major dietary source is fish oil. Dietary EPA is incorporated into cell membranes where it modulates neurotransmitter and hormone receptor function and where it is stored before liberation by phospholipase for eicosanoid production. EPA-derived eicosanoids have anti-inflammatory properties, including a reduction in the production of pro-inflammatory eicosanoids such as LT-B4, PAFs, and cytokines such as TNF-alpha and IL-1, and a large

291 "Indo and Ghoshroushie showed that while keeping the amount of dietary LA constant, 3.7 g ALA appears to have biological effects similar to those of 0.3 g long-chain n-3 PUFAs with conversion of 11 g ALA to 1 g long-chain n-3 PUFAs." Simopoulos AP. Essential fatty acids in health and chronic disease. Am J Clin Nutr 1999 Sep;70(3 Suppl):S650-S659
292 Frances CA, Connor SL, Botweic LC, Connor WE. Supplementing lactating women with flaxseed oil does not increase docosahexaenoic acid in their milk. Am J Clin Nutr 2003 Jan;77(1):228-33
293 "Linear relationships were found between dietary alpha-LA and EPA in plasma fractions and in cellular phospholipids. ... There was an inverse relationship between dietary alpha-LA and docosahexaenoic acid concentrations in the phospholipids of plasma, neutrophils, mononuclear cells, and platelets." Mantross E, James MJ, Gibson RA, Cleland LG. Differences exist in the relationships between dietary linoleic and alpha-linolenic acids and their respective long-chain metabolites. Am J Clin Nutr 1995 Feb;61(2):320-4
295 "CONCLUSIONS: Dietary supplementation with ALA for 3 months decreases significantly CRP, SAA and IL-6 levels in dysbiotic patients. This anti-inflammatory effect may provide a possible additional mechanism for the beneficial effect of plant n-3 polyunsaturated fatty acids in primary and secondary prevention of coronary artery disease." Rallidis LS, Paschos G, Likois GK, Vetelosanitou AH, Vrasidas G, Zampelas A. Dietary alpha-linolenic acid decreases C-reactive protein, serum amyloid A and interleukin-6 in dysbiotic patients. Atherosclerosis. 2003 Apr;172(2):237-42
301 "CONCLUSIONS: Dietary supplementation with ALA for 3 months decreases significantly CRP, SAA and IL-6 levels in dysbiotic patients. This anti-inflammatory effect may provide a possible additional mechanism for the beneficial effect of plant n-3 polyunsaturated fatty acids in primary and secondary prevention of coronary artery disease." Rallidis LS, Paschos G, Likois GK, Vetelosanitou AH, Vrasidas G, Zampelas A. Dietary alpha-linolenic acid decreases C-reactive protein, serum amyloid A and interleukin-6 in dysbiotic patients. Atherosclerosis. 2003 Apr;172(2):237-42
reduction in PG-E2 and TX-B2.304 Unfortunately, EPA can decrease production of DGLA, the metabolite of GLA that has health-promoting properties.305 EPA doses of at least 4 grams per day are needed to increase bleeding time.306 EPA supplementation reduces urinary excretion of calcium in patients with hypercalciuria and may therefore help prevent the development of calcium urolithiasis.307 Due to its anti-inflammatory, membrane-enhancing, and other nutrigenomic benefits, EPA supplementation has proven beneficial for patients with lupus, cancer,309 borderline personality disorder,310 mental depression,311,312,313 schizophrenia,314 and osteoporosis (when used with GLA).315

**Docosahexaenoic acid: DHA, 20:6n-3:** DHA is found only in plants of the sea, phytoplankton/microalgae, and consumers of microalgae (such as fish). Like EPA, DHA is an important component of cell membranes and generally appears to improve cell membrane function via improving receptor function and signal transduction. In late bioactive metabolites of DHA—the docosatrienes and resolvins—were discovered to mediate potent anti-inflammatory benefits.316 Animal studies have shown that induction of DHA deficiency causes memory deficits and a reduction in hippocampal cell size317, and DHA deficiency in humans is consistently associated with mental depression, learning disorders (e.g., ADD/ADHD), and other neuropsychiatric disorders such as schizophrenia—these findings are consistent with the view that the nervous system has an absolute requirement for DHA for proper function.318 DHA appears essential for optimal cognitive function in infants and adults, and DHA in fish oil provides some protection against thrombosis, arrhythmia, cardiovascular death, Alzheimer’s disease,319 otitis media (when used with nutritional supplementation320), and coronary restenosis following angioplasty.321 Supplementation with DHA (often in the form of fish oil, which includes EPA) has been shown to benefit patients with bipolar disorder,322 Crohn’s disease,323 rheumatoid arthritis,324,325,326 lupus,327 cardiovascular disease,328 psoriasis,329, and cancer.330 DHA appears to have an “anti-stress” benefit manifested by 30% reductions in norepinephrine and improved resilience to psychoemotional stress.331,332 Supplementation with EPA+DHA in fish oil is extremely safe and reduces all-cause mortality.333

**Gamma (γ-linolic acid: GLA, 18:3n-6:** The most powerful health-promoting n-6 fatty acid, GLA is found in varying concentrations in evening primrose oil, borage seed oil, hemp seed oil, and black currant seed oil. Most if not all of the actions of GLA are mediated following its elongation to the bioactively active DGLA, from which eicosanoids that have cardioprotective and anti-inflammatory benefits are derived. Low levels of DGLA...
are associated with increased risk for stroke and myocardial infarction. GLA metabolites reduce the formation of the arachidonate-derived 2-series prostaglandins, 4-series leukotrienes and platelet-activating factor. GLA supplementation results in the formation of two biologically active metabolites from DGLA formed by cyclooxygenase and lipooxygenase. Prostaglandin E-1 (PG-E1) is the main metabolite formed from DGLA by cyclooxygenase and its production is increased by vitamin C. PG-E1 decreases platelet aggregation, inhibits vascular smooth muscle cell proliferation in vitro, helps lower blood pressure. PG-E1 has anti-inflammatory benefits and is probably the most potent prostaglandin with respect to bronchodilation. Production of PG-E1 is increased by n-3 fatty acids. 15-HETE is the second main metabolite from GLA/DGLA and is formed from DGLA via 15-lipoxygenase. 15-HETE has potent anti-inflammatory action by inhibiting the conversion of arachidonic acid to leukotrienes via inhibition of 5-lipoxygenase and 12-lipoxygenase. Clinically, this is very important because several common and serious health problems including allergy, asthma, cardiovascular disease, and cancer are at least partially dependent upon the function of lipooxygenase for the production of leukotrienes. Notably, prostate cancer cells can be rapidly killed in vitro by lipooxygenase inhibition. Clinical benefit associated with GLA supplementation is seen in patients with, eczema, breast cancer (when used with tamoxifen), premenstrual syndrome, rheumatoid arthritis, diabetic neuropathy (when used with ALA), and respiratory distress syndrome (when used with EPA).

Oleic acid: N-9 oleic acid appears to have health-promoting benefits, namely cardioprotection and anti-inflammation which are both partially mediated via suppression of NF-kappaB. Most clinical trials in humans have used olive oil as a source of oleic acid, and since olive oil is a complex mixture of oleic acid, squalene, and phenolic antioxidants/anti-inflammatories, therefore, determination of the benefits of oleic acid alone (i.e., without squalene and phenolics) is difficult. Other sources of oleic acid include flax seed oil and borage oil. Olive oil should be consumed in the diet to attain sufficient quantity of oleic acid along with the health-promoting, anti-inflammatory, anti-cancer, and cardioprotective squalene and phenolic antioxidants. Dietary consumption of olive oil is consistently associated with reductions in cancer and cardiovascular disease, particularly when used as a component of a health-promoting diet.

Nutrigenomics: Modulation of Genetic Expression via Interventions in Nutrition
The study of how dietary components and nutritional supplements influence genetic expression is referred to as "nutrigenomics" or "nutritional genomics" and has been described as "the next frontier in the postgenomic era." Various nutrients have been shown to modulate genetic expression and thus alter phenotypic manifestations of disease by upregulating or downregulating specific genes, interacting with nuclear receptors, altering hormone receptors, and modifying the influence of transcription factors, such as proinflammatory NF-kappaB and the anti-inflammatory peroxisome-proliferator activated receptors (PPARs). Indeed, the previous view that nutrients only interact with human physiology at the metabolic/post-transcriptional level


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must be updated in light of current research showing that nutrients can, in fact, modify human physiology and phenotype at the genetic/pre-transcriptional level.

Fatty acids and their end-products modulate gene expression in several ways, as these examples will illustrate. In general, n-3 fatty acids decrease inflammation and promote health while n-6 fatty acids (except for GLA, which is generally health-promoting) increase inflammation, oxidative stress, and the manifestation of disease. Corn oil, probably as a result of its high n-6 LA (linoleic acid) content, rapidly activates NF-kappaB and thus promotes tumor development, atherosclerosis, and elaboration of pro-inflammatory mediators such as TNFα. Similarly, n-6 arachidonic acid increased production of the free radical superoxide approximately 4-fold when added to isolated Kupffer cells in vitro. Prostaglandin-E2 is produced from arachidonic acid by cyclooxygenase and increases genetic expression of cyclooxygenase and IL-6; thus, inflammation manifested by an increase in PG-E2 leads to additive expression of cyclooxygenase, which further increases inflammation and elevates C-reactive protein. Some of the unique health-promoting effects of GLA are nutrigenomically mediated via activation of PPAR-gamma, resultant inhibition of NF-kappaB, and impairment of estrogen receptor function. Supplementation with ALA leads to a dramatic reduction of prostaglandin formation in humans and this effect is probably mediated by downregulation of proinflammatory transcription, as evidenced by reductions in CRP, IL-6, and serum amyloid A. EPA appears to exert much of its anti-inflammatory benefit by suppressing NF-kappaB activation and thus reducing elaboration of proinflammatory mediators. EPA also indirectly modifies gene expression and cell growth by reducing intracellular calcium levels and thus activating protein kinase N1-2Alpha and inhibits protein synthesis through the delayed initiation of translation, thereby mediating an anti-cancer benefit. DHA is the precursor to docosatrienes and resolvins which downregulate gene expression for proinflammatory IL-1, inhibit of TNF, and reduce neutrophil entry to sites of inflammation. Oxidized EPA activates PPAR-alpha and thereby suppresses NF-kappaB and the activation of proinflammatory genes. Other nutrients that inhibit the activation of NF-kappaB include vitamin D, lipic acid, green tea, rosemary, grape seed extract, resveratrol, caffeic acid phenethyl ester (CAPE) from bee propolis, indole-3-carbinol, N-acetyl-L-arginine, and resveratrol's anticarcinogenic, anti-inflammatory, and growth-modulatory effects may thus be partially ascribed to the inhibition of activation of NF-kappaB and AP-1 and the associated kinases.

References:

Therefore, we see that fatty acids and nutrients directly affect gene expression by complex and multiple mechanisms, as graphically demonstrated in Figure 6, and the synergism and potency of these numerous anti-inflammatory nutraceuticals supports the rationale for the use of nutrition and select botanicals for the safe and effective treatment of inflammatory disorders.

Figure 6. An integrated model of fatty acid effects on eicosanoid production and nutrigenomics. Used here with permission of Vasquez. (Vasquez A. Reducing Pain and Inflammation Naturally. Part 2: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression. Nutr Perspect 2005; January: 5-16)
Glucosamine and chondroitin sulfate: Glucosamine and chondroitin are the “building blocks” from which cartilage is built and oral supplementation is intended to enhance cartilage anabolism and to thus counteract the enhanced cartilage catabolism seen in destructive arthritis processes. Clinical trials with glucosamine and chondroitin sulfates have shown consistently positive results in clinical trials involving patients with osteoarthritis of the hands, hips, knees, temporomandibular joint, and low-back. For example, glucosamine sulfate was superior to placebo for pain reduction and preservation of joint space in a 3-year clinical trial in patients with knee osteoarthritis. Arguments against the use of glucosamine due to inflated concern about inefficacy or exacerbation of diabetes are without scientific merit as evidenced by a 90-day trial of diabetic patients consuming 1500 mg of glucosamine hydrochloride with 1200 mg of chondroitin sulfate which showed no significant alterations in serum glucose or hemoglobin A1c and by the previously cited 3-year study which found significant clinical benefit and no adverse effects on glucose homeostasis.

The adult dose of glucosamine sulfate is generally 1500-2000 mg per day in divided doses, and the dose of chondroitin sulfate is approximately 1000 mg daily. Both treatments are safe for multiyear use, and rare adverse effects include allergy and nonpathologic gastrointestinal upset. Clinical benefit is generally significant following 4-6 weeks of treatment and is maintained for the duration of treatment. In contrast to coxib and other mislabeled “anti-inflammatory” drugs that consistently elevate the incidence of cardiovascular disease, death, and other adverse effects, supplementation with chondroitin sulfate appears to safely reduce the pain and disability associated with osteoarthritis while simultaneously reducing incidence of cardiovascular morbidity and mortality.

In a study with animals that spontaneously develop atherosclerosis, administration of chondroitin sulfate appears to have induced regression of existing atherosclerosis. In a six-year study with 120 patients with established cardiovascular disease, 60 chondroitin-treated patients suffered 6 coronary events and 4 deaths compared to 42 events and 14 deaths in a comparable group of 60 patients receiving “conventional” therapy; chondroitin-treated patients reported enhancement of well-being while no adverse clinical or laboratory effects were noted during the 6 years of treatment.
Nicotinamide: Nicotinamide is a form of vitamin B3 that was first shown to be highly effective in the treatment of osteoarthritis by Kaufman more than 50 years ago. Furthermore, Kaufman’s documentation of an “anti-aging” effect of vitamin supplementation in general and nicotinamide therapy in particular is consistent with recent experimental data demonstrating rapid reversal of aging phenotypes by nicotinamide through possible modulation of histone acetylation. A recent double-blind placebo-controlled repeat study found that nicotinamide therapy improved joint mobility, reduced objective inflammation as assessed by ESR, reduced the impact of the arthritis on the activities of daily living, and allowed a reduction in medication use. While the mechanism of action is probably multifaceted, inhibition of joint-destructing nitric oxide appears to be an important benefit. The standard dose of 500 mg given orally 6 times per day is more effective than 1,000 mg 3 times per day. Hepatic dysfunction is rare when daily doses are kept below 3,000 mg per day, yet Gaby suggests measurement of liver enzymes after 3 months of treatment and yearly thereafter. Antirheumatic benefit is generally significant following 2-6 weeks of treatment, and patients may also notice an anxiolytic benefit, which is probably due to the binding of nicotinamide to GABA/benzodiazepine receptors.

Vitamin D (cholecalciferol): Vitamin D insufficiency is epidemic in the United States and is extremely prevalent (>90%) among patients with chronic musculoskeletal pain, limb pain, and low back pain. The mechanism by which this pain is produced has been clearly elucidated: 1) vitamin D deficiency causes a reduction in calcium absorption, 2) production of parathyroid hormone (PTH) is increased to maintain blood calcium levels, 3) PTH results in increased urinary excretion of phosphorus, which leads to hypophosphatemia, 4) insufficient calcium phosphate results in deposition of unmineralized collagen matrix on the endosteal (inside) and periosteal (outside) of bones, 5) when the collagen matrix hydrates and swells, it causes pressure on the sensory-innervated periosteum resulting in pain. In patients with vitamin D deficiency, oral supplementation with vitamin D clearly produces anti-inflammatory benefits, and treatment with vitamin D can safely lead to dramatic reductions in musculoskeletal pain in a large percentage of patients. Routine annual measurement of vitamin D status should be the standard of care, since failure to diagnose vitamin D deficiency and to provide adequate replacement doses are both ethically questionable and scientifically unjustifiable in light of the low cost, manifold benefits, rare adverse effects, and high prevalence of vitamin D deficiency. Physiologic requirements are approximately 4,000 IU per day in men and can only be achieved with high-dose oral supplementation or full-body sun exposure on a frequent or preferably daily basis. As reviewed in the recent monograph by Vasquez et al., relative contraindications include the use of thiazide diuretics or presence of a vitamin D hypersensitivity syndrome such as primary hyperparathyroidism, adenral insufficiency, hyperthyroidism, hypothyroidism, or granulomatous disease such as sarcoidosis, Crohn’s disease, or tuberculosis. Serum calcium is periodically monitored in patients receiving moderate doses of vitamin D (adult range 4,000 – 10,000 IU per day), as hypercalcemia is the best laboratory indicator of vitamin D excess. High doses of vitamin D (up to 100,000 IU per day) have been safely used during pregnancy, and periodic testing of serum calcium is required to monitor for hypercalcemia.
**Proteolytic enzymes:** Oral administration of proteolytic enzymes (such as pancreatin, bromelain, papain, trypsin and alpha-chymotrypsin) for therapeutic purposes is well established on physiologic, biochemical, and clinical grounds, and a brief review of their historical use is warranted. One of the first experimental studies was published by Beard in 1906 in the *British Medical Journal* wherein he showed that proteolytic enzymes significantly inhibited tumor growth in mice with implanted tumors, and a year later in that same journal, Cutfield reported tumor regression and other objective improvements in a patient treated with proteolytic enzymes. In the American research literature, anti-cancer effects of proteolytic enzymes were reported during this same time in the *Journal of the American Medical Association* in anecdotal case reports of patients with fibrosarcoma, breast cancer, and head and neck malignancy—all of whom responded positively to the administration of proteolytic enzymes; no adverse effects were seen. Although nearly a century would pass before Beard’s study and results were replicated with modern techniques by now it is well established that orally administered proteolytic enzymes are well absorbed from the gastrointestinal tract into the systemic circulation and that the anti-tumor, anti-metastatic, anti-inflammatory, analgesic, and anti-edematous actions result from synergism between a variety of mechanisms of action, including the dose-dependent stimulation of reactive oxygen species production and anti-cancer cytotoxicity in human neutrophils, a pro-differentiative effect, reduction in PG-E2 production, reduction in substance P production, modulation of adhesion molecules and cytokine levels, fibrinolytic effects and an anti-thrombotic effect mediated at least in part by a reduction in 2-series thromboxanes. Unfortunately, enthusiasm for the enzyme treatment of cancer waned prematurely when trypsin was judged to not be a “miracle cure”, when the mechanism of action could not be determined, and as enthusiasm surrounding drug and radiation treatments grabbed the attention of allopathic. However, modern controlled clinical trials in cancer patients have established the value of enzyme therapy, which produces important clinical benefit (e.g., symptom reduction and prolonged survival) for little cost and with negligible adverse effects. Research in other clinical applications for proteolytic enzymes has consistently shown benefit when properly formulated and manufactured preparations are administered appropriately in the treatment of cellulitis, diabetic ulcers, sinusitis, and bronchitis. For example, in a double-blind placebo-controlled trial with 59 patients, Taub documented that oral administration of bromelain significantly promoted the resolution of congestion, inflammation, and edema in patients with acute and chronic refractory sinusitis; no adverse effects were seen in any patient.

When not treating patients with cancer or infectious disease, chiropractic and naturopathic physicians today use these enzymes mostly for the treatment of inflammatory and injury-related disorders. Reporting from the Tulane University Health Service Center, Trickett reported that a papain-containing preparation benefited 40 patients with various injuries (e.g., contusions, sprains, lacerations, strains, fracture, surgical repair, and muscle tears); no adverse effects were seen. In a recent open trial of patients with knee pain, Walker et al. found a dose-dependent reduction in pain and disability as well as a significant improvement in psychological well-being in patients consuming bromelain orally. Most of the bromelain studies reviewed by Brien et al were suggestive of a positive benefit in patients with knee osteoarthritis, but inadequate dosing clearly prohibited the attainment of optimal results. Bromelain also attenuates experimental contraction-induced

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441) Wiggins RH. Case of Multiple Fibrosarcoma of the Tongue, With Remarks on the Use of Trypsin and Amylopism in the Treatment of Malignant Disease. *Journal of the American Medical Association* 1906; 47: 2003-8
455) Gaspani L, Limiroli E, Ferrario P, Bianchi M. In vivo and in vitro effects of bromelain on PGE(2) and SP concentrations in the inflammatory exudate in rats. *Pharmazie.* 1999;54(6):496-500
skeletal muscle injury, reduces production of hyperalgesic PG-E2 and substance P, is generally effective in the amelioration of trauma-induced injury, edema, and inflammation, and is practically non-toxic. Although bromelain may be used in isolation, enzyme therapy is generally delivered in the form of polypenzyme preparations containing pancreatic, bromelain, papain, amylase, lipase, trypsin and alpha-chymotrypsin.

**Devil’s Claw (Harpagophytum procumbens):** Harpagophytum has a long history of use in the treatment of musculoskeletal complaints, and recent clinical trials have substantiated its role as an effective analgesic suitable for clinical utilization. At least 12 clinical trials have been published on the use of *Harpagophytum* in the treatment of musculoskeletal pain, and all trials have found the botanical to be clinically valuable and with adverse effects comparable to placebo. Harpagophytum’s clinical benefit appears to derive chiefly from its analgesic effect which appears to be mediated at least in part by activating antinociceptive neurons located in the periaqueductal gray, and administration of the herb does not alter eicosanoid production in humans.

In patients with osteoarthritis of the hip and knee, *Harpagophytum* is just as effective yet safer and better tolerated than the drug diclofenac. In a study involving 183 patients with low-back pain, *Harpagophytum* was found to be safe and moderately effective in patients with “severe and unbearable pain” and radiating pain with neurologic deficit. Most recently, *Harpagophytum* was studied in a head-to-head clinical trial with the formerly popular but dangerous selective cox-2 inhibitor Vioxx (rofecoxib); the data indicate that *Harpagophytum* was safer and at least as effective. About 8% of patients may experience diarrhea or other mild gastrointestinal effects, and fewer patients may experience dizziness; *Harpagophytum* may potentiate anticoagulants. Treatment should be continued for at least 4 weeks, and many patients will continue to improve after 8 weeks from the initiation of treatment. Products are generally standardized for the content of harpagosides, with a target dose of at least 30 and preferably up to 60 mg harpagoside per day. However, the whole plant is considered to contain effective constituents, not only the iridoid glycosides.

**Cat’s Claw (Uncaria spp):** Thirty patients with osteoarthritis of the knees benefited from highly-concentrated freeze-dried aqueous extraction of *U. guianensis* dosed at 1 capsule of 100 mg daily. Reduction in pain was approximately 36% at 4 weeks. A year-long study of patients with active rheumatoid arthritis (RA) treated with sulfasalazine or hydroxychloroquine showed “relative safety and modest benefit” of *Uncaria tomentosa* (UT). *Uncaria* inhibits NF-κB, TNFα, COX-2, and thus PGE-2 production. No major adverse effects have been noted; however, headache and dizziness are more common in patients receiving *Uncaria* than...
in patients in placebo groups. This herb should probably not be used during pregnancy based on its historical use as a contraceptive. Most products are between 250-500 mg and are standardized to 3.0% alkaloids and 15% total polyphenols dose 1-3 times per day. Other studies with *Uncaria tomentosa* have shown enhancement of post-vaccination immunity and enhancement of DNA repair in humans.

**Willow bark (Salix spp):** In a double-blind placebo-controlled clinical trial in 210 patients with moderate/severe low-back pain (20% of patients had positive straight-leg raising test), extract of willow bark showed a dose-dependent analgesic effect with benefits beginning in the first week of treatment. In a head-to-head study of 228 patients comparing willow bark (standardized for 240 mg salicin) with Vioxx (rofecoxib), treatments were equally effective yet willow bark was safer and 40% less expensive. Because willow bark’s salicylates were the original source for the chemical manufacture of acetylsalicylic acid (aspirin), researchers and clinicians have erroneously mistaken willow bark to be synonymous with aspirin; this is certainly inaccurate and therefore clarification of willow’s mechanism of action will be provided here. Aspirin has two primary effects via three primary mechanisms of action: 1) anticoagulant effects mediated by the acetylation and permanent inactivation of thromboxone-A synthase, which is the enzyme that makes the powerful proaggregatory thromboxane-A2; 2) antiprostaglandin action via acetylation of both isoforms of cyclooxygenase (COX-1 inhibition 25-166x more than COX-2) with widespread inhibition of prostaglandin formation, and 3) antiprostaglandin formation via “retroconversion” of acetylsalicylic acid into salicylic acid which then inhibits cyclooxygenase-2 gene transcription. Notice that the acetylation reactions are specific to aspirin and thus actions #1 and #2 are not seen with willow bark; whereas #3—inhibition of COX-2 transcription by salicylates—appears to be the major mechanism of action of willow bark extract. Proof of this principle is supported by the lack of adverse effects associated with willow bark in the research literature. If willow bark were pharmacodynamically synonymous with aspirin, then we would expect case reports of gastric ulceration, hemorrhage, and Reye’s syndrome to permeate the research literature; this is not the case and therefore—with the exception of possible allergic reactions in patients previously allergic to aspirin and salicylates—extensive “warnings” on willow bark products are unnecessary. Salicylates are widely present in fruits, vegetables, herbs and spices and are partly responsible for the anti-cancer, anti-inflammatory, and health-promoting benefits of plant consumption. With willow bark products, the daily dose should not exceed 240 mg of salicin, and products should include other components of the whole plant. Except for rare allergy in patients previously sensitized to aspirin or salicylates, no adverse effects are known, yet use during pregnancy and with anticoagulant medication is discouraged.

**Boswellia (Boswellia serrata):** Boswellia shows anti-inflammatory action via inhibition of 5-lipoxygenase with no apparent effect on cyclooxygenase. A recent clinical study showed that *Boswellia* was able to reduce pain and swelling while increasing joint flexion and walking distance in patients with osteoarthritis of the knees. While reports from clinical trials published in English are relatively rare, a recent abstract from the German medical research stated, “In clinical trials promising results were observed in patients with rheumatoid arthritis, chronic colitis, ulcerative colitis, Crohn’s disease, bronchial asthma and peripheral brains edema.” Additional recent studies have confirmed the effectiveness of *Boswellia* in the treatment of asthma and ulcerative colitis. Minor gastrointestinal upset has been reported. Products are

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**References:**


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generally standardized to contain 37.5–65% boswellic acids, which are currently considered the active constituents with clinical benefit. The target dose is approximately 150 mg of boswellic acids thrice daily; dose and number of capsules/tablets will vary depending upon the concentration found in differing products.

Ginger (Zingiber officinale): Ginger is a well known spice and food with a long history of consumption and use as an anti-inflammatory and anti-nausea agent. Components of ginger have been shown to reduce production of the leukotriene LTB4 by inhibiting 5-lipoxygenase and to reduce production of the prostaglandin PG-E2 by inhibiting cyclooxygenase. With its dual action in the reduction of inflammation-promoting prostaglandins and leukotrienes, as well as its ability to inhibit nitric oxide production, ginger has been shown to safely reduce the pain and disability associated with osteoarthritis, rheumatoid arthritis, muscle aches, osteoarthritis of the knees, and migraine headaches. Doses up to one gram of ginger per day have been safely used during pregnancy to reduce the nausea and vomiting of pregnancy and hyperemesis gravidarum, while doses for the treatment of rheumatic conditions has ranged from 1 gram (one-half teaspoon) of powdered ginger to up to 50 grams per day of fresh or lightly cooked root. The pungent principles of ginger often create a warm or burning sensation in the stomach that is mild, reducible with food consumption, and not indicative of tissue irritation. In contrast with pharmaceutical NSAIDs, ginger appears to have a protective benefit against gastric ulceration. No significant adverse effects due to ginger are known; gall stones and the use of coumadin/Warfarin may possibly be relative contraindications due to the mild cholangic and anticoagulant actions, respectively.

MSM (Methylsulfonylmethane): MSM is a fairly popular nutritional supplement for the amelioration of allergies, interstitial cystitis, and joint pain, although the research supporting its use is quite limited. MSM is relatively inexpensive and appears safe, especially for short-term use; one clinical trial used 2,600 mg for 30 days with no major adverse effects. Doses of 1-3 grams per day appear safe and are reasonable for patients who may derive benefit.

Spinal Manipulation: Mechanisms of Action and Synergism with Nutritional/Botanical Interventions

Using the state of the sciences before the year 1910, chiropractic was founded with a profound appreciation of the integrated nature of health and the therapeutic focus was on spinal manipulation. In describing the chiropractic model of health, DD Palmer wrote, “The human body represents the actions of three laws—spiritual, mechanical, and chemical—united as one trine. As long as there is perfect union of these three, there is health.” While the therapeutic focus of the profession has been spinal manipulation, from its inception the chiropractic profession has emphasized a holistic, integrative model of therapeutic intervention, health, and disease, and chiropractic was the first healthcare profession in America to specifically claim that the optimization of health requires attention to spiritual/emotional/psychological, mechanical/physical/structural, and biochemical/nutritional/hormonal/chemical considerations. Accordingly, these cornerstones are fundamental to the modern definition of the chiropractic profession recently articulated by the American Chiropractic Association. “Doctors of Chiropractic are physicians who consider man as an integrated being and give special attention to the physiological and biochemical aspects including structural, spinal, musculoskeletal, neurological, vascular, nutritional, emotional and environmental relationships.”

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Applied to either the spine or peripheral joints, high velocity-low amplitude joint manipulation appears to have numerous physical and physiological effects, including but not limited to the following: 1) releasing entrapped intraarticular menisci and synovial folds, 2) acutely reducing intradiscal pressure, thus promoting replacement of decentralized disc material, 3) stretching of deep periaricular muscles to break the cycle of chronic autonomous muscle contraction by lengthening the muscles and thereby releasing excessive actin-myosin binding, 4) promoting restoration of proper kinesthesia and proprioception, 5) promoting relaxation of paraspinal muscles by stretching facet joint capsules, 6) promoting relaxation of paraspinal muscles via "postactivation depression", which is the temporary depletion of contractile neurotransmitters, 7) temporarily elevating plasma beta-endorphin, 8) temporarly enhancing phagocytic ability of neutrophils and monocytes, and 9) activation of the diffuse descending pain inhibitory system located in the periaqueductal gray matter—this is an important aspect of nociceptive inhibition by intense sensory/mechanoreceptor stimulation, which will be discussed in a following section for its relevance to neurogenic inflammation. While this list of mechanisms-of-action is certainly not complete, for purposes of this paper it is sufficient to have established that, indeed, joint manipulation in general and spinal manipulation in particular have objective mechanistic effects that correlate with their clinical benefits. Additional details are provided in numerous published reviews and primary research\(^{517,518,519,520,521,522,523}\) and by Leach\(^{524}\), whose extensive description of the mechanisms of action of spinal manipulative therapy is unsurpassed. Given such a wide base of experimental and clinical support published in peer-reviewed journals and widely-available textbooks, denigrations directed toward spinal manipulation on the grounds that it is "unscientific" or "supported by research" are unfounded and are indicative of selective ignorance. The clinical benefits and cost-effectiveness of chiropractic management of musculoskeletal/spinal manipulations include improved pulmonary function and/or quality of life in patients with asthma\(^{534,535,536,537}\) and improvement or restoration of vision in patients with post-traumatic visual loss. More research is required to quantify the potential benefits of spinal manipulation in patients with wide-ranging conditions such as epilepsy\(^{546,547}\), attention-deficit hyperactivity disorder\(^{548,549}\), and Parkinson's disease\(^{550}\). Given that most pharmaceutical drugs work on single

536) "There were small increases (7 to 12 liters per minute) in peak expiratory flow in the morning and the evening in both treatment groups, with no significant differences between the groups." Balon, J, Aker, PD, Crowther, ER, Danielson, C, Cox, PG, O'Shaughnessy, D, Walker, E, Goldsmith, CH, Duku, E, Sears, MR. A comparison of active and simulated chiropractic manipulation as adjunctive therapy for childhood asthma. N Engl J Med. 1998 Oct 8;339(16):1013-20
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biochemical pathways, spinal manipulation is discordant with the medical/drug paradigm because its effects are numerous (rather than singular) and physical and physiological (rather than biochemical). Thus, when viewed through the allopathic/pharmaceutical lens, spinal manipulation (like acupuncture and other physical modalities), will be viewed as “unscientific” and “does not make sense.” In this case, the fault lies with the viewer and the lens, not with the object.

Research documenting the systemic and “nonmusculoskeletal” benefits of spinal manipulation mandates that our concept of “musculoskeletal” must be expanded to appreciate that musculoskeletal interventions benefit nonmusculoskeletal body systems and physiologic processes. This conceptual expansion applies also to soft tissue therapies such as massage, which can reduce adolescent aggression, improve outcome in preterm infants, alleviate premenstrual syndrome, and increase serotonin and dopamine levels in patients with low-back pain.  

Neurogenic inflammation causes catabolism of articular structures and thus promotes joint destruction, a phenomena that the current author has termed “neurogenic chondrolysis.” The biologic and scientific basis for this concept rests on the following sequence of events which ultimately form a self-perpetuating cycle: 1) tissue irritation by allergens, injury, degradation, or chemical xenobiotics results in the release of proinflammatory mediators in local tissues (immunogenic inflammation); 2) nociceptive input is received centrally and results in release of proinflammatory mediators from sensory neurons (neurogenic inflammation), and results in a neurologically-mediated catabolic effect in articular cartilage (neurogenic chondrolysis) and in tissues distant from the site of irritation (neurogenic switching). 3) inflammation and catabolism in articular structures mediated by the nervous system promotes joint destruction and thus exacerbates immunologic inflammation, 4) exacerbation of immunologic inflammation promotes additional neurogenic inflammation.

Based on recently published research, an additional mechanism of action for musculoskeletal manipulation is described here: the current author proposes that intense mechanoreceptor activation via high-velocity low-amplitude spinal manipulation inhibits C-fiber-mediated nociceptive input and thus suppresses neurogenic inflammation. Since neurogenic chondrolysis is inhibited by interference with C-fiber (type IV) mediated nociception, and since it appears that chiropractic manipulation inhibits C-fiber mediated nociception, then chiropractic manipulation may promote health and wellness by reducing neurogenic inflammation and may promote articular integrity by inhibiting neurogenic chondrolysis. This would explain the benefits of spinal manipulation in the treatment of asthma, since asthma is known to be mediated in large part by neurogenic inflammation. Therefore, for the promotion of wellness and the treatment of inflammatory disorders, I propose that the most effective means for inhibiting this self-perpetuating vicious cycle is
therapeutic intervention directed toward as many of the loci of activity as possible—namely the inflamed tissues, proinflammatory nerves, spinal cord, and the brain—and this can be accomplished with py photonutritive antinflammatories (as described in previous sections), meditative stress reduction571, inhibition of nociception with spinal manipulation572,573 (and perhaps acupuncture574 and other physical modalities), and by botanical and nutritional medicines that inhibit neurogenic inflammation575,576, respectively (Figure 7). In addition to these biochemically- and neurologically-mediated effects, other health benefits potentially mediated by piezoelectric physiology should also be considered.577,578,579

Figure 7: Hypothetical model of the vicious cycle of immunogenic and neurogenic inflammation and their inhibition by multicomponent intervention.

Furthermore, I propose that select nutritional interventions as surveyed in this paper may have enhanced effects and benefits when combined with spinal manipulative therapy. For example, enhanced respiratory burst clearly carries both antioxidant and antimicrobial benefits, and this physiologic effect can be induced by oral consumption of proteolytic enzymes580 as well as by chiropractic spinal manipulative therapy.581,582 Likewise, we would expect synergism between spinal manipulative therapy583,584,585 and nutritional586 and botanical587,588.

584) "There were small increases (7 to 12 liters per minute) in peak expiratory flow in the morning and the evening in both treatment groups. …Symptoms of asthma and use of beta-agonists decreased and the quality of life increased in both groups, with no significant differences between the groups.” Balon J, Aker PD, Croxton ER, Danilson C, Cox PG, O'Shaughnessy D, Walker C, Goldsmith CH, Duke E, Sears MR. A comparison of active and simulated chiropractic manipulation as adjunctive treatment for childhood asthma. N Engl J Med. 1998 Oct 8;339(15):1013-20
interventions in the treatment of asthma, particularly since these treatments are mediated primarily via different mechanisms—namely the neurophysiologic inhibition of neurogenic inflammation (proposed) and the biochemical reduction in pro-inflammatory mediators such as leukotrienes, respectively. As a final example, synergism would be expected in the treatment of low-back pain when spinal manipulation, therapeutic exercise, proprioceptive retraining, oral vitamin D supplementation, and botanical medicines such as *Harpagophytum* and Willow Bark are used together in holistic, integrative, multicomponent treatment plans. Taken together, these data form an integrative model that incorporates and mechanistically validates the chiropractic “triad of health” (Figure 8).

**Figure 8: The chiropractic “Triad of Health”: a conceptual model for understanding the interconnected nature of various physiologic processes and systems.**

![Chiropractic Triad of Health Diagram](image)

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**Chiropractic and Naturopathic Medicine within Healthcare Systems Tailored to the Medical Paradigm**

The term “paradigm” refers to the unconsciously assumed “lens” by which individuals view and interact with (their perception of) reality. Even before asked, questions are phrased and framed to within the conceptual boundaries of the prevailing paradigm, and the end result is that the answers that appear “right” are the ones that coincide with the underlying assumptions and which reinforce and support the status quo. A vicious cycle of informational inbreeding is created that, unless acted upon by an influence outside of the paradigm, essentially creates a “house of mirrors” where indoctrinated individuals cannot escape their own worldview and wherein these same individuals repeatedly reflect to themselves and each other misinformation that is only “right” insofar as it agrees with and sustains the prevailing *modus operandi*. In this regard, the allopathic medical model of healthcare delivery is indeed its own paradigm—one that is increasingly described in articles that discuss its characteristics, influence, shortcomings, and the facility with which is misappropriated.
described as a system of healthcare that emphasizes the use of chemical drugs and invasive surgery as its primary means of intervention; technological, “sophisticated” assessments and interventions are favored over those of greater simplicity (ie, “unsophisticated”) and lower cost regardless of efficacy; patients are responsible only for “compliance” to the doctor’s orders and are generally placed in a position of disempowerment because the options presented (drugs and surgery) are outside of their control and understanding while self-directed nonchemical nonsurgical options are either not discussed or are subtly or blatantly disdained; treatment of the disease assumes predominance over the needs and uniqueness of the patient. Within certain contexts, this paradigm is appropriate and produces favorable results, namely in the treatment of acute trauma and immediately life-threatening disease. However, when this paradigm is applied to the vast majority of outpatient clinical encounters, it is generally inferior in cost-effectiveness and global impact than other approaches to healthcare delivery that emphasize patient empowerment for the implementation of self-directed healing and which improve underlying physiology so that health is restored and symptoms are alleviated, rather than merely suppressed with drugs. Most medications are designed to block the body’s normal functioning, and this is clearly indicated by the most popular categories of medications, e.g., calcium channel blockers, serotonin antagonists, HMG-CoA reductase inhibitors, angiotensin converting enzyme (ACE) inhibitors, and serotonin reuptake inhibitors. The near exclusive reliance upon “single pathway” drugs and surgery by our current medical system is most ironic considering the complexity of disease and the powerful influence of lifestyle and environment in the generation of the epidemics of today, namely heart disease, cancer, depression, and autoimmune disease. Doctors who fail to appreciate the presentations and prevalence of nutritional deficiencies/imbalances or who cannot escape their drug/surgery paradigm of intervention will by necessity turn to drugs/surgery when clinical intervention is called for—not on the basis of the appropriateness of these interventions but rather simply because they know no other options. The treatment of nutritional imbalances and lifestyle diseases with drugs and surgery (rather than the correction of the underlying nutritional imbalance or habit) appears illogical and potentially unethical, but it is no large leap of faith to extrapolate that it is a common occurrence affecting millions of patients every day; this is true even if we limit the discussion to the clinical consequences of vitamin D deficiency, and fatty acid imbalance, both of which are epidemic and are the underlying causes of numerous “diseases” that, when viewed through the allopathic lens of most practicing doctors, will be treated with pharmaceutical drugs, perhaps surgery. By the very nature of their incongruence with reality and failure to intervene at the primary level of causality, defective paradigms will repeatedly produce lackluster results regardless of the amount of effort, talent, or funding that is poured into them. In this situation, additional investment of resources (intellectual, financial, material, and social) is not the answer; what is needed is a “paradigm shift” that permeates the entirety of the system in question. Building upon phraseology offered by Wilson and the concepts solidified by Beckman et al, one might articulate that the required shift is that from materialistic reductionism and biomedical objectivism to what integrative natural medicine practitioners have been espousing for decades—science-based integrative subjectivism: the consideration of all data, influences, and possible interventions and the application of these considerations within a broad-based nonexclusive context that foremost respects patient uniqueness and the web-like matrix of interconnected biologic, psychosocial, environmental, and neuromusculoskeletal phenomena.
The pharmaceutical/drug paradigm rose to power following the questionable attribution of improvements in societal health to the increased use of drugs, particularly antibiotics. Soon thereafter, the “external invader” model of disease became accepted by the medical profession, and patients were seen as victims of and separate from their disease(s), and the roles of interventional nutrition, responsible lifestyle modification, and other natural treatments were marginalized to obscurity and trivialized to quackery. More specifically, this paradigm contends that chemical drugs are the only reasonable (ie, “scientific”, “proven” and “rational”) means for treating and preventing disease. Aided by ample funding from state and federal subsidies for education and research, cash from the pharmaceutical industry, and the falsification of research that was and is still used to denigrate chiropractic, the medical profession conspired to illegally destroy the osteopathic, chiropractic, naturopathic professions, and the effects of these actions are still seen and felt today.

The naivety and acquiesce of the public also played a role, since the seductive pharmaceutical paradigm generally supports that patients are exonerated from responsibility and discipline, save for “compliance” (ie, “submission”) to life-long medicalization.

Although Kuhn is credited with introducing the term “paradigm” within the academic and intellectual arena, it is the treatise by Breton and Largent that makes this concept and its implications relevant for the systems that shape our lives and create our “reality” on a day-to-day basis. Early in their review (page 54), they note that one of the ways that old systems maintain power is by ignoring the pain and suffering that they directly create, and by justifying these “side effects” as “necessary evils”—i.e., that widespread suffering is justified for the attainment of what is reported as widespread benefit. However, the data presented in this paper show that widespread iatrogenic suffering is not justified for the illusion of widespread benefit. Almost all of the natural treatments employed by chiropractic and naturopathic physicians as described in this paper provide clinically significant relief of musculoskeletal symptoms while improving rather than detracting from overall health. What Breton and Largent say of dysfunctional paradigms can be seen to apply to the medical paradigm and the system of medical healthcare that results: “Sick paradigms make sick institutions that make sick people…” In this case, the “sick paradigm” is the medical model in which chronic diseases caused by unhealthy lifestyles and/or nutritional deficiencies are “treated” with drugs and surgery. The “sick institutions are the exorbitantly expensive medical systems that kill 180,000 Americans per year—493 patients per day. The “sick people” are the American population with progressively deteriorating health status, as well as members within the healthcare community. Medical physicians consistently show higher rates of suicide and depression than the general population. North and Ryall noted, “More than half of female physicians may experience a psychiatric illness during their lifetime. Depression is by far the most common such disorder, and the suicide rate is alarmingly high. However, female physicians appear to be at lower risk for substance abuse than male physicians.”

Relocating the modern chiropractic profession to a marginalized position in the healthcare arena simply because some (not all) of the founding assumptions of the profession c.1903 have since been determined to be simplistic or inaccurate would be as ridiculous as it would be to castigate the entire allopathic profession as incompetent simply because their forebears utilized treatments such as “bloodletting”, administration of “therapeutic mercury”, refusing care to African-Americans with syphilis, or, more recently, injections of cancer cells into

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617) Heaney RP. Vitamin D, nutritional deficiency, and the medical paradigm. J Clin Endocrinol Metab. 2003;88:5107-8
621) Heaney RP. Vitamin D, nutritional deficiency, and the medical paradigm. J Clin Endocrinol Metab. 2003;88:5107-8
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625) Trevino W. In the Public Interest. Los Angeles, Scriptures Unlimited; 2005

A Detailed Review of Current Research with Implications for Clinical Practice and Healthcare Policy - Alex Vasquez, D.C., N.D. Copyright © 2005. 37 of 58
hospital patients without their consent for the sake of conducting research on the course of the disease.\textsuperscript{636} It is a malicious act to continue denigrating (and thereby restricting) the modern chiropractic profession based on scientific shortcomings that were inherent in all of the healthcare professions 100 years ago, or even 40 years ago. To this day, the American Medical Association continues to berate the entire chiropractic profession based on controversial and politically influenced reports which found “deficits” in chiropractic education in the 1960’s; these shortcomings that occurred more than 40 years ago are used as justification to restrict the profession even now.\textsuperscript{637} Furthermore, since it appears that most allopathic medical doctors have received inadequate training in fundamental musculoskeletal medicine\textsuperscript{638,639,640}, they would therefore not be expected to be aware of the complex physiological effects of spinal manipulation and modern integrative chiropractic care (reviewed previously; see Leach\textsuperscript{641}, Haldeman\textsuperscript{642}, Bergman et al\textsuperscript{643}, and Vasquez\textsuperscript{644} for more details). In his noteworthy, critique of his own profession, former JAMA editor George Lundberg MD\textsuperscript{645}, even though he admits to having been taught essentially nothing but misinformation about chiropractic in his formal medical education, had an occasion of uncommon insight which allowed him to distinguish pre-scientific chiropractic theory from contemporary chiropractic practice. He writes, “Putting aside my early bias against chiropractic, it is important for me to note the distinction between theory and practice. [Early chiropractic theory] may be one thing, but [the modern chiropractic profession] may be something entirely different.” Likewise, it is incumbent upon policymakers and other healthcare professionals to relinquish their simplistic and inaccurate perceptions of the chiropractic profession and to access current articles and texts so that they can become informed of the developments that have modernized the chiropractic profession in the course of the past 100 years since its inception. Selective misunderstanding and intentional ignorance of chiropractic by medical organizations and policymakers serves only to maintain the status quo and to justify resistance to the full inclusion of chiropractic physicians into the healthcare system despite overwhelming and consistent evidence that chiropractic care is safe, effective, and more cost-effective than allopathic management.

In contrast to the promulgations decreed by those aligned with the drug/medical paradigm, the body of evidence supporting the majority of natural therapeutics is uniquely solid and consistent. For example, evidence supports that the anxiolytic herb Kava kava has superior safety and cost-effectiveness when compared to pharmaceutical anxiolytics\textsuperscript{646,647}, and that St. John’s Wort has shown antidepressant efficacy that is equal or superior to that of the more expensive pharmaceutical antidepressants\textsuperscript{648,649,650}, and it does not appear to increase the risk for suicide as do the commonly used “antidepressant” drugs\textsuperscript{651,652,653,654,655}. Alan Goldhamer, a chiropractic physician, appears to have created the most effective treatment plan for chronic hypertension that has ever been documented\textsuperscript{656,657}—yet most insurance companies will not pay for chiropractic management of hypertension, and most allopathic cardiologists remain clinically ignorant of non-drug treatments for hypertension. Preventive research by Orme-Johnson and Herron\textsuperscript{658} utilizing a “multicomponent prevention program” that included meditation, yoga, herbal dietary supplements, and diet recommendations documented that total medical expenses were reduced by 59% over 4 years and by 63% over 11 years compared to patients under ‘conventional’ medical care; hospital admission rates were reduced by 11.4-fold for cardiovascular disease, 3.3-fold for cancer, and 6.7-fold for mental health and substance abuse. Simple nutritional supplementation of patients in intensive care units dramatically reduces infection rates, mortality, and hospital
and this benefit is so significant and consistent that failure to implement nutritional intervention in acutely ill patients should be deemed unethical and clear grounds for malpractice litigation. Based on these and other illustrative examples described elsewhere by the current author, it is reasonable to conclude that American healthcare would be more effective, more affordable, and safer if providers of holistic natural healthcare were fully integrated into the healthcare system rather than being politically excluded, either because restrictive licensure laws or functionally excluded (e.g., discriminatory CPT codes and HMO policies) by a system of drug- and surgery-based medicine that financially depletes the people, business, and communities of our nation while failing to deliver competent healthcare and cost-effective nation-wide health improvements that are proportional to the continuous increase in spending. The current author has referred to this disparity of investment and reward as the “American paradox”—Americans spend more per healthcare than any other nation in the world, yet the health status of Americans is the worst among developed nations and is continuing to decline despite ever-increasing technological sophistication, overall expenses, and iatrogenic morbidity and mortality. Thus it appears that spending and technology may not be the answers to our national healthcare dilemma, and that conservative natural treatments deserve more attention—by extension, this implies that physicians trained in natural lower-cost therapeutics should be afforded greater opportunities to contribute to national healthcare efforts.

The pharmaceutical industry aggressively promotes its own interests in medical schools and in post-graduate medical education for physicians including misleading advertising and the direct influence of patients with direct-to-consumer advertising. Drug companies spend $8,000 - $15,000 per doctor per year to advertise their products to their sales force: medical physicians. In their prophetic 2001 review criticizing the overuse of pharmaceutical “anti-inflammatory drugs”, Van der Steen and Ho write, “Unofficial and official sources tend to inform the general public that the drugs promote human health. We argue that their being used on a massive scale is actually a medical disaster. The health of many patients would be served better if the drugs they take were replaced by proper forms of diet, but the pharmaceutical industry, the most potent force affecting our nation’s health, is continuing to spend billions of dollars on research and development in the hope that our patients will be healthy enough to purchase even more of their products.”

Despite consistent evidence that pharmaceutical/medical interventions kill not less than 180,000 and up to 225,000 Americans per year, doctorate-level providers of nonallopathic healthcare such as chiropractic, 659,660,661,662,663,664,665

666 "The Sola plaintiffs argued that each HMO defendant is "by itself a combination in restraint of trade, and that there is no concerted action requirement for an illegal combination." Sola Case DISMISSED!"
669 "The USA’s $5.8 million small companies… Health care costs are rising about 15% this year for those with fewer than 200 workers vs. 13.5% for those with 500 or more… But many small employers cite increases of 20% or more. That’s made insurance the No. 1 small business problem…”. Jim Hopkins. Health care tops taxes as small business cost drain. USA TODAY. http://www.usatoday.com/news/health/2003-04-20-small-business-costs_x.htm Accessed July 28, 2004
670 "In 1994, we spent $1 trillion on health care in the US, or, more accurately, we spent most of this astounding sum on disease treatment. This represents an increase of 300% in the last 15 years. Health care costs now consume 15% of the gross national product (GNP), with the percentage of GNP spent on health care continuing to increase at twice the rate of inflation. If the rate of increase continues, health care costs will consume the entire GNP within 50 years. Corporations now spend an incredible 48% of their after-tax profits on health care, and it is projected that by the year 2000, healthcare costs will equal 60% of after-tax profit at the average Fortune 500 company.” Pizzorno J. Total Wellness. Rocklin; Prima; 1996 page 9
673 "The results of the study demonstrate that, over the past four decades, the United States has been spending more and accomplishing less when compared with other industrialized nations. “Sti L. Healthcare spending, delivery, and outcomes in developed countries: a cross-national comparison.” Am J Med Qual. 1997;12(2):63-65
674 "Basically, you die earlier and spend more time disabled if you’re an American rather than a member of most other advanced countries.” Christopher Murray MD PhD, Director of World Health Organization’s Global Program on Evidence for Health Policy. http://www.who.int/inf-pr-2000/en/pr2000-life.html Accessed July 12, 2004
676 Drug-company influence on medical education in USA. Lancet. 2000 Sep 2;356(9232):781
679 "Mintzes B, Barer ML, Kazanjian A, Bassett K, Lexchin J, Pan R, Marion SA. Influence of direct to consumer pharmaceutical advertising and patients’ requests on prescribing decisions: two site cross sectional survey. BMJ. 2002;324(7332):278-81

naturalopathic and (to a much lesser extent) osteopathic physicians continue to be denigrated, 

684 discriminated or misbranded as “nonphysicians” and are legislatively, financially, and politically limited from the opportunity to fully provide evidence-based healthcare with equitable payment and insurance coverage for medical doctors. 

687 According to internal reviews by allopathic physicians and epidemiologists, allopathic physicians commonly deliver care that is “substandard” and which poses “serious threats to the health of the American public.” 

688 Unless we are intentionally choosing to pay more money and to “die earlier and spend more time disabled,” then we must enact nationwide healthcare reform to mandate the complete integration of, access to, and reimbursement for integrative and naturopathic physicians in the American healthcare system. 

689 Allopathic/pharmaceutical hegemony of the American healthcare system might possibly justified if its particular style of diagnosis and treatment provided superior overall outcomes at reduced cost; however this has never been proven. 

690 Rather, to the contrary, the American system of allopathic/pharmaceutical healthcare is wantonly expensive, delivers care that is commonly “substandard,” and which poses “serious threats to the health of the American public” and which is a direct cause of death for approximately 493 Americans each day. 

The healthcare landscape of America has been dominated by the allopathic medical community and pharmaceutical industry, which formerly sought to monopolize healthcare delivery by disenfranchising and slandering other healthcare providers with the goal of extinguishing the chiropractic, naturopathic, and osteopathic professions. 

693,694,695 Due in large part to the successful anti-trust lawsuit brought by Chester Wilk et al against the American Medical Association and other medical groups, this conspiracy was formally ended by court injunction in the late 1980s, yet its negative political, financial, and social consequences are ongoing. 

Medical journals have historically allowed and thus condoned many biased, unfounded, and fraudulent “research” articles by medical authors which denigrate chiropractic and other natural forms of healthcare through the repeated misuse of references, misleading statements, highly selective use of certain published papers, failure to refer to relevant literature, inaccurate reporting of the contents of published work, and errors in citation. 

696-698 Given that the biomedical information system is strongly biased in favor of pharmaceutical/surgical interventions and sharply against biologic/natural interventions, there is an extreme shifting of “the balance of evidence” in favor of the medical paradigm; this creates a self-serving and self-perpetuating vicious cycle wherein prevailing paradigms are supported by a biased database of articles which systematically create the illusion that comparatively little research exists to support “alternative” conceptualizations and interventions. 

Adherence to high standards of intellectual integrity and academic propriety is frequently sidelined in slanderous “critical reviews” of chiropractic and naturopathic medicine that range from subdude to venomous in tone and tact. Recent examples are plentiful, including biased and occasionally profane polemics listed as “book reviews” published by the American Medical Association which condone such positions as “I almost never initiate a referral to a non-allopathic physician” and offensive and intellectually paradoxical statements such as “That’s the kind of crap I would not believe in, even if it were true.” 

703 Harvard Medical School recently stepped into the libelous unscientific fray in a 2004 promotional mailing which included the unreferenced statement “…about half the people who seek spinal manipulation from chiropractors and other natural forms of healthcare experience problems caused by the treatment.” The 2003 unbridled ambush against chiropractic


686 Cooper RA, Henderson T, Delchrow CL. Roles of nonphysician clinicians as autonomous providers of patient care. JAMA. 1999 Sep 2;282(9):795-802 


695 Wak CA. Meltdown, Monopolies, and Malice: How the Medical Establishment Tried to Destroy Chiropractic. Garden City Park: Avery, 1996 

696 Trever W. In the Public Interest. Los Angeles: Scriptures Unlimited; 1972. 


and naturopathic medicine by WebMD and Medscape\textsuperscript{705} publicly disclosed their lack of objectivity and peer review of this so-called “trustworthy, credible, and timely” internet journal, and these polemics have been authoritatively redressed in a two-part article in \textit{American Journal of Family Practice} (Pizzorno, Dunne et al; in press). The on-going polemic by Stephen Barrett MD at \url{www.chirobase.org} constantly reaches new lows in professionalism and objectivity, finding every negative aspect of anything related to chiropractic and presenting it as if it were reflective of the entire profession and each of its members. Institutionalized violence such as these attacks against their fellow healthcare providers is what fuels animosity and mistrust against what is perceived to be “the medical establishment.”\textsuperscript{706} This is particularly true when, according to the American Medical Association\textsuperscript{707}, “organized medicine” is “ready to fight their efforts” whenever naturopathic/chiropractic physicians seek to implement the holistic broad-spectrum care they are trained to provide, and when medical organizations such as the AMA use the rhetoric of “patient safety” as the justification to impose restrictions on naturopathic/chiropractic physicians and to resist the implementation of meaningful change in a healthcare system that is unduly expensive, disempowering, and lethal. “Patient safety” was the same façade used by the AMA during the decades in which chiropractic and naturopathic medicine were crushed to the point of near extinction by what was later made clear to be a system-wide conspiracy which violated America’s anti-trust laws and threatened to create a medical monopoly over US healthcare by destroying other healthcare professions.\textsuperscript{708, 709} The osteopathic profession—labeled as “cultists” by the American Medical Association, which stated in 1953 that “……all voluntary associations with osteopaths are unethical”—was likewise faced with extinction, until merger with allopathic medicine was the only remaining strategy—a strategy which the medical profession believed would eventually destroy the osteopathic profession. In his review of osteopathic history, Gevitz\textsuperscript{710} writes, “…the M.D.’s gradually came to believe that the only way to destroy osteopathy was through the absorption of D.O.’s, much as the homeopaths and eclectics had been swallowed up early in the century.” Even today, the AMA continues to list osteopathic medicine under “alternative medicine”\textsuperscript{721} even though several osteopathic medical colleges have consistently provided training that is superior to most “conventional” medical schools.\textsuperscript{712}

The image of the superiority of medical physicians and medical education was conjured at a time when the vast majority of the population had no access to higher education or health-related information. Public policies, legislative acts, and systems of government subsidization of medical schools and the pharmaceutical industry were enacted decades ago during times of primitive comprehensions of disease processes and the blind faith that we would achieve “better living through chemistry” and that drugs were the solutions to our healthcare problems. Medical doctors were socially deified by the public acceptance of their self-purported elitism and their condemnation of other competitors in the healthcare arena, namely those physicians brazen enough to refute the pharmaceutical paradigm by studying and advocating such things as nutrition, exercise, and effective yet conservative and low-cost options to drugs and surgery. Now, however, the accumulated research documents the fallacy of applying the drug/surgery paradigm to most chronic, lifestyle-generated diseases\textsuperscript{713, 714} and past and current medical education is now acknowledged as “inadequate” for the treatment of chronic diseases in general\textsuperscript{715} and musculoskeletal conditions in particular.\textsuperscript{716, 717} If we accept recent authoritative publications concluding that “medical education is failing to prepare students adequately for their future practice”\textsuperscript{718} and that, in another article published by the American Medical Association, medical education “is currently being held together by peanut butter and bubble gum”\textsuperscript{719} then the only logical and responsible action that can be taken to provide patients with immediate and equitable access to physicians with training in the management of chronic illness is to remove the outdated financial and legislative barriers that restrict patients from access to the scientific, cost-effective, patient-centered and patient-driven healthcare that chiropractic and

\begin{itemize}
\item \textsuperscript{706} WIK CA. Medicine, Monopolies, and Malice: How the Medical Establishment Tried to Destroy Chiropractic. Garden City Park: Avery, 1996.
\item \textsuperscript{708} Gevitz N. The D.O.’s: Osteopathic Medicine in America. Garden City Park: Avery, 1996.
\item \textsuperscript{709} Wilk CA. Medicine, Monopolies, and Malice: How the Medical Establishment Tried to Destroy Chiropractic. Garden City Park: Avery, 1996.
\item \textsuperscript{713} Hyman M. Paradigm shift: the end of “normal science” in medicine understanding function in nutrition, health, and disease. \textit{Am J Therapeut}. 2004;10(5):10-5, 90-4.
\item \textsuperscript{714} Haney RP. Vitamin D. nutritional deficiency, and the medical paradigm. J Clin Endocrinol Metab. 2003;88(11):5107-8.
\item \textsuperscript{715} Holman H. Chronic disease—the need for a new clinical education. \textit{JAMA}. 2004;292:1057-9.
\item \textsuperscript{716} Joy EA, Hala SV. Musculoskeletal Curricula in Medical Education: Filling In the Missing Pieces. The Physician and Sportsmedicine. 2004; 32: 42-48.
\item \textsuperscript{718} Holman H. Chronic disease—the need for a new clinical education. \textit{JAMA}. 2004;292:1057-9.
\item \textsuperscript{719} DeAngelis CD. Professors not professing. \textit{JAMA}. 2004;292:1060-1.
\end{itemize}
Critics of chiropractic/naturopathic medicine consistently berate and denigrate natural medicine practitioners and interventions as "unproven" and "unscientific." Authors who make broad-based statements like these are publicly confessing their ignorance of relevant medical research and their inability to effectively access biomedical databases such as Medline. Their ignorance of the science is assumed to imply a lack of science. Failure to have learned the science supporting natural medicine does not make natural medicine "unscientific." Encapsulating this phenomenon with simple wit, the American orator Upton Sinclair once noted, "It is difficult to get a man to understand something when his salary depends upon his not understanding it." Indeed, if the allopathic medical community were to objectively evaluate chiropractic solely on the basis of its therapeutic indices (e.g., ratio of benefit to risk and expense), there is little question that chiropractic management in general and spinal manipulation in particular would become one of the favored treatments for musculoskeletal pain. But because chiropractic is not a "drug" and perhaps because referring patients to "other" physicians might connote that they are peers rather than subordinates, chiropractic continues to be allowed within but not fully integrated into the American healthcare arena. There is no scientific basis for this continued exclusion, and evidence repeatedly shows that chiropractic management is associated with superior cost-effectiveness compared to medical management for many conditions. Now that the data on the "coxibs" has been made public, comparative cost-effectiveness data should be recalculated to include the financial and human costs associated with drug-related morbidity and mortality manifested as myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, transient ischemic attacks, hypertension, and so-called idiosyncratic reactions.725,726,727,728 In the end, chiropractic/naturopathic management will be found to be clearly superior.

A favored tool for enforcing inertia in healthcare is the claim that alternative healthcare providers must meet the same high standards as "conventional" medicine.729 Declaring accountability to an undefined "standard" is an obfuscatory tool ready to be leveraged for corruption, exploitation, the postponement of meaningful dialogue, and additional procrastination in the face of urgently needed change. What standards? Created, endorsed, enforced, reviewed, and updated by whom? In consideration of which options and "alternatives"? Which of the following examples from the allopathic community meet high standards of excellence in healthcare to which all healthcare providers should aspire and be held accountable?

A) Most antidepressant drugs increase the risk of suicide and have long lists of other "side effects" in children and adults.730,731 A 2004 review by Jick et al732 published in JAMA showed that "The risk of suicidal behavior after starting antidepressant treatment is similar among users of amitriptyline, ...
fluoxetine, and paroxetine compared with the risk among users of dothiepin. The risk of suicidal behavior is increased in the first month after starting antidepressants, especially during the first 1 to 9 days.”

B) Many antipsychotic drugs have a dubious record of long-term efficacy\(^{733}\) and concentrate in the myocardium\(^{734}\) to produce a 2.4-fold to 3.5-fold increased risk of sudden cardiovascular death, mostly due to arrhythmia.\(^{735}\) Recently, Straus et al\(^{736}\) noted, “Current use of antipsychotics in a general population is associated with an increased risk of sudden cardiac death, even at a low dose and for indications other than schizophrenia. Risk of sudden cardiac death was highest among recent users but remained elevated during long-term use.” Tricyclic antidepressants when used at “higher” doses also cause increased sudden death.\(^{737}\) Surely, most patients are not advised of this.

C) Cox-2 inhibitors for the treatment of osteoarthritis are exorbitantly expensive compared to older NSAIDs, do not have increased efficacy compared with the older drugs, do not cure arthritic disease, increase the risk of cardiovascular death, and are overall clinically less reasonable than many “natural alternatives.” In contrast, for example, the simple anti-inflammatory treatment known as “fish oil” reduces pain in patients with rheumatoid arthritis\(^{738,739}\), and carries additional “side-benefits” such as alleviating mental depression\(^{740,741,742}\) and reducing cardiovascular and total mortality in patients with cardiovascular disease.\(^{743,744,745}\) Likewise, chondroitin sulfate safely alleviates arthritic disease while simultaneously reducing incidence of cardiovascular morbidity and mortality.\(^{746,747,748}\)

D) Type-2 diabetes and obesity generally result from dietary indiscretion (macronutrient excess), subclinical nutritional deficiencies (micronutrient insufficiency), and lack of exercise which results in insulin resistance and sarcopenia. Rather than nutritional supplementation and aggressive diet and lifestyle modification, the medical treatment for dietabegenic obesity focuses on drugs (e.g., metformin) and surgery (e.g., gastropathy and biliopancreatic diversion). Davies and Jenkinson\(^{753}\) remark, “Treating obesity with drugs is about as honest and effective as treating jaundice with camoufage cream.”

E) Despite billions of dollars and accolades to the contrary, the consensus is that—overall—the “war on cancer” is being lost\(^{754,755}\), the incidence of cancer has increased significantly since the 1970s\(^{756}\), the incidence of childhood cancers is accelerating\(^{757}\), and several commonly used chemotherapy and radiation treatments increase the likelihood of “secondary neoplasms” that is: medical treatments such as chemotherapy and radiation actually cause a secondary/iatrogenic cancer to develop in a significant proportion of cancer patients.\(^{758,759,760,761}\) Philpott et al\(^{762}\) reported, “With the increasing use
of chemotherapy for many different primary malignancies, secondary or therapy-related acute myeloid leukaeas (AML) and myelodysplastic syndromes (MDS) are becoming more common. The risk of developing sAML has been estimated to be between 2% and 10%, depending upon the type, duration and dosage of previous therapy. It is therefore one of the most serious long-term complications of current cancer treatment and is likely to increase as longer survival rates for the primary tumour are achieved.”

F) Drug treatment for hypertension typically lowers blood pressure by 12/6, whereas dietary modification and exercise achieves a reduction of 17/13, and diet modification with fasting under nutritional supervision achieves average reductions of 37/13 and can achieve reductions of 60/17 in severely hypertensive patients.763,764 Chiropractic physicians are the only nationwide licensed physicians with extensive training in therapeutic nutrition, yet insurance will not generally cover chiropractic management of hypertension, despite its clearly superior cost-effectiveness compared to pharmaceutical management. Hypertension as an industry in the United States is valued at more than $23 billion per year.765

G) Cardiovascular disease is the leading cause of death in America and results in direct and indirect healthcare expenses that reach into the billions of dollars. Associated interventions, technologies, and consequences include angioplasty, cardiac catheterization, heart transplant, pacemakers, heart scans, cholesterol-lowering drugs, anti-hypertensive drugs, stroke, heart failure, and sudden cardiac death. In societies where people exercise regularly and eat healthy natural diets, cardiovascular disease does not exist. The average cholesterol level of most animals and most humans who obtain sufficient exercise and eat a natural diet is approximately 130 mg/dL, whereas among Americans, the average cholesterol level is 205 mg/dL766, which leads to astronomical expenses for medications, doctor visits, loss of patient work, transportation, laboratory tests, etc.

H) At a cost of approximately $4,000 per intervention, surgical “treatment” for recurrent otitis media is no better than placebo767 and appears to be far more dangerous, far more expensive, and less effective than so-called “naturopathic treatment”768 or nutritional prevention with vitamins, minerals, and cod-liver oil.769

I) Corticosteroids are advised as standard care for the treatment of idiopathic pulmonary fibrosis yet this treatment carries undue risk such as infection and osteoporosis, expedites declines in pulmonary function, and leads to more rapid death than does non-treatment—placebo.770,771 In another recent clinical trial, compared with patients who received no treatment, patients treated with corticosteroids and cyclophosphamide died faster.772

J) Giving post-menopausal women biodiverse estrogen extracted from horse urine along with synthetic biodiverse progesterone derivative (“progestins”) was dubiously labeled “hormone replacement therapy” despite that both of these substances are foreign to the human body. Equine estrogen is a known carcinogen773,774,775, and progesterins are well known to be prothrombotic. The medical profession

765 O'Keefe JH Jr, Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. J Am Coll Cardiol. 2004 Jun 24;43(12):1242-6
strongly advocated this “treatment” for millions of women before it was finally publicly disclosed that these drugs increase the risk for breast cancer, ovarian cancer, gall bladder disease, urinary incontinence, and cardiovascular death. 776, 777, 778, 779

K) Only 30-50% of medial interventions are supported by evidence-based research from randomized clinical trials. 780, 781

L) Documentation of subtle and overt corruption within the medical-pharmaceutical-regulatory triad is consistently reported in first-tier “conventional” medical journals, the popular press, and internet websites. Writing in the New England Journal of Medicine, Blumenthal794 noted, “When a great profession and the forces of capitalism interact, drama is likely to result… On display in the relationship between doctors and drug companies is the grandeur and weaknesses of the medical profession — its noble aspirations and its continuing inability to fulfill them.”

Yes, indeed we need high standards in healthcare; but those standards should be designed and enforced for the protection of patients, not for the protection of paradigms, medical hegemony, and the maintenance of the status quo. Indeed, nearly every routine ambulatory outpatient condition can be either cured or ameliorated by nonsurgical nonpharmacologic means; the evidence in support of these natural treatments is already published in peer-reviewed medical journals. An integrative mindset and willingness to deflate the expansive illusions of complexity that surround many illnesses are prerequisites to the successful acquisition and implementation of this data. This monograph represents only a very small portion of the research supporting natural treatments for a wide range of conditions.

Medicolegal considerations deserve mention any time that clinical practice and scientific research are at odds with each other, and the importance of “voluntary informed consent” has been internationally established since the Nuremberg Medical Trial of 1946-1947 that condemned medical experiments on unconsenting prisoners.798 Minimum requirements for informed consent include 1) competence—the patient must be coherent and have the mental and emotional faculties to make rational decisions, 2) procedures—the patient is informed of the procedures involved and “what will be done”, 3) options—the patient is informed of the alternatives and options that are available for the treatment of the condition, 4) risk—the patient is informed of the risks and expenses involved, 5) benefits—the patient is given a realistic appraisal of the nature (e.g., breadth, duration) of the potential benefits resulting from the procedure(s), and 6) voluntariness—the patient is the ultimate decision-maker with respect to his/her body. Voluntariness requires that options be presented in a manner and within a context that makes these options equally accessible. Based on these minimal criteria for informed consent, and given the extensive documentation substantiating the effectiveness and safety of natural treatments for pain and inflammation, we can reasonably conclude that patients suffering from painful musculoskeletal disorders are entitled to receive from their healthcare providers information about these treatments as valid and reasonable options in the management of their health concerns. Failure to provide patients with non-drug non-surgical options for the management of their musculoskeletal symptoms is therefore ethically questionable and medicolegally untenable. For example, a physician who tells his patient “There is no research to support ‘alternative’ treatments for your [painful musculoskeletal disorder]” has clearly misrepresented the facts and has
Conclusions

The chiropractic profession continues to develop and mature over time and with advances in research that further our understanding of health and disease and the value of diet, nutrition, exercise, spinal manipulation and other natural therapeutics. In contrast to their allopathic counterparts, chiropractic and naturopathic physicians are the only healthcare providers trained to consider each patient as an integrated being and to give specific attention to the physiological and biochemical aspects of health and disease, including structural, spinal, musculoskeletal, neurological, vascular, nutritional, emotional and environmental relationships. Accordingly, chiropractic and naturopathic physicians are in progressively greater demand for the provision of healthcare that includes and yet increasingly extends beyond the relatively narrow scope of musculoskeletal specialization. Research documenting the visceral and systemic benefits of spinal manipulation mandates that our concept of “musculoskeletal” must be expanded to appreciate that musculoskeletal interventions benefit nonmusculoskeletal body systems and systemic processes. To that end, this article has provided a review of the nutritional aspects of a health-promoting lifestyle, characterized by proper ergonomics and abundant physical activity, the selective use and skilled application of noninvasive natural therapeutics, and the supplemented Paleo-Mediterranean diet which is characterized by intake of lean meats, fresh fruits and vegetables, supplemental vitamins and minerals (excluding excess iron and vitamin A, and with physiologic doses of vitamin D), and balanced broad-spectrum fatty acid supplementation. The anti-inflammatory and analgesic nutritional and botanical medicines described in this review are generally appropriate for the treatment of inflammatory and degenerative musculoskeletal conditions, and they comprise an attractive alternative to the too-often lethal effects of pharmacologic anti-inflammatory and anti-rheumatic drugs.

If we consider that medical/surgical interventions result in an excess of 110,000 – 225,000 iatrogenic American deaths each year of nonmusculoskeletal body systems and systemic processes, we could reasonably conclude that undue restriction of chiropractic and naturopathic physicians to practice preventive healthcare and the discriminatory legal and financial barriers that inhibit patients from accessing alternatives to drugs and surgery are unethical and may represent a violation of patients’ [human] rights insofar as these restrictions ultimately deny patients’ access to safe, effective, cost-effective, and abundant physical activity, the selective use and skilled application of noninvasive natural therapeutics, and the supplemented Paleo-Mediterranean diet which is characterized by intake of lean meats, fresh fruits and vegetables, supplemental vitamins and minerals (excluding excess iron and vitamin A, and with physiologic doses of vitamin D), and balanced broad-spectrum fatty acid supplementation. The anti-inflammatory and analgesic nutritional and botanical medicines described in this review are generally appropriate for the treatment of inflammatory and degenerative musculoskeletal conditions, and they comprise an attractive alternative to the too-often lethal effects of pharmacologic anti-inflammatory and anti-rheumatic drugs.

800) Washington State Chiropractic Association, “Maintain and Protect ‘Every Category of Provider’ Law: As always, the WSCA’s top priority is to maintain a patient’s right to choose the provider of their choice for the treatment of conditions covered in a health insurance plan.” http://www.chirohealth.org/legislation/legislationAgendaDetails.htm. Accessed February 17, 2005

A Detailed Review of Current Research with Implications for Clinical Practice and Healthcare Policy - Alex Vasquez, D.C., N.D. Copyright © 2005.
harm and greater financial expense. With ever-increasing costs and ever-worsening health outcomes, the American healthcare system is destined for collapse unless we change the model upon which our healthcare system is founded—namely that surgery and chemical drugs are the solutions to chronic diseases induced by nutritional deficiencies, oxidative stress, impaired detoxification, defects in fatty acid metabolism, altered gastrointestinal function, and neuromusculoskeletal dysfunction. We have reached an irrevocable impasse in which our current healthcare system dominated by drugs and surgery is no longer consistent with the balance of scientific research.

The time has come for patients and practitioners of natural healthcare to demand change and equitable access within the healthcare arena. Financial and legislative barriers imposed upon the general population which impede access to the safer and more cost-effective healthcare are intolerable if we intend to reverse the well-documented trends of progressive decline in American health and the escalating costs of medical health services. Rapid policy and legislative changes should be enacted to facilitate the public’s access to the healthcare services provided by chiropractic and naturopathic physicians so that we can reverse current trends enacted by overutilization of overpriced and hazardous medical interventions that threaten to bankrupt the nation and kill 200,000 Americans per year. If we assume that current trends will continue for the next five years as they have over the past several decades, then failure to enact progressive changes in national healthcare policy will continue to have adverse financial effects on the people, business, and communities of our nation and will precipitate an additional one million American deaths due to iatrogenic causes (200,000 deaths per year for five years = 1 million iatrogenic deaths). If the community of healthcare providers is to succeed in its purported altruistic mission of enacting improvements in healthcare delivery and improving the health of our fellow citizens and patients, and if we are to reverse the ongoing crises in American health and healthcare, we must actualize tangible and authentic reform as quickly as possible for the sake of our patients and the nation’s health. “Authentic reform” in this context specifically implies but is not limited to 1) naturopathic licensure with autonomous prescriptive authority for the remaining 37 states that currently deny their citizens access to the healthcare providers with the most training in therapeutic diets, interventional nutrition, botanical medicines, and lifestyle counseling, 2) limited prescriptive authority for chiropractic physicians at least for the purpose of legally discontinuing and thereby protecting their patients from pharmaceutical drugs known to significantly increase the risk of injury and death, 3) the nation-wide passage and enforcement of “every category of provider laws” to empower the public with financial access to and insurance coverage for nondrug nonsurgical healthcare providers.

The claim that “alternative medicine” is “unscientific” is no longer intellectually defensible. The American healthcare system is an exorbitantly expensive healthcare system that is failing to improve national health and is failing protect our citizens from a holocaust of iatrogenic morbidity and mortality while imposing an impressive financial burden on the citizens, families, communities, and small businesses of our nation. The only scientifically responsible action is to effect political change to empower equitable access to duly trained doctorate-level physicians. Each and every day, approximately 493 American patients die prematurely as a direct consequence—“side effect”—of allopathic medical care, and the numbers of patients who receive ineffectual, inadequate, inappropriate, and/or substandard medical care reaches into the millions; these are not issues for contention or debate—they are consistently documented and reported in mainstream, first-tier conservative “conventional” medical journals, such as JAMA, New England Journal of Medicine, American Family Physician, American Journal of Medical Quality, and Quality and...
Each chiropractic and naturopathic physician should commit to effective action or material contribution to organized efforts on a regular basis. Safe, effective, natural healthcare is what the public wants and what the public is demanding. The research has been and will continue to be in our favor because our low-cost, low-risk interventions effectively intervene at the primary level of disease causality rather than masking the symptoms of underlying dysfunction with higher-cost higher-risk chemical drugs. Direct and indirect support of the medical hegemony that unduly limits chiropractic and naturopathic physicians from access to patients and which results in unnecessary financial burdens on a large percentage of the individuals, families, businesses, and communities of this nation while killing with "side-effects" approximately 493 Americans per day is no longer scientifically, ethically, or financially defensible. Rectification of this situation requires primarily three components: 1) national licensure for naturopathic physicians who have graduated from residential 4-6 year doctorate programs\textsuperscript{825,826,827,828}, 2) limited prescriptive authority for chiropractic physicians at least for the purpose of legally discontinuing and thereby protecting their patients from pharmaceutical drugs known to significantly increase the risk of injury and death, 3) the nation-wide passage and enforcement of "every category of provider laws" to empower the public with financial access to and insurance coverage for nondrug nonsurgical healthcare providers.\textsuperscript{829,830} Progressively expensive medical costs absorb nearly 25% of America’s economic growth potential\textsuperscript{831} while medical treatments kill 493 Americans per day. Clearly, in the interests of patient care and national economic stability and growth, the time for change is now.

\textsuperscript{822} Holland EG, Degnuy FV. Drug-induced disorders. \textit{Am Fam Physician}. 1997 Nov 1;56(7):1781-8, 1791-2
\textsuperscript{823} “The results of the study demonstrate that, over the past four decades, the United States has been spending more and accomplishing less when compared with other industrialized nations.” Shi L. Health care spending, delivery, and outcome in developed countries: a cross-national comparison. \textit{Am J Med Qual} 1997;12(2):83-93
\textsuperscript{829} “Most health insurance plans in Washington state must provide access to every category of licensed health-care provider.” Mike Kestler, Washington Insurance Commissioner. \textit{Every Category Law and Your Health Insurance}. \url{http://www.insurance.wa.gov/factsheets/factsheet_detail.asp?FctShtRcdNum=54} Accessed February 17, 2005
\textsuperscript{830} Washington State Chiropractic Association. “Maintain and Protect “Every Category of Provider” Law: As always, the WSCA’s top priority is to maintain a patient’s right to choose the provider of their choice for the treatment of conditions covered in a health insurance plan.” \url{http://www.wschc.org/regulation/regulationAgendaDetails.htm} Accessed February 17, 2005
## Appendix A: Clinical and Physiologic Considerations of Vitamins and Minerals

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<th>Nutrients</th>
<th>Physiology, toxicity, and contraindications</th>
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| Vitamin A          | • Vitamin A comes in different forms with different characteristics; of these, all-trans retinol is the most common, and retinol palmitate is one of the least toxic. The richest dietary source of vitamin A is liver. Vitamin A has little or no antioxidant activity; carotenoids are antioxidants.  
  • Daily dose is should generally be <10,000 IU/d. Most patients should not consume more than 20,000 IU of vitamin A per day without express supervision by a healthcare provider. Vitamin A is present in some multivitamins, in cod liver oil, and in other supplements—read labels to ensure that the total daily intake is not greater than 20,000 IU per day. Approximately 200 cases of vitamin A toxicity are reported worldwide each year—a miniscule fraction of adverse effects compared to the number of people taking vitamin A supplements and compared to the number of people poisoned or killed by pharmaceutical drugs each year.  
  • Vitamin A is necessary for proper immune function, vision, cell growth and differentiation (especially epithelial tissue). Insufficiency of vitamin A causes epithelial tissue to produce excess keratin; hence the keratinization of the eye and skin in patients with vitamin A deficiency.  
  • Manifestations of vitamin A deficiency are night blindness (flash blindness), follicular hyperkeratosis, frequent infections, and poor wound healing. Tissue damage (ie, burns and trauma) and infections greatly increase the requirement for and tolerability of vitamin A supplementation.  
  • Short-term prescription of 100,000 – 200,000 IU per day is common in children and adults. Vitamin A toxicity is seen with chronic ingestion of therapeutic doses (for example: 25,000 IU per day for 6 years, or 100,000 IU per day for 2.5 years). Do not administer high doses to patients on numerous medications or with liver disease.  
  • Doses of vitamin A ≥ 10,000 IU are controversially associated with an increased risk for birth defects; therefore women who are pregnant or might soon become pregnant should keep their daily intake of vitamin A below 10,000 IU from all sources.  
  • Clinical applications for supraphysiologic doses of vitamin A include: adult acne, menorrhagia, and viral infections, especially measles.  
  • Patients must be advised of limited duration of use (e.g., 1 week) and to reduce or stop supplementation if signs of toxicity occur such as skin problems (dry skin, flaking skin, chapped or split lips, red skin rash, hair loss), joint pain, bone pain, headaches, anorexia (loss of appetite), edema (water retention, weight gain, swollen ankles, difficulty breathing), fatigue, and/or liver damage.  
  • Clinical experience: Any time you prescribe high-dose vitamin A (ie, greater than 25,000-50,000 IU per day), you must clearly define the time limit of this treatment in writing so that the patient will not mistakenly continue taking the vitamin and end up with vitamin A toxicity. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Carotenoids        | • Carotenoids are antioxidants and have additional specific functions. Fewer than 10% of carotenoids can serve as precursors to vitamin A; of these, beta-, alpha-, and gamma-carotene are the most efficient. Provitamin carotenoids are converted to all-trans retinal which is then converted to retinyl ester.  
  • Carotenoids are generally administered in microgram doses and should be delivered in a broad-spectrum combination including: beta carotene, alpha carotene, zeaxanthin, cryptoxanthin, and lutein.  
  • Virtually non-toxic when administered in rational doses from natural sources and in balanced combination. Conversion of carotenones to vitamin A is impaired in patients with diabetes and hypothyroidism. | • Antioxidant  
  • Immunosupportive (eg, in HIV)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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### Appendix A: Clinical and Physiologic Considerations of Vitamins and Minerals—continued

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| **Vitamin D3** (cholecalciferol) | - Vitamin D deficiency is well documented to be extremely common: ~40% of the general population and >90% of patients with musculoskeletal pain.  
  - The physiologic requirement for vitamin D3 is approximately 4,000 IU per day in adult men. Clinical guidelines for supplementation are as follows: 1,000 – 2,000 IU for infants; 2,000 IU for children and adolescents; 2,000-4,000 IU for adults, may go up to 10,000 IU per day for adults for up to 6 months and/or with laboratory supervision. Dietary sources of vitamin D are insufficient to meet physiologic needs—vitamin D needs can only be met by sun exposure (full-body, without sunscreen, near equatorial, near noon, for 10-20 minutes) or by high-dose vitamin D supplementation.  
  - Physiologic doses are non-toxic except in patients with vitamin D hypersensitivity or those taking certain medications that induce hypercalcemia.  
  - The thiazide class of diuretics (including hydrochlorothiazide) can induce hypercalcemia. Correction of underlying hypovitaminosis D may precipitate hypercalcemia.  
  - "Vitamin D hypersensitivity" is seen in granulomatous diseases including tuberculosis, sarcoidosis, Crohn’s disease, and some types of cancer; also adrenal failure, hypothyroidism and hyperthyroidism.  
  - Implement vitamin D replacement in all patients unless contraindicated. Vitamin D assessment and administration is becoming the standard of care and failure to implement vitamin D therapy may be grounds for malpractice.  
  - Assess vitamin D status with 25-OH-vitamin D.  
  - Monitor for vitamin D toxicity by measuring serum calcium.  
|                         | **Conditions Associated with Vitamin D Deficiency:**  
  - Rickets (children) and osteomalacia (adults)  
  - osteoporosis  
  - diabetes mellitus  
  - osteoarthritis  
  - hypertension  
  - cardiovascular disease  
  - metabolic syndrome  
  - depression  
  - multiple sclerosis  
  - rheumatoid arthritis  
  - Grave’s disease  
  - ankylosing spondylitis  
  - systemic lupus erythematosus  
  - cancers of the breast, prostate, and colon  
  - polycystic ovary syndrome  
  - musculoskeletal pain  
  - epilepsy  
  - migraine headaches  
  - Chronic low-back pain  
  - Inflammation |
| **Vitamin E**           | - Deficiency of vitamin E is rarely recognized but can present as ataxia and neurologic dysfunction, especially in patients with malabsorption. Best dietary sources are seed and nut oils, especially sesame seeds, almonds, sunflower seeds, and wheat germ oil.  
  - A reasonable preventive dose is 200-800 IU per day. Doses up to 3,200 IU per day are generally considered nontoxic.  
  - Vitamin E is commonly described as a "chain breaking antioxidant" with special importance in protecting cell membranes and lipoproteins from oxidative damage.  
|                         | "Vitamin E" is a family of related chemicals including:  
  - DL-tocopherol: this is synthetic and should never be used. Don’t even give this to your dog.  
  - Alpha-tocopherol: commonly used but it depletes the body of the more important gamma-tocopherol.  
  - Beta-tocopherol:  
  - Delta-tocopherol:  
  - Gamma-tocopherol: this is the most important form of vitamin E and should be provided at approximately 40% when "mixed tocopherols" are consumed.  
  - Tocopherol succinate: specific for improving mitochondrial function and for its anti-cancer effect.  
  - Tocotrienols: appear protective against breast cancer |
Appendix A: Clinical and Physiologic Considerations of Vitamins and Minerals—continued

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| Vitamin K1 (phylloquinone): from plants | • Vitamin K1 (phylloquinone)—this is the form of vitamin K found in plants  
• Vitamin K2 (menaquinone)—found in animal tissues and synthesized by bacteria  
• Vitamin K3 (menadione)—synthetic form that must be alkylated in the body prior to use; this form of vitamin K is difficult to obtain and is generally not used for nutritional supplementation.  
  • 500-1000 mcg is a common supplemental dose.  
• Vitamin K must not be taken by patients needing anticoagulation and taking coumadin-warfarin-heparin. Vitamin K is necessary for the production of clotting factors: factor II (prothrombin), factor VII, factor IX, and factor X.  
  • Vitamin K is also necessary for the formation of osteocalcin—a calcium-binding protein in bone. | • Vitamin K is necessary for bone formation and blood clotting, thus obvious clinical applications include osteoporosis/osteopenia and menorrhagia/ecchymosis.  
• Vitamin K1 (phylloquinone)—doses of at least 1,000 IU per day of K1 are needed in order to optimize carboxylation of osteocalcin.  
• Vitamin K2 (menaquinone)—A recent study with 21 patients in the treatment group published in JAMA used 45 mg/d (forty five milligrams per day = 45,000 mcg per day) of vitamin K2 for an 80% reduction in liver cancer in patients with viral cirrhosis: “Compliance with vitamin K2 in the treatment group was good; no patient had adverse reactions or dropped out of the study.”  
| Vitamin K2 (menaquinone): from animals and bacteria | | |
| Vitamin K3 (menadione): synthetic | | |
| B-1 (thiamine) | • Classic deficiency is dry beriberi (central and peripheral neurologic dysfunction, dementia, psychosis, weakness, neuropathy) and wet beriberi (congestive heart failure). The classic CNS manifestations of thiamine/magnesium deficiency seen in alcoholics is Wernicke-Korsakoff syndrome.  
• Conversion from the inactive form to the active form of the vitamin requires magnesium.  
• Functions include: enzyme cofactor, aldehyde transfer, modulates chloride ion channels in the CNS, energy production in hexose monophosphate shunt, phagocytic respiratory burst, neurotransmitter synthesis and release.  
• Anaphylaxis to parenteral thiamine has been reported. | • 20-100 mg is a common supplemental dose; one study used 5,000 mg to find evidence of a cholinergic effect.  
• The densest food source of thiamine is brewer’s yeast.  
• Thiamine insufficiency is common in patients with cardiomyopathy. Alleviates congestive heart failure in some patients, especially when used with CoQ10 and magnesium.  
• Deficiency is common in the demented elderly; alleviates “Alzheimer’s disease” in some patients |
| B-2 (riboflavin) | • Classic deficiency: angular stomatitis  
• 20-200 mg is a common supplemental dose. The richest dietary sources are yeast and liver.  
• Several studies have used 400 mg per day in patients with migraine and have not reported any serious adverse effects.  
• Functions include: enzyme cofactor (especially for energy production as FAD in the electron transport chain), drug/xenobiotic detoxification via support of Cy-P450, antioxidant functions via glutathione reductase. | • 400 mg per morning is safe and effective for the alleviation of migraine. |

### Appendix A: Clinical and Physiologic Considerations of Vitamins and Minerals—continued

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<tr>
<td><strong>B-3: niacin</strong></td>
<td>- Classic deficiency is pellagra: depression, dermatitis, dementia, diarrhea, death. Endogenous production requires 60 mg tryptophan to make 1 mg niacin. Richest dietary sources are yeast, rice bran, wheat bran, liver, and poultry breast meat.</td>
<td>- Dyslipidemia: Niacin at 2000-3000 mg per day in divided doses can lower total and LDL cholesterol, fibrinogen, triglyceride levels, and raise HDL. In a head-to-head study 2,000 mg niacin was more powerful than 1,200 mg gemfibrozil for favorably modifying lipids.845</td>
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<td>- 20-100 mg is a common supplemental dose; doses up to 2,000 mg per day in divided doses are used for the treatment of hypercholesterolemia and must be monitored with lab tests to assess for possible liver dysfunction. Up to 6 grams (6,000 mg) per day in divided doses has been used safely.</td>
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<td>- Liver damage has been seen with doses &gt; 2,000 mg per day. Patients on high doses must be monitored with periodic measurements of liver enzymes; not to be used in patients with liver disease. “Time-release niacin” is the most hepatotoxic form of niacin.</td>
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<tr>
<td><strong>B-3: niacinamide</strong></td>
<td>- 20-100 mg is a common supplemental dose.  - 500 mg 4-6 times per day for 2,000 – 3,000 mg per day is safe and effective for osteoarthritis.  - Toxicity is rare; however monitoring liver enzymes at 1 and 4 months and yearly thereafter is encouraged when doses ≥ 2000 mg are used.</td>
<td>- anti-aging (reversal of aging phenotypes via histone acetylation)  - osteoarthritis</td>
</tr>
<tr>
<td><strong>B-3: inositol hexaniacinate (“no-flush niacin”)</strong></td>
<td>- This is a slow release form of vitamin B3 that allows supplementation with niacin at high doses without the flushing and hepatotoxicity seen with plain niacin. However, despite one enthusiastic article stating that this is the preferred form of B3 for treating lipid disorders, inositol hexaniacinate appears clinically ineffective for the treatment of dyslipidemia.</td>
<td>- 2000 mg per day in divided doses of 500-1000 mg each is common.  - 4,000 mg per day safely improves circulation in patients with Raynaud’s phenomenon846</td>
</tr>
<tr>
<td><strong>B-5 (pantothenic acid)</strong></td>
<td>- Deficiency is generally unrecognized, but may include depression, acne, anemia, and weight gain; richest dietary sources are yeast and liver.  - Main physiologic functions include its structural role in the formation of the Coenzyme A molecule.</td>
<td>- 20-100 mg is a common supplemental dose, and doses of 10,000 mg calcium pantothenate have been used safely; it is virtually non-toxic.  - May help alleviate fatigue in some patients.  - May alleviate acne.</td>
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<td><strong>B-6</strong></td>
<td>♦ Deficiency can cause widespread—subtle or severe—problems and manifestations since this cofactor is used in more than 100 enzymatic reactions. Modest dietary sources are yeast, sunflower seeds, and wheat germ. Deficiency of B6 can be induced by the drug Isoniazid. ♦ 20-100 mg is a common supplemental dose; 250 mg per day with breakfast is safe and reasonable when higher doses are needed; this should be co-administered with a multivitamin/multimineral supplement that supplies other vitamins and minerals, especially replacement doses (200-600 mg) of magnesium. Very high doses of vitamin B6 (600-900 mg) are supported by the literature for the treatment of specific conditions, and doses ≤ 1,000 mg per day have been used safely with doctor supervision. ♦ Peripheral sensory (and motor) neuropathy has been reported in patients taking gram doses for several years. Most of these reports appear associated with synthetic pyridoxine HCl and the toxicity is likely due to untreated magnesium deficiency which impairs conversion of neurotoxic pyridoxine HCl into the safe and active pyridoxal 5′ phosphate. Doses of B6 greater than 150 mg may suppress prolactin and lactation.</td>
<td>♦ Pyridoxine HCl is synthetic and somewhat neurotoxic until it is converted to pyridoxal 5′ phosphate which requires magnesium. Pyridoxine HCl must always be coadministered with magnesium. ♦ Clinical applications: carpal tunnel syndrome, autism, epilepsy, PMS, calcium oxalate nephrolithiasis, nausea/vomiting of pregnancy. ♦ Vitamin B6 is commonly used to promote various forms of detoxification; however high doses may paradoxically inhibit the sulfotransferase aspect of detoxification.</td>
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<tr>
<td><strong>B-12 (cobalamin)</strong></td>
<td>♦ Classic deficiency manifests as megaloblastic anemia, dorsal column lesions (ie, loss of pedal vibration and proprioception), mental depression, fatigue, peripheral neuropathy. “Pernicious anemia” is a type of B12 deficiency caused by autoimmune atrophic gastritis wherein parietal cells are destroyed, leaving the host without intrinsic factor. Best dietary sources are liver, clams, and kidneys—vegetarian diets are notoriously deficient in B12. ♦ 100 – 2,000 mcg is a common supplemental dose; at least 2,000 mcg per day is required to increase blood levels in patients with B12 deficiency and malabsorption ♦ essentially non-toxic ♦ cyanocobalamin contains cyanide and should be avoided; anaphylaxis to parenteral b12 has been reported</td>
<td>♦ Cyanocobalamin contains cyanide and should be avoided as it can contribute to chronic cyanide toxicity and loss of vision (tobacco-alcohol amblyopia)—the treatment for the latter problem is administration of nutrients with an emphasis on hydroxocobalamin ♦ “active” forms include methylcobalamin and hydroxocobalamin ♦ At least 2,000 mcg per day is required to increase blood levels in patients with B12 deficiency to the same levels that can be obtained with standard regimens of parenteral/intramuscular administration. ♦ Vitamin B12 in high doses appears to help alleviate low-back pain: this study used intramuscular administration, but high-dose oral supplementation should be superior if doses &gt;2,000 mcg are used. ♦ Can alleviate fatigue, especially neurogenic fatigue in patients with chronic infections</td>
</tr>
</tbody>
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847) Ames BN, Elson-Schwab I, Silver EA. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K(m)): relevance to genetic disease and polymorphisms. Am J Clin Nutr. 2002 Apr;75(4):616-58
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<td><strong>Biotin</strong></td>
<td>♦ Necessary for fatty acid metabolism and mitochondrial function. Deficiency can include hyperlactatemia, ataxia, seizures, hypotonia, seborheic dermatitis, and hair loss. Richest dietary source is brewer’s yeast. Deficiency is uncommon in the general population however it is commonly seen in patients taking inadequate parenteral nutrition. ♦ <strong>Virtually non-toxic:</strong> In 2001, the Food and Nutrition Board (FNB) reported that no adverse effects had been documented due to either dietary or supplemental consumption of biotin, and this document was still presented as accurate/current as of September 2005.851 ♦ Avidin in raw egg whites irreversibly binds to biotin and prevents absorption ♦ 50 – 3,000 mcg is a common supplemental dose. ♦ May provide benefit to diabetics, especially for the treatment/prevention of peripheral neuropathy852 ♦ Biotin deficiency during pregnancy is common may result in birth defects; supplementation of pregnant women with ~300 mcg is warranted853</td>
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<tr>
<td><strong>Folic acid</strong></td>
<td>♦ Found in low doses in foliage. Numerous functions include the transfer of methyl groups, necessary for the formation of myelin, neurotransmitters, and for the protection of DNA. Brewer’s yeast is clearly the densest dietary source of folic acid. Deficiency causes macrocytic anemia, fatigue, depression, and hyperhomocysteinemia. B12 and folic acid should be coadministered. ♦ 800 mcg is a reasonable supplemental dose and should be considered the minimal supplemental dose. Doses of 5, 10, and 20 mg (ie, up to 20,000 mcg) are commonly used and are generally safe. ♦ Use folic acid cautiously in patients with a history of seizure or those who are taking anti-seizure medications. Anti-seizure medications induce deficiency of folate, and if folate is replaced, then anti-seizure protection may be lost. ♦ Always use with B-12 and other b-vitamins ♦ Potentiates antidepressants by addressing the previously undiagnosed folic acid deficiency ♦ Improves efficacy and reduces toxicity of methotrexate ♦ Lowers homocysteine levels, may also require B12, B6, NAC, etc.</td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin C</strong></td>
<td>♦ Classic deficiency is scurvy: bleeding gums, subcutaneous bleeding (ecchymoses, petechiae), weak and friable skin and mucus membranes, reduced immunity, corkscrew hairs, and follicular hyperkeratosis. Vitamin C has some function as an antioxidant, in immune support, and in (dopaminergic) neurotransmission. The best dietary sources are fresh fruits and vegetables, which also contain the phytochemicals necessary to optimize the function of vitamin C. ♦ 500-1,000 mg is a reasonable daily dosage for preventive healthcare; ♦ High doses cause benign loose stools; this varies from patient to patient and time to time; some patients get loose stools with 500 mg while others can tolerate 10,000 mg with no problems. ♦ Intravenous ascorbate can induce hemolysis in patients with G6PD deficiency ♦ Oral supplementation can exacerbate cardiac complications of iron overload.854 ♦ Anti-allergy benefits in high doses due to mechanisms including ~40% reductions in serum histamine ♦ 6,000 mg/d in divided doses has been shown to have anti-stress benefits.855 ♦ Anticancer effects may require bowel-tolerance dosing or intravenous administration. ♦ High doses benefit autistic children via a dopaminergic mechanism856</td>
<td></td>
</tr>
</tbody>
</table>

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### Appendix A: Clinical and Physiologic Considerations of Vitamins and Minerals—continued

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Physiology, toxicity, and contraindications</th>
<th>Clinical applications and notes (for adult patients)</th>
</tr>
</thead>
</table>
| **Calcium** | ♦ 500 - 1,500 mg is the common supplemental dose.  
♦ 1,000 - 1,500 mg is the recommended supplemental dose in patients with osteopenia  
♦ may promote constipation, especially if not balanced with magnesium, supplementation should provide a 1:2 to 1:1 ratio of calcium to magnesium  
♦ do not administer with certain medications, especially antibiotics such as tetracycline, due to the binding effect which renders the drug systemically unavailable and can result in death in patients with life-threatening infections like pneumonia | ♦ can promote constipation  
♦ always use with magnesium  
♦ alleviates bruxism  
♦ alleviates PMS  
♦ significantly lowers blood pressure when used with vitamin D |
| **Magnesium** | ♦ Magnesium deficiency is clearly one of the most common nutritional deficiencies in all populations.  
♦ 200 -800 mg is a common supplemental dose; high doses cause loose stools.  
♦ Do not administer high doses to patients with severe constipation or with renal failure due to potential for hypermagnesemia.  
♦ Do not administer with certain medications, especially antibiotics such as tetracycline, due to the binding effect; spironolactone is a magnesium-sparing diuretic that can potentiate hypermagnesemia. | ♦ alleviates bruxism  
♦ alleviates PMS  
♦ alleviates migraine headaches  
♦ alleviates constipation  
♦ alleviates muscle spasm and hypertonicity  
♦ helps with asthma, hypertension, insomnia, irritability, anxiety, detoxification, |
| **Zinc** | ♦ 10 – 25 mg per day is common in supplements;  
♦ Doses up to 150 mg can be used therapeutically, preferably for short-term only or used with 2-4 mg copper  
♦ Excess or imbalanced zinc supplementation can promote copper deficiency by competition for absorption  
♦ Do not use high-dose zinc in patients with Alzheimers disease.  
♦ Must be administered with food in order to avoid stomach irritation | ♦ Improves mucosal integrity in patients with Crohn’s disease when used at 150 mg per day  
♦ Promotes tissue healing: trauma, diabetic ulcers |
| **Copper** | ♦ 2 mg is the most common supplemental dose  
♦ Excess or imbalanced copper supplementation can promote zinc deficiency by competition for absorption  
♦ Wilson’s disease is a type of copper toxicity associated with liver disease and neuropsychiatric disorder | ♦ A good multivitamin should have enough so that you don’t have to use a separate supplement.  
♦ up to 4 mg per day can be used in patients with connective tissue disorders such as Marfan’s syndrome and/or to promote healing |
| **Chromium** | ♦ 200 is the most common supplemental dose  
♦ 500 mcg is commonly used in diabetics  
♦ doses up to 1,000 mcg have been used safely in diabetics  
♦ may potentiate diabetic medications; start slowly and with 6xdaily glucose monitoring in severe diabetics | ♦ A good multivitamin should have enough so that you don’t have to use a separate supplement.  
♦ Can alleviate diabetes  
♦ Can alleviate hypoglycemia |

### Appendix A: Clinical and Physiologic Considerations of Vitamins and Minerals—continued

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</table>
| **Iodide**  | • Necessary for the formation of thyroid hormone                                                             | • Daily doses greater than 750 mcg iodide contribute to exacerbation of hypothyroidism in patients with pre-existing thyroid disorders or borderline thyroid function.\(^{858}\)  
• May beneficially modulate estrogen metabolism in women                                                                 |  
• High doses of iodine 3-6 mg per day can reduce breast pain during 6 months of treatment\(^{859}\); long-term safety and efficacy have not been demonstrated with high-dose oral supplementation.  
• Lecithin-bound iodine modulates cytokine release and may improve symptoms in patients with asthma\(^{860}\)  
• At least one author/researcher/clinician has advocated the use of high-dose iodine supplementation (“orthoiodosupplementation”) and has used 50 mg per day (fifty milligrams per day) in patients; it may be that the toxicity associated with iodine-containing drugs (Amiodarone: antiarrythmic) is due to the drug itself and not the iodine.\(^{861}\)  
• Rationale for “high dose” iodine supplementation is suggested by the increased prevalence of halogenated/brominated pesticides/herbicides and other pollutants in our environment which are known to have adverse health effects. |
| **Potassium** | • get this from fruits and vegetables, not from supplements                                                | • lowers blood pressure  
• high-normal intake of potassium from fruits and vegetables can cause fatal hyperkalemia in patients with renal failure such as due to diabetes  
• potassium reduces risk of stroke independently from its ability to lower blood pressure  
• promotes urinary alkalinization, which is important for mineral retention and increased excretion of most xenobiotics                                                                 |  
| **Selenium** | • 200 mcg is considered the standard supplemental and therapeutic dose                                      | • antioxidant  
• daily doses should be kept below 800 mcg  
• protects against cancer and heart disease  
• immunosupportive; powerfully inhibits risk of serious infection in patients with HIV                                                                 |  

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\(^{858}\) Chow CC, Phillips DI, Lazarus JH, Parkes AB. Effect of low dose iodide supplementation on thyroid function in potentially susceptible subjects: are dietary iodide levels in Britain acceptable? Clin Endocrinol (Oxf). 1991 May;34(5):413-6  
\(^{860}\) Kawano Y, Saeki T, Noma T. Effect of lecithin-bound iodine on the patients with bronchial asthma. Int Immunopharmacol. 2005 Apr;5(4):805-10  
\(^{861}\) Abraham GE. Serum inorganic iodide levels following ingestion of a tablet form of Lugol solution: evidence for an enterohepatic circulation of iodine. The Original Internist. 2004; 11: 29-35
# Appendix A: Clinical and Physiologic Considerations of Vitamins and Minerals—continued

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<th>Nutrients</th>
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</tr>
</thead>
</table>
| **Iron**  | ♦ Iron supplementation should not be used in patients unless their iron levels are low, and this is determined by measuring serum ferritin—not by performing a CBC which can show anemia that is unrelated to iron deficiency and which may be associated with iron overload.  
♦ The finding of iron deficiency in any adult patient requires that the patient be referred to a gastroenterologist for endoscopic evaluation. Failure to make a timely referral for any adult patient with iron deficiency is grounds for malpractice litigation.  
♦ Iron promotes the formation of “free radicals” and is thus implicated in several diseases, such as infections, cancer, liver disease, diabetes, and cardiovascular disease. Iron supplements should not be consumed except by people who have been definitively diagnosed with iron deficiency by measurement of serum ferritin. See [http://vix.com/menmag/alexiron.htm](http://vix.com/menmag/alexiron.htm) | ♦ Never use iron supplementation without first testing serum ferritin.  
♦ Replacement dose for iron deficiency is 60-180 mg of iron per day. 40-60 mg 3x per day is reasonable for correcting iron deficiency; may promote constipation and stomach upset; consume with food, especially meat;  
♦ All adult patients with iron deficiency have a gastrointestinal lesion such as cancer until proven otherwise. YOU MUST REFER THESE PATIENTS TO A GASTROENTEROLOGIST.  
♦ See diagram below from [Integrative Orthopedics: www.OptimalHealthResearch.com](http://www.OptimalHealthResearch.com) |

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**Screen asymptomatic patients.**

**Follow-up abnormal laboratory results.**

(high serum iron, elevated liver enzymes, high blood glucose, etc.)

**Assess iron status with transferrin saturation and serum ferritin.**

*Use fasting morning specimen.*

**IRON-DEFICIENCY**

* serum ferritin:<10-15 in women, <20 in men, transferrin saturation:<16%  

In adults with no obvious cause of blood loss: Assume pathologic gastrointestinal bleeding until proven otherwise. Simply testing for occult blood in the stool is insufficient. Refer for complete (endoscopic) evaluation.

**“HEALTHY IRON STATUS”**

transferrin saturation:25-30%  

serum ferritin: 30-70

Periodically assess iron status as part of routine health assessment. Consider assessment for impending iron deficiency. Consider periodic blood donation and low-iron diet to maintain healthy iron status.

**“MODERATE IRON OVERLOAD”**

transferrin saturation: >33-45%  

serum ferritin: 80-160

No treatment is mandatory. Periodically assess iron status as part of routine health assessment. Consider low-iron diet and regular blood donation to reduce risk of cancer and myocardial infarction.

**POSSIBLE SEVERE IRON OVERLOAD**

transferrin saturation: >40% and/or serum ferritin: >160 in women; >200 in men

Repeat tests with fasting morning specimen. Consider other causes of elevated transferrin saturation or elevated serum ferritin.*

**PROBABLE SEVERE IRON OVERLOAD**

Ferritin >200 in women, or Ferritin >300 in men  

Confirm with diagnostic phlebotomy, or liver biopsy, or MRI.

* Factors that alter iron assessment tests:
  
False elevations of transferrin saturation: cancer, liver disease, inflammation, infection, excess alcohol consumption, non-fasting specimens.

False elevations of ferritin: inflammation, infection, cancer, excess alcohol consumption, liver disease, early pregnancy, hyperthyroidism, tissue necrosis, hyperferremia-cataract syndrome and other rare genetic/congenital syndromes.

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Dr. Alex Vasquez

OptimalHealthResearch.com

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A Detailed Review of Current Research with Implications for Clinical Practice and Healthcare Policy - Alex Vasquez, D.C., N.D. Copyright © 2005. 57 of 58.
### Resources

**The American Association of Naturopathic Physicians**

3201 New Mexico Avenue, NW Suite 350
Washington, DC 20016
Toll free: 1-866-538-2267
Local: 202-895-1392
Fax: 202-274-1992

Website: [www.naturopathic.org](http://www.naturopathic.org)

**American Chiropractic Association**

1701 Clarendon Blvd, Arlington, VA 22209
Phone 800/986-4636
Website: [www.amerchiro.org](http://www.amerchiro.org)

**Worstpills.org**

1600 20th Street, North West
Washington, DC 20009
Website: [www.WorstPills.org](http://www.WorstPills.org)

### Misprescribing and Overprescribing of Drugs

The numbers are staggering: in 2003, an estimated 3.4 billion prescriptions were filled in retail drugstores and by mail order in the United States. That averages out to 11.7 prescriptions filled for each of the 290 million people in this country. But many people do not get any prescriptions filled in a given year, so it is also important to find out how many prescriptions are filled by those who fill one or more prescriptions. In a study based on data from 2000, more than twice as many prescriptions were filled for those 65 and older (23.5 prescriptions per year) than for those younger than 65 (10.1 prescriptions per year). Another way of looking at the high rate of prescriptions among older people is the government finding that although Medicare beneficiaries comprise only 14% of the community population, they account for more than 44% of prescription medicine expenses. 
About the Author: Alex Vasquez, B.S., D.C., N.D.

Dr. Alex Vasquez began his professional studies at Texas Chiropractic College and later graduated from Western States Chiropractic College with his Bachelor of Science and Doctor of Chiropractic degrees. Following graduation and chiropractic licensure, Dr. Vasquez attended the Bastyr University to complete his Doctor of Naturopathic Medicine degree. He maintained a private practice of chiropractic and naturopathic medicine in Seattle while serving as Adjunct Professor of Orthopedics, Rheumatology, and Radiographic Interpretation before returning to Houston in 2001. He is a licensed naturopathic physician with prescriptive authority in Washington and Oregon and is a licensed chiropractic doctor in Texas. Dr. Vasquez is the author of more than 20 scientific articles and a 486-page textbook, *Integrative Orthopedics: The Art of Creating Wellness while Effectively Managing Acute and Chronic Musculoskeletal Disorders*. His plans for the future include pursuing an MD or DO degree and completing his upcoming textbooks in Rheumatology and Oncology.

Publications and Presentations—an incomplete listing:

- Vasquez A, Cannell J. Calcium and vitamin D in preventing fractures: data are not sufficient to show inefficacy. *BMJ: British Medical Journal* 2005;331:108-9
- Vasquez A. High-Dose Vitamin D - One of the Best Nutritional Supplements on the Market. *Nutritional Wellness* July, 2006
- Vasquez A. Reducing pain and inflammation naturally - Part 4: Nutritional and Botanical Inhibition of NF-kappaB, the Major Inflammatory Cascade of the Inflammatory Cascade: A Practical Clinical Strategy Exemplifying Anti-Inflammatory Nutrigenomics. *Nutritional Perspectives* July 2005; 5-12
- Vasquez A. Subphysiologic Doses of Vitamin D are Subtherapeutic: Comment on the Study by The Record Trial Group. *TheLancet.com* June 16, 2005
- Dave N. Muanza, Ph.D., Alex Vasquez, John Cannell, M.D., William P Grant, Ph.D. Isoflavones and Postmenopausal Women. *JAMA: Journal of the American Medical Association* 2004; 292: 2337
- Vasquez A. John Cannell, MD. Better Bones and Beyond: Vitamin D Plays Role in Inflammatory and Metabolic Disease. *Holistic Primary Care* 2004; (Fall) 5: 3,6,7
- Vasquez A. Alternative Treatments for Hepatitis. *Hepatitis Magazine Conference in Houston, Texas* November 9, 2002
- Vasquez A. Holistic and Natural Approaches to Helping People with Narcolepsy. *Narcolepsy Network’s Convention in Las Vegas, Nevada* 2002, October 18-20
- Vasquez A. Natural Approaches to Menopause. *Impressions - A publication of The Women’s Fund for Health Education and Research* 2002 Fall, page 10
- Vasquez A. Gender inequality in health and healthcare. *Wingspan* 1999; April-June, 8-9
- Vasquez A. Men’s Health: Valuing gender equality in health and healthcare. *MEN Magazine* 1997; August: 10-11, 19
- Vasquez A. Men’s Health: Mind and body, soul: the need for re-creation and the art of building a walled garden. *MEN Magazine* 1997; July: 10-11
- Vasquez A. Musculoskeletal disorders and iron overload disease: comment on the American College of Rheumatology guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. *Arthritis & Rheumatism—Official Journal of the American College of Rheumatology* 1996; 39:1767-8
- Vasquez A. Hereditary Hemochromatosis: It’s not just for Caucasians.*Townsend Letter for Doctors and Patients* 1996;July:88
- Vasquez A. Knowledge of hemochromatosis is prerequisite to its diagnosis and treatment. *Townsend Letter for Doctors and Patients* 1995; December: 96-8
- Vasquez A. Iron in Men: Why men store this nutrient in their bodies and the harm that it does. *Mentor* 1995; Fall: 24-25
- Vasquez A. High body iron stores: causes, effects, diagnosis, and treatment. *Nutritional Perspectives* 1994;17:13,15-7,19,21,28
- Vasquez A. Hemochromatosis and iron. *Townsend Letter for Doctors* 1994; August/September: 914-6
The following section describes some of the nutritional and botanical products from Biotics Research Corporation (BioticsResearch.com) that might be used for clinical implementation of the concepts described in this paper.
The new high-potency multivitamin/multimineral from Biotics

The most potent broad-spectrum multivitamin and multimineral supplement on the professional market.

Includes Green Tea, Quercetin, and Bioflavonoids.

Piperine—from black peper—enhances nutrient absorption.

<table>
<thead>
<tr>
<th>Dose: 3 capsules twice per day serving (highest RDA) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (palmitate)</td>
</tr>
<tr>
<td>Mixed carotenoids</td>
</tr>
<tr>
<td>Vitamin E: tocopherol succinate with mixed tocopherols</td>
</tr>
<tr>
<td>Vitamin D3 (cholecalciferol)</td>
</tr>
<tr>
<td>Vitamin C</td>
</tr>
<tr>
<td>Vitamin K1</td>
</tr>
<tr>
<td>Thiamin (B1) active cocarboxylase</td>
</tr>
<tr>
<td>Riboflavin (B2)</td>
</tr>
<tr>
<td>Riboflavin-5-phosphate (B2)</td>
</tr>
<tr>
<td>Vitamin B3: Niacinamide</td>
</tr>
<tr>
<td>Inositol hexaniacin (niacin)</td>
</tr>
<tr>
<td>Pantothenic Acid</td>
</tr>
<tr>
<td>Vitamin B6 (pyridoxine HCL)</td>
</tr>
<tr>
<td>Vitamin B6 (active form P5P)</td>
</tr>
<tr>
<td>Folic Acid</td>
</tr>
<tr>
<td>B-12: Hydroxocobalamin</td>
</tr>
<tr>
<td>Biotin</td>
</tr>
<tr>
<td>Calcium (citrate)</td>
</tr>
<tr>
<td>Magnesium (citrate/ oxide)</td>
</tr>
<tr>
<td>Zinc (citrate)</td>
</tr>
<tr>
<td>Selenomethionine</td>
</tr>
<tr>
<td>Sodium selenite</td>
</tr>
<tr>
<td>Copper (citrate)</td>
</tr>
<tr>
<td>Manganese (citrate)</td>
</tr>
<tr>
<td>Molybdenum (glycinate)</td>
</tr>
<tr>
<td>Chromium picolinate</td>
</tr>
<tr>
<td>Iodine (potassium iodide)</td>
</tr>
<tr>
<td>Boron (gluconate)</td>
</tr>
<tr>
<td>Vanadium (aspartate)</td>
</tr>
<tr>
<td>Green tea extract</td>
</tr>
<tr>
<td>Quercetin</td>
</tr>
<tr>
<td>Citrus Bioflavonoids</td>
</tr>
<tr>
<td>Piperine</td>
</tr>
</tbody>
</table>

No fillers, no colors, no allergens, no sugar, no junk

3 capsules 2 times per day provides the most potent multivitamin and multimineral on the Professional healthcare market. It is as simple as that—this is an excellent multivitamin supplement: potent, balanced, and with bioflavonoids. Includes piperine for increased nutrient absorption.
CHONDROSAMINE PLUS

CHONDROSAMINE-S

Joint cartilage is dynamic, living tissue that requires a constant supply of many nutrients to maintain structure and function and to resist degeneration from traumatic injury and from normal "wear and tear" which occurs with everyday activities.

Three (3) capsules supply:
- Vitamin C (as ascorbic acid) 180 mg
- Niacin (as niacinamide) 50 mg
- Pantothenic Acid (as calcium pantothenate) 45 mg
- Folic Acid 200 mcg
- Vitamin B12 (as cobalamin) 3 mcg
- Manganese (as manganese gluconate) 6 mg
- Purified chondroitin sulfate (bovine) 500 mg
- MSM (methylsulfonylmethane) 100 mg
- Saccharum Officinarum extract (shoots) 25 mg
- Superoxide Dismutase (vegetable culture) 20 mcg
- Catalase (from vegetable culture) 20 mcg
- CHONDROSAMINE PLUS provides Glucosamine (1000 mg elemental) derived from glucosamine HCL
- CHONDROSAMINE-S provides Glucosamine (600 mg elemental) derived from glucosamine sulfate

3 capsules 2 times per day of Chondrosamine Plus or Chondrosamine-S provides proven doses of chondroprotective nutrients and is an excellent treatment for osteoarthritis. 865,866,867,868

3 capsules once per day is sufficient for "maintenance" once acute symptoms of osteoarthritis have subsided.

Research also suggests that purified chondroitin sulfate can protect against cardiovascular disease and myocardial infarction. 869,870,871,872

No drug interactions are known.

Allergy to chondroitin/glucosamine has been reported once or twice in the research.

866) van Blitterswijk WJ, ... Glucosamine and chondroitin sulfate supplementation to treat symptomatic disc degeneration: biochemical rationale and case report. BMC Complement Altern Med. 2003;3(1/2
Proteolytic enzymes are known to break-down proteins into amino acids. Therefore, proteolytic enzymes can be used to support the body's digestion of protein-containing foods.

Proteolytic enzymes have also been shown to facilitate tissue healing after injury by breaking-down products of inflammation.

Each tablet supplies:
- Pancreatin 4X (from porcine) 100 mg
- Bromelain 50 mg
- Papain 50 mg
- Lipase 10 mg
- Amylase 10 mg
- Trypsin & Alpha Chymotrypsin (from porcine) 100 mg
- Superoxide Dismutase (from vegetable culture) 10 mcg
- Catalase (from vegetable culture) 10 mcg

Orally administered proteolytic enzymes are well absorbed from the gastrointestinal tract into the systemic circulation. The anti-tumor, anti-metastatic, anti-infectious, anti-inflammatory, analgesic, and anti-edematous actions result from the dose-dependent (about 8 tablets 3 times per day) stimulation of reactive oxygen species production and anti-cancer cytotoxicity in human neutrophils, a pro-differentiative effect, reduction in PG-E2 production, reduction in substance P production, modulation of adhesion molecules and cytokine levels, fibrinolytic effects and a anti-thrombotic effect mediated at least in part by a reduction in 2-series thromboxanes.

8 tablets 3 times per day between meals is reasonable for clinical use in adults. Lower doses (such as 2 tablets 2-3 times per day) are also effective, especially for treating benign conditions like osteoarthritis or bursitis.

---

878) Gaspani L, Limondi E, Ferraro P, Bianchi M. In vivo and in vitro effects of bromelain on PGE(2) and SP concentrations in the inflammatory exudate in rats. Pharmacology. 2002;65(2):83-6
Bio-D-Mulsion and Bio-D-Mulsion Forte

Vitamin D has a well-established role in calcium homeostasis and the maintenance of bone health. Biotics’ Bio-D-Mulsion has excellent absorption due to the unique emulsification process. Previous research with emulsification showed that absorption of CoQ-10 was greatly increased by emulsification, resulting in higher serum levels and improved cost-effectiveness. 881,882,883,884

Recent articles indicate that the prevalence of vitamin D deficiency is much higher than previously recognized (more than 90% in patients with chronic pain, according to a recent study published by the Mayo Clinic), and that vitamin D supplementation is much safer than previously recognized (up to 4,000 IU rather than 400 IU for adults). Recent articles have also suggested that vitamin D may have a role in the prevention and treatment of many chronic diseases. We are clearly on the verge of a paradigm shift with regard to our understanding and clinical use of vitamin D. 885

Bio-D-Mulsion
Servings per bottle: 750
Product code: # 1007

Bio-D-Mulsion: Each drop supplies 400 IU of vitamin D in the form of cholecalciferol.

Bio-D-Mulsion Forte
Servings per bottle: 750
Product code: # 1012

Bio-D-Mulsion Forte: Each drop supplies 2,000 IU of vitamin D in the form of cholecalciferol

Dr Vasquez generally recommends 800-1,200 IU of vitamin D per day for infants based on research showing that this is safe and results in a dramatic reduction in the incidence of type-1 diabetes. 886 The emulsified drop/liquid form of Bio-D-Mulsion is perfect for infants and children, who commonly have problems with pills and capsules.

The dose for children is 2,000 IU per day, while the requirement for adults is approximately 4,000 IU per day. 887 Nutritional interventions for treatment and preventive healthcare should be supervised by clinicians trained in nutrition. Specifically, serum calcium should be monitored periodically. 888 These high/physiologic doses of vitamin D must be used cautiously—if at all—in patients taking thiazide diuretics and those with granulomatous diseases such as Crohn’s disease, tuberculosis, sarcoidosis, lymphoma and other types of cancer. It is absolutely imperative that these patients be monitored closely with measurement of serum calcium every 2-4 weeks.

882) Bucci LR, Pilors .... Enhanced uptake in humans of coenzyme Q10 from an emulsified form. Third International Congress of Biomedical Gerontology; Acapulco, Mexico; June 1989
### Cautions

- Dose reduction is appropriate when patients experience significant sun exposure, since sun exposure can easily induce production of 10,000 IU.
- Serum testing of 25-OH-vitamin D is advisable during treatment, and levels tend to plateau after about 8 weeks of supplementation.
- Patients should be tested for hypercalcemia (and/or screened for hyperparathyroidism) before the initiation of treatment and monitored for hypercalcemia and/or hypervitaminosis D during treatment.
- Causes of hypercalcemia include: hyperparathyroidism, cancer, sarcoidosis, adrenal insufficiency, and thyroid disease.

### Drug interactions

- Several drugs increase the risk for and severity of vitamin D deficiency.
- A few drugs may cause adverse effects when administered with vitamin D.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allopurinol</strong></td>
<td>Patients with gout have been shown to have reduced levels of the active form of vitamin D 1,25-dihydroxycholecalciferol.</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td>The use of anti-convulsant drugs is associated with an increased risk for vitamin D deficiency and osteomalacia.</td>
</tr>
<tr>
<td><strong>Bile Acid Sequestrants</strong></td>
<td>Bile acid sequestrants impair fat absorption and thus impair absorption of fat-soluble vitamins.</td>
</tr>
<tr>
<td><strong>Cimetidine</strong></td>
<td>Cimetidine might reduce the formation of active 1,25-dihydroxycholecalciferol.</td>
</tr>
<tr>
<td><strong>Colestipol</strong></td>
<td>Bile acid sequestrants impair fat absorption and thus impair absorption of fat-soluble vitamins.</td>
</tr>
<tr>
<td><strong>Oral Corticosteroids</strong></td>
<td>Corticosteroids increase the risk of osteoporosis, reduce calcium absorption in the intestine, and appear to inhibit the formation of 1,25-dihydroxycholecalciferol.</td>
</tr>
<tr>
<td><strong>Estradiol, Estrogens</strong></td>
<td>Estrogen supplementation appears to make vitamin D deficiency less common.</td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
<td>The use of anti-convulsant drugs is associated with an increased risk for vitamin D deficiency and osteomalacia.</td>
</tr>
<tr>
<td><strong>Heparin</strong></td>
<td>Heparin interferes with vitamin D function and increases the risk for osteomalacia and osteoporosis.</td>
</tr>
<tr>
<td><strong>Hydroxychloroquine</strong></td>
<td>Clinical and laboratory monitoring is necessary, especially among patients with sarcoidosis, who have an increased prevalence of hypercalcemia.</td>
</tr>
<tr>
<td><strong>Indapamide</strong></td>
<td>Thiazide diuretics enhance the actions of vitamin D and therefore patients taking vitamin D should do so only under the supervision of a health practitioner who monitors clinical status and laboratory tests—serum calcium and 25-OH-vitamin D.</td>
</tr>
<tr>
<td><strong>Isoniazid</strong></td>
<td>Drug may interfere with action of vitamin.</td>
</tr>
<tr>
<td><strong>Mineral Oil</strong></td>
<td>Interferes with absorption</td>
</tr>
<tr>
<td><strong>Neomycin</strong></td>
<td>Drug reduces absorption</td>
</tr>
<tr>
<td><strong>Orlistat</strong></td>
<td>Drug reduces absorption</td>
</tr>
<tr>
<td><strong>Phenobarbital</strong></td>
<td>The use of anti-convulsant drugs is associated with an increased risk for vitamin D deficiency and osteomalacia.</td>
</tr>
<tr>
<td><strong>Thiazide Diuretics (See text)</strong></td>
<td>Thiazide diuretics enhance the actions of vitamin D and therefore patients taking vitamin D should do so only under the supervision of a health practitioner who monitors clinical status and laboratory tests—serum calcium and 25-OH-vitamin D.</td>
</tr>
<tr>
<td><strong>Valproic Acid</strong></td>
<td>The use of anti-convulsant drugs is associated with an increased risk for vitamin D deficiency and osteomalacia.</td>
</tr>
<tr>
<td><strong>Verapamil</strong></td>
<td>Vitamin D supplementation may interfere with the action of verapamil.</td>
</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td>Only one case report has been published suggesting that vitamin D may potentiate warfarin/coumadin; this may increase the risk for bleeding. Patients taking coumadin/Warfarin along with changes in vitamin D intake should be monitored clinically and with lab tests to ensure that INR is stable. Frequent monitoring of anticoagulation is required to maintain the International Normalized Ratio (INR) between 2.0 to 3.5 for most clinical indications.</td>
</tr>
</tbody>
</table>

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**Notes from Dr. Vasquez**

Bio-Multi Plus

Multivitamin and multimineral support available with iron, without iron, and without iron and copper

BioMultiPlus
Capsules per bottle: 90
Product code: 1161
Capsules per bottle: 270
Product code: 1162

Iron- and Copper-free BioMultiPlus
Capsules per bottle: 90
Product code: 1163
Capsules per bottle: 270
Product code: 1164

Iron-free BioMultiPlus
Capsules per bottle: 90
Product code: 1168
Capsules per bottle: 270
Product code: 1169

Contents: Three (3) tablets supply:

- Vitamin A (as palmitate and natural mixed carotenoids) 7,500 IU
- Vitamin C (as mixed ascorbates) 100 mg
- Vitamin D (as cholecalciferol) 400 IU
- Vitamin E (as d-alpha tocopheryl acetate) 30 IU
- Vitamin K (as phytonadione) 35 mcg
- Thiamin (B1) (as mononitrate) 10 mg
- Riboflavin (B2) 10 mg
- Niacin (as niacinamide) 20 mg
- Vitamin B6 (as pyridoxine HCl) 10 mg
- Folic Acid 400 mcg
- Vitamin B12 (as resin-bound cobalamin) 10 mcg
- Biotin 300 mcg
- Pantothenic Acid (as calcium pantothenate) 25 mg
- Calcium (as citrate) 200 mg
- Iron (as gluconate) 18 mg (optional)
- Iodine (from kelp) 150 mcg
- Magnesium (as aspartate, gluconate, glycinate) 100 mg
- Zinc (as gluconate, aspartate) 15 mg
- Selenium (from vegetable cultures) 50 mcg
- Copper (as gluconate, aspartate) 2 mg
- Manganese (as gluconate, aspartate) 2 mg
- Chromium (from vegetable culture) 50 mcg
- Molybdenum (from vegetable culture) 10 mcg
- Potassium (as gluconate, chloride, aspartate) 99 mg
- Boron (as calcium borogluconate) 1 mg
- Lithium (from vegetable culture) 20 mcg
- Rubidium (from vegetable culture) 25 mcg
- Vanadium (from vegetable culture) 5 mcg
- Citrus Bioflavonoids 10 mcg
- L-Lysine (as L-Lysine HCl) 30 mg
- L-Methionine 30 mg
- N-Acetyl-L-Cysteine 10 mg
- Coenzyme Q10 1 mg
- Superoxide Dismutase (from vegetable culture) 20 mcg
- Catalase (from vegetable culture) 20 mcg

An excellent general purpose multivitamin and multimineral supplement: 3 tablets twice per day with meals is customary. Most adults in America (and other industrialized nations) do not consume sufficient amounts of vitamins and minerals from diet alone and therefore nutritional supplements are necessary.

Note: Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults: clinical applications. JAMA. 2002;287:3127-9
**Optimal EFAs**

A new combination fatty acid product comprised of the finest fish oil, flaxseed oil, and borage seed oil, which provides ALA, EPA, DHA, GLA, and oleic acid.

Product Information: liquid
Servings per bottle: 36 teaspoons
Product code: # 1404

Product Information: capsules
Servings per bottle: 120 capsules, 2 capsules per serving
Product code: # 1407

Product Information: liquid, PER TEASPOON
* ALA: 420 mg
* EPA: 238 mg
* DHA: 158 mg
* GLA: 168 mg
* Oleic acid: 306 mg

Product Information: liquid, per TWO CAPSULES
* ALA: 280 mg
* EPA: 159 mg
* DHA: 105 mg
* GLA: 112 mg
* Oleic acid: 204 mg

For prevention, 3-6 caps per day is reasonable. When using fatty acids for therapeutic and interventional purposes, higher doses are commonly required and therefore the liquid form (which can be mixed in juice or a smoothie) is preferred for both palatability and practicality. One to two tablespoons per day is reasonable for treatment and preventive medicine, and doses up to 8 TBS per day would be within the safe parameters delineated in peer-reviewed research. High doses such as 8 TBS per day must be supervised by a knowledgeable clinician and must be appropriate for the clinical situation.
KappArest

NF-kappaB is a molecule inside each cell that becomes activated to stimulate the production of inflammatory chemicals that promote pain, inflammation, and variety of diseases such as cancer, arthritis, heart disease, and autoimmune diseases such as lupus and rheumatoid arthritis.

Modulation of NF-kappaB is emerging as a primary clinical goal in the management of inflammatory disorders.  

Serving Size: 3 Capsules
Servings Per Container: 60

Amount Per Serving Proprietary Blend 1,150 mg
- Curcuminoids (turmeric extract)(rhizome)*
- Boswellia serrata extract (gum)*
- Propolis*
- Green tea extract (camellia sinensis)(leaves)*
- Ginger extract (rhizome)*
- Rosemary extract (leaves)*
- Celery seed extract*
- Resveratrol (polygonium cuspidatum extract)(root)*
- Alpha Lipoic acid*
- Saccharium officinarium extract (shoots)*
- Phytolens™ (lens esculenta extract)(husks)*
- BioPerine® (from piper nigrum)*

*Daily Values not established

RECOMMENDATION: Three (3) capsules taken two (2) times daily as a dietary supplement or as otherwise directed by a health care professional.

4 capsules 2-3 times per day is the customary dose. Can be taken with food if necessary.

Piperine is required for the absorption of curcumin/turmeric in humans.

Without piperine, nearly all of the health benefits of curcumin/turmeric are not available to humans due to low absorption of curcumin/turmeric.  Piperine also increases the absorption of other nutrients and medications. Therefore, products with piperine must be used judiciously in patients taking pharmaceutical medications, especially those detoxified via CYP3A4, CYP2D6, and CYP1A2 such theophylline and propranolol.


Notes from Dr. Vasquez Page 9
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quote/example from the research literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turmeric-curcumin</td>
<td>“Curcumin, EGCG and resveratrol have been shown to suppress activation of NF-kappa B.”(^892)</td>
</tr>
<tr>
<td>Lipoic acid</td>
<td>“ALA reduced the TNF-alpha-stimulated ICAM-1 expression in a dose-dependent manner, to levels observed in unstimulated cells. Alpha-lipoic acid also reduced NF-kappaB activity in these cells in a dose-dependent manner.”(^893)</td>
</tr>
<tr>
<td>Green tea extract</td>
<td>“In conclusion, EGCG is an effective inhibitor of IKK activity. This may explain, at least in part, some of the reported anti-inflammatory and anticancer effects of green tea.”(^894)</td>
</tr>
<tr>
<td>Rosemary</td>
<td>“These results suggest that carnosol suppresses the NO production and iNOS gene expression by inhibiting NF-kappaB activation, and provide possible mechanisms for its anti-inflammatory and chemopreventive action.”(^895)</td>
</tr>
<tr>
<td>Propolis</td>
<td>“Caffeic acid phenethyl ester (CAPE) is an anti-inflammatory component of propolis (honeybee resin). CAPE is reportedly a specific inhibitor of nuclear factor-kappaB (NF-kappaB).”(^896)</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>“Resveratrol’s anticarcinogenic, anti-inflammatory, and growth-modulatory effects may thus be partially ascribed to the inhibition of activation of NF-kappaB and AP-1 and the associated kinases.”(^897)</td>
</tr>
<tr>
<td></td>
<td>“Both resveratrol and quercetin inhibited NF-kappaB-, AP-1- and CREB-dependent transcription to a greater extent than the glucocorticosteroid, dexamethasone.”(^898)</td>
</tr>
<tr>
<td>Phytolens (Biotics exclusive; patented)</td>
<td>Phytolens is Biotics’ patented polyphenolic extract from lentils. Published experimental research has documented the in vivo antioxidant activity against superoxide other free radicals.(^899)</td>
</tr>
<tr>
<td>Celery seed extract</td>
<td>Contains anti-inflammatory components</td>
</tr>
<tr>
<td>Ginger</td>
<td>Contains anti-inflammatory components with long history of empiric and clinical use</td>
</tr>
</tbody>
</table>

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899) Sandrola MA, Ronzo RA, Muanza DN, Clark DA, Miller MJ. Peroxynitrite-induced apoptosis in epithelial (T84) and macrophage (RAW 264.7) cell lines: effect of legume-derived polyphenols (phytolens). Nitric Oxide. 1997;1(6):476-83
Bio-Allay

Biotics Research Corporation recently produced a new product combing well-researched herbs known to support normal neurologic function and inflammatory balance.

Servings per bottle: 120 capsules

Product Information:
Contents per capsule: Proprietary blend containing 950 mg

1. White Willow (Salix Alba) bark
2. Devil’s Claw extract (Harpagophytum procumbens)
3. Boswellia (Boswellia serrata)

These three herbs were specifically selected based on peer-reviewed research documenting their effectiveness in the treatment of low-back pain and osteoarthritis.

2-4 capsules 2 times per day is a reasonable dose. Do not use this product in patients with a history of allergy to aspirin or salicylates. There seems to be no need to worry about other aspirin-related adverse effects since these are generally the result of acetylation which occurs only with acetylsalicylate and not with the salicylic acid derivatives resultant from willow bark supplementation.