
FROST & SULLIVAN
THE PROMISE OF MEDICAL FOODS
Nutritional Management of Disease States
A Frost & Sullivan White Paper

INTRODUCTION

The connections among nutrition, disease prevention, and health maintenance are established and accepted. However, the proven nutritional requirements associated with common disease states are less well understood by the medical profession. Most, if not all, illnesses are associated with underlying nutritional requirements, and meeting these distinctive nutritional needs associated with specific diseases is recognized as an essential therapeutic step. Moreover, many diseases have increased nutritional requirements that cannot be met by normal diet alone, or by merely altering the diet.

Why do increased nutritional requirements occur in disease states? Increased nutritional requirements can be the result of inadequate ingestion of nutrients, malabsorption, impaired metabolism, loss of nutrients due to diarrhea, increased nutritional turnover rates inherent in certain disease states, or the impact of drug therapies. If a nutritional requirement of a disease is not met, a nutrient deficiency can develop. The consequences of a nutritional deficiency that has evolved over time can range from structural alterations in tissue to intracellular changes in biochemical function and structure.[1] The nutritional requirements of an individual in a disease state can be considerably different from those of a healthy individual. Recognizing and managing these increased nutritional requirements should be an integral part of the medical management of clinical conditions. This may be accomplished through the use of an FDA-regulated therapeutic product class known as Medical Foods.

Nutritional Requirements in Disease States

FDA officials have offered the following physiological interpretation of nutritional requirements of a disease state thus: "[T]he distinctive nutritional needs associated with a disease reflect the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism and excretion."[2]

The need for nutritional support in the management of many clinical conditions is well appreciated.[3] **Pancreatic insufficiency** is associated with reduced amounts of digestive enzymes and consequently, its management requires replacement of enzyme and also a reduced-fat diet to control steatorrhea. Surgical procedures such as intestinal resection result in **short bowel syndrome**, whose management requires oral hyperalimentation of nutrients that can be absorbed elsewhere other than the missing bowel.

Patients with **renal insufficiency** need to monitor diet carefully to minimize uremic toxicity, avoid malnutrition, and delay progression of kidney diseases. Uremic toxicity is reduced by a low protein diet, while a reduction in phosphorus intake helps maintain blood phosphate levels. Administration of water-soluble vitamins is often necessary, and Vitamin D_3 and calcium are needed to prevent secondary hyperparathyroidism.[4] Thus, diet changes are an essential part of the clinical management of some disease states, particularly in the early stages.

"[T]he distinctive nutritional needs associated with a disease reflects the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism, and excretion."

- FDA Officials[2]

Medical foods, however, go beyond simple dietary interventions, and are specifically formulated to meet the distinctive nutritional requirements of a specific disease that cannot be met with a simple dietary shift.

Several studies have demonstrated that nutritional modifications can reduce blood pressure in patients with **hypertension**. In these studies, administration of arginine, a precursor to nitric oxide production, has been shown to reduce blood pressure. This effect is due to arginine induced vasodilatation, and is particularly true in blood vessels damaged by atherosclerosis.[5]

Increased need for nutritional elements may result from the use of certain prescription drugs. For example, **Isoniazid**, an antibiotic commonly used to treat tuberculosis, combines with pyridoxine (Vitamin B_6) to create inactive isoniazid-pyridoxal hydrozones, thus depleting pyridoxine levels in the body. **Methotrexate** depletes folate stores by inhibiting the production of tetrahydrofolate from the inactive dihydrofolate. When **Methotrexate** is used to treat rheumatoid arthritis, lupus, inflammatory bowel disease or psoriasis, folic acid administration is necessary to avoid the adverse effects of treatment. Loop diuretics, particularly furosemide (Lasix®), used for treating congestive heart failure and hypertension, cause increased urinary excretion of thiamin (Vitamin B_1), which may lead to thiamin deficiency. Many anticonvulsants, antibiotics, or appetite suppressants require specific nutritional modifications to maintain function of the drugs or to prevent side effects of the drugs.

It is known that infections, trauma, hyperthyroidism, extensive burns, and fever lead to increased metabolic demands[6] and may require specific nutritional interventions. What is less well appreciated is that specific nutritional requirements are also associated with common health conditions such as hypertension, asthma, pain, sleep disorders, and psychiatric conditions such as dementia, depression, and anxiety. The nutritional needs associated with these highly prevalent diseases are considered in greater detail in later sections.

The nutritional requirements associated with a disease state can sometimes be met by modifying the nutrient content and density of food. This can be accomplished by changing the number of feedings, by incorporating high-nutrient foods into the diet, or by modifying texture by chopping, blending, pureeing, or thickening. Modified nutrient density and texture, however, may not be enough to meet the nutritional requirements of a particular disease state. At this juncture, consideration of prescription medical foods is appropriate to restore normal metabolic function.

WHAT ARE MEDICAL FOODS?[7]

Medical foods is a unique category of FDA regulated products that meet the distinctive nutritional requirements or metabolic deficiencies of a particular disease state. For example, a special formulation of amino acids and proteins that meets the distinctive

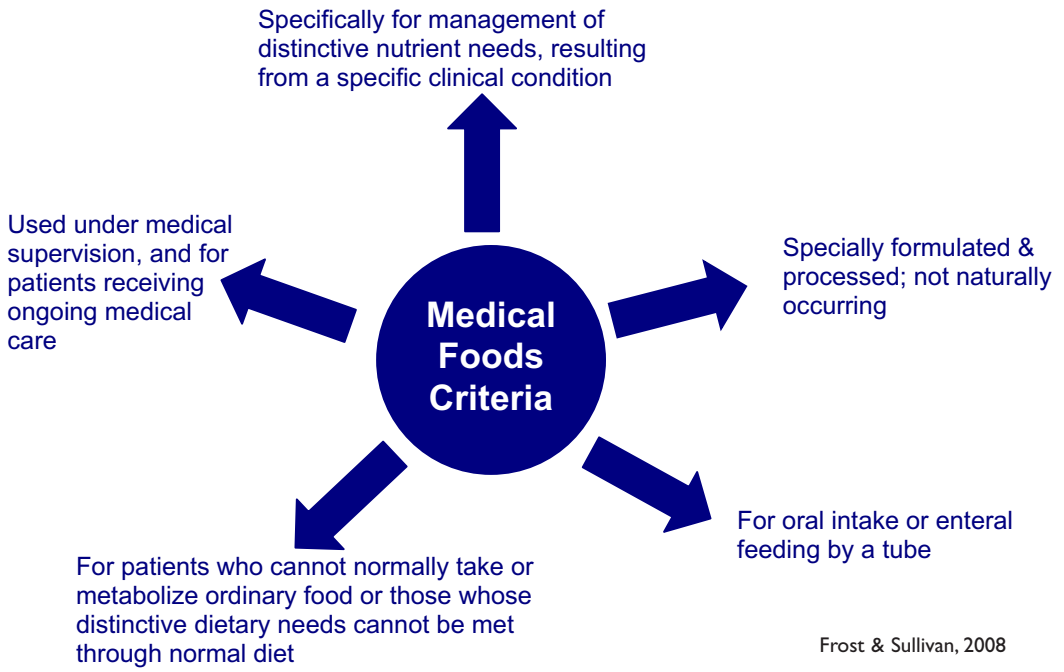
nutritional requirements of burn or wound injuries, and is necessary to heal the skin or to grow new skin, could be classified as a medical food. One of the first medical foods to be developed was the infant formula, ***Lofenalac***, designed for the dietary management of Phenylketonuria (PKU), a condition where infants lack adequate amounts of the enzyme needed to metabolize the essential amino acid phenylalanine. Medical foods such as ***Lofenalac*** contain a reduced dose of phenylalanine, while providing other essential nutrients.

Legal Definition of Medical Foods

Prior to 1972, medical foods like ***Lofenalac***, that mitigated serious adverse effects of the underlying diseases, were regulated by the FDA as "drugs" under the Federal Food, Drug, and Cosmetic Act. In 1972, in an effort to encourage innovation and availability of such products, the FDA revised its regulatory approach and classified these products as "foods for special dietary use."[8] The Orphan Drug Amendments of 1988 provided a statutory definition of a medical food: *The term "medical food" means a food that is formulated to be consumed or administered entirely under the supervision of a physician and which is intended for the specific dietary management of a disease or condition, for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.*[9]

In the Nutrition Labeling and Education Act of 1990, Congress exempted medical foods from the nutrition labeling, health claim, and nutrient disclosure requirements applicable to most other foods, further distinguishing this category from conventional food products. Three years later, when the final rules for food labeling were published, the FDA enumerated criteria clarifying the characteristics of medical foods,[10] which are illustrated in Figure 1 below.

Figure 1: Criteria for Medical Foods, Nutrition Labeling and Education Act of 1990



Frost & Sullivan, 2008

The FDA issued strict guidelines for ensuring the safety and nutritional adequacy of medical foods, restricting their use to particular clinical conditions, and requiring scientific substantiation for any disease claims. While most products in this category are eminently safe, and are required to be formulated using only approved food additives and GRAS (Generally Recognized as Safe) ingredients, it is recognized that they could be inadequate for healthy individuals if they replace the normal diet. For example, a formulation designed for infants with PKU would be nutritionally inadequate for a normal infant. Therefore, for reasons of patient safety, and because these products are intended for patients requiring on-going care and monitoring, medical foods must be administered only under physician supervision.

Medical Foods: A Special Product Category Regulated by the FDA

Medical foods must meet the distinctive nutritional requirements of a disease state, and are different from both drugs and dietary supplements under the statutory definition from Congress, and per FDA classification. Medical foods are intended for a specific diseased population of patients, and can be administered only under the supervision of a physician. This distinguishes them from dietary supplements that are intended for consumption by healthy individuals. The safety of medical foods is ensured by the requirement that all ingredients be either approved food additives or classified as GRAS (Generally Recognized As Safe). The FDA has stated: "For a particular use of a substance to be GRAS, there must be both technical evidence of safety and a basis to conclude that this evidence is generally known and accepted by qualified experts. The technical element of the GRAS standard requires that the information about the substance establish that the intended use of the substance is safe, i.e., that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use. In addition, the data and information to establish the technical element must be generally available, and there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use."[11]

For this reason and others, medical foods do not require pre-approval from the FDA for marketing, unlike pharmaceutical drug products. Disease claims for medical foods must be supported by sound scientific evidence, including clinical investigations, to substantiate claims of successful nutritional management of the disease. In this respect, they are closer to drug products than they are to dietary supplements, which can make health benefit claims (called structure/function claims) based on existing scientific literature or a history of traditional use, and do not require specific studies for the particular formulations. Figure 2 summarizes the significant differences among the three categories:

Figure 2: Salient Distinguishing Features of Three Discrete Regulatory Categories: Drugs, Medical Foods and Dietary Supplements[12]

	Drugs	Medical Foods	Dietary Supplements
Physician Supervision	Required (for Prescription Drugs)	Required	Not Required
Pre-market Scientific Testing	Required	Required	Not Required
Pre-market FDA approval	Required	Not Required	Not Required
Target Population	Specifically formulated for patients with a specific indication or symptoms	Specially formulated for meeting nutritional requirements of a specific diseased population	Intended for normal, healthy adults
Claims	Make therapeutic claims for treating, preventing or mitigating specific indications	Make medical claims for dietary management of a specific disease characterized by distinctive nutritional requirements	Make structure/function claims to support healthy function of body parts, systems, organs or processes
Safety Profile	Need to establish safety through clinical trials	All ingredients must be GRAS Generally Recognized as Safe) or approved food additives	New supplements with new dietary ingredients (NDIs) need only be demonstrated as "reasonably expected to be safe"
Scientific Requirements	Preclinical and Clinical phases I, II and III	Based on recognized scientific principles, established by medical evaluation	Not required if no claims. Claims may be based on existing scientific literature or traditional use.

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Examples of Medical Foods:

There are many medical foods on the market today. Some of these are listed below:[13]

- ***Ultrase MT®***: This medical food, manufactured by Axcan Pharma, is used to manage exocrine pancreatic insufficiency caused by cystic fibrosis or chronic pancreatitis. It corrects the nutritional deficiency in these patients by providing digestive enzymes like lipase, protease, and amylase.
- ***Conison Capsules™*** : This medical food, manufactured by Ethex Corporation, provides vitamins B_{12}, C and folic acid, and iron fumarate, with Intrinsic factor that improves the absorption of Vitamin B_{12}. This is indicated for the management of pernicious and megaloblastic anemias.
- ***Limbrel™*:** This medical food, manufactured by Primus Pharmaceuticals Inc., is used in the nutritional management of metabolic processes associated with osteoarthritis.

Damaged joints release excess phospholipids, which increase the production of prostaglandins and leukotrienes, leading to an inflammatory response. Limbrel is formulated with naturally occurring ingredients that inhibit the two enzymes lipoxygenase and cycloxygenase responsible for the production of inflammatory irritants.

- ***Folgard RX 2.2***®: This medical food, manufactured by Upsher-Smith, is indicated for the management of elevated homocysteine, or hyperhomocysteinemia, associated with cardiovascular disease, stroke, and other diseases. Folgard is a formula containing folic acid, vitamin B_6 and vitamin B_{12}, designed to lower plasma homocysteine levels.

MEDICAL FOODS FOR MAINTAINING NEUROTRANSMITTER LEVELS

The examples discussed above demonstrate that most disease states impose nutritional requirements that are different from the nutritional needs of healthy individuals. While the use of medical foods for the management of diseases such as pancreatic insufficiency and phenylketonuria is standard practice, their use in more commonly occurring disease states is less well appreciated. The remainder of the paper will review highly prevalent disease states such as chronic pain, insomnia and asthma, and the medical foods that can be used to manage these conditions and ameliorate symptoms.

Figure 3: Release of synaptic vesicles containing neurotransmitters at a synaptic cleft

Image credit: Gary Carlson/Photo Researchers, Inc.

Many disease states are known to have disruptions in the metabolic process that alter neurotransmitter production. Neurotransmitters are chemical entities that relay signals between neurons, muscle, and other cells. Neurotransmitters are synthesized within neurons from amino acid precursors, released by the nerve terminal into the synaptic cleft, and are absorbed back into the neuron by specialized transporter molecules in the pre-synaptic membrane. Antidepressants, such as fluoxetine and citalopram, which belong to the category of Selective Serotonin Reuptake Inhibitors (SSRIs), have their effect by blocking the re-uptake of serotonin after it has been released. The importance of the serotonergic system in mood disorders is further substantiated by the observation that a deficiency of tryptophan, or a diet that does not include tryptophan, the amino acid precursor to serotonin, can produce significant increases in self ratings of depression in healthy subjects, and can cause a relapse into clinical depression in some previously treated patients.[14] These examples illustrate the importance of nutritional modification in modulating neurotransmitter levels in associated disease states.

Medical foods that modulate production of neurotransmitters in different disease states have been shown to deliver therapeutic benefits to the patients. We discuss some of these products in greater detail below.

Targeted Cellular Technology™

While simple administration of amino acids, the precursors to some neurotransmitters, causes an increase in production of these neurotransmitters as evidenced by physiologic response, the effects are inconsistent and not sustained. The physiologic response to the administration of amino acids alone is variable, weak in magnitude, and subject to rapid attenuation, requiring large quantities of the precursors to sustain even a modest improvement.[15] Physician Therapeutics, a Los Angeles based company, has developed a proprietary, five-component process, known as *Targeted Cellular Technology* that allows milligram quantities of neurotransmitter precursors to enter the neurons and stimulate the production of neurotransmitters for a sustained response. The five components that comprise this technology are formulated to execute a cascade to sustain the production of neurotransmitters and eliminate attenuation. This proprietary process includes a neurotransmitter precursor, an uptake stimulator, a neuron activator, an adenosine brake inhibitor, and an attenuation releaser. Clinical evidence demonstrates that medical food products based on *Targeted Cellular Technology* can selectively stimulate the production of neurotransmitters with the desired, consistent physiological responses. This effect occurs with low doses of amino acids, and does not attenuate with repeated or continuous use.[16]

GABAdone and Sentra PM: Medical Foods for the Dietary Management of Sleep Disorders and Fibromyalgia

Sleep physiology is still incompletely understood, but it is known that it depends upon a complex interplay of several different neurotransmitter systems in the brain. The serotonergic system plays a pivotal role in sleep modulation, including initiation of sleep, and maintenance of the various stages of sleep. Acetylcholine facilitates REM sleep and the cholinergic system may play an important role in memory consolidation that takes place during sleep.[17] GABA, the main inhibitory neurotransmitter in the central nervous system, is known to promote sleep. Succesive generations of hypnotics (barbiturates, benzodiazepines, and imidazopyridines and cyclopyrrolones) are based on activation of $GABA_A$ receptors, while $GABA_B$ and $GABA_C$ receptors are also known to promote different stages of the sleep cycle. Serotonin deficiency induced experimentally by depletion of tryptophan leads to disruption of sleep patterns in both healthy subjects and in insomnia patients.[18] Chronic cholinergic insufficiency is also linked to disturbances in the sleep-wake cycle.[19]

Decreased serotonin levels have been documented in patients with fibromyalgia—a musculoskeletal pain and fatigue disorder manifested by diffuse myalgia, fatigue, lowered pain thresholds, and nonrestorative sleep.

The administration of tryptophan, which is converted to serotonin in the body, has ameliorative effects on patients with primary fibromyalgia syndrome.[20]

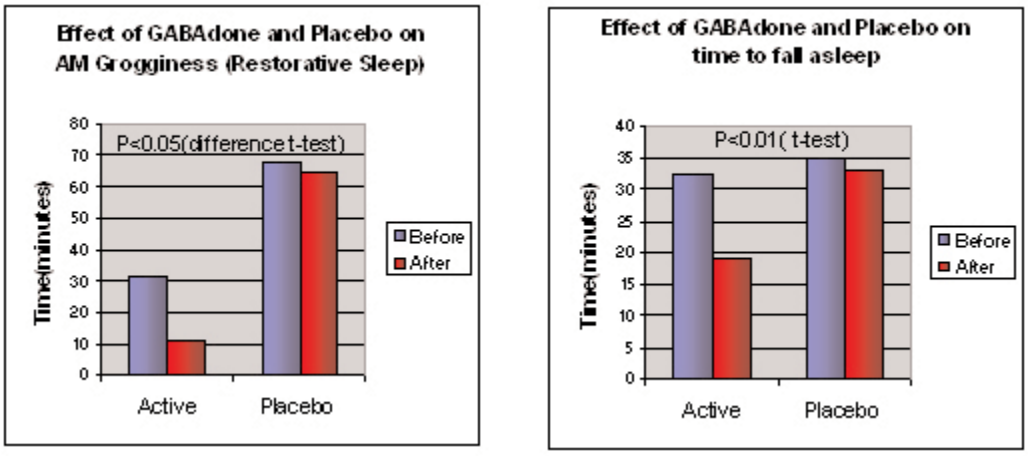
Sentra PM is a medical food formulated to stimulate the production of serotonin, acetylcholine, and GABA – neurotransmitters that play an important role in sleep physiology and fibromyalgia. *Sentra PM* provides the precursors for all three of these neurotransmitters, and is intended for dietary management of sleep disorders and the non-restorative sleep associated with fibromyalgia. *GABAdone* is another medical food indicated for the dietary management of sleep disorders, which is also designed to increase levels of serotonin, acetylcholine and GABA in the body.

Clinical Evidence

Clinical studies using *GABAdone* have shown that it can help patients with insomnia fall asleep sooner (reduction in sleep latency), increase the duration of sleep and reduce awakenings. A double-blind placebo controlled study was carried out for *GABAdone* in 18 subjects. Nine patients were randomized to *GABAdone* (active group) while the rest were randomized to placebo (control group). Study endpoints measured, before and after the administration of *GABAdone*, were ability to fall asleep, validated questionnaires reflecting sleep quality, and measurements of autonomic nervous system function using heart rate variability analysis from 24-hour electrocardiograph recordings.

As shown in Figure 4, the active group achieved a 43% reduction in sleep latency, as compared to only 5% reduction in the control group. Also, the average number of minutes of morning grogginess was reduced by 64% in the active group patients, while it was reduced by only 4% with placebo.[21]

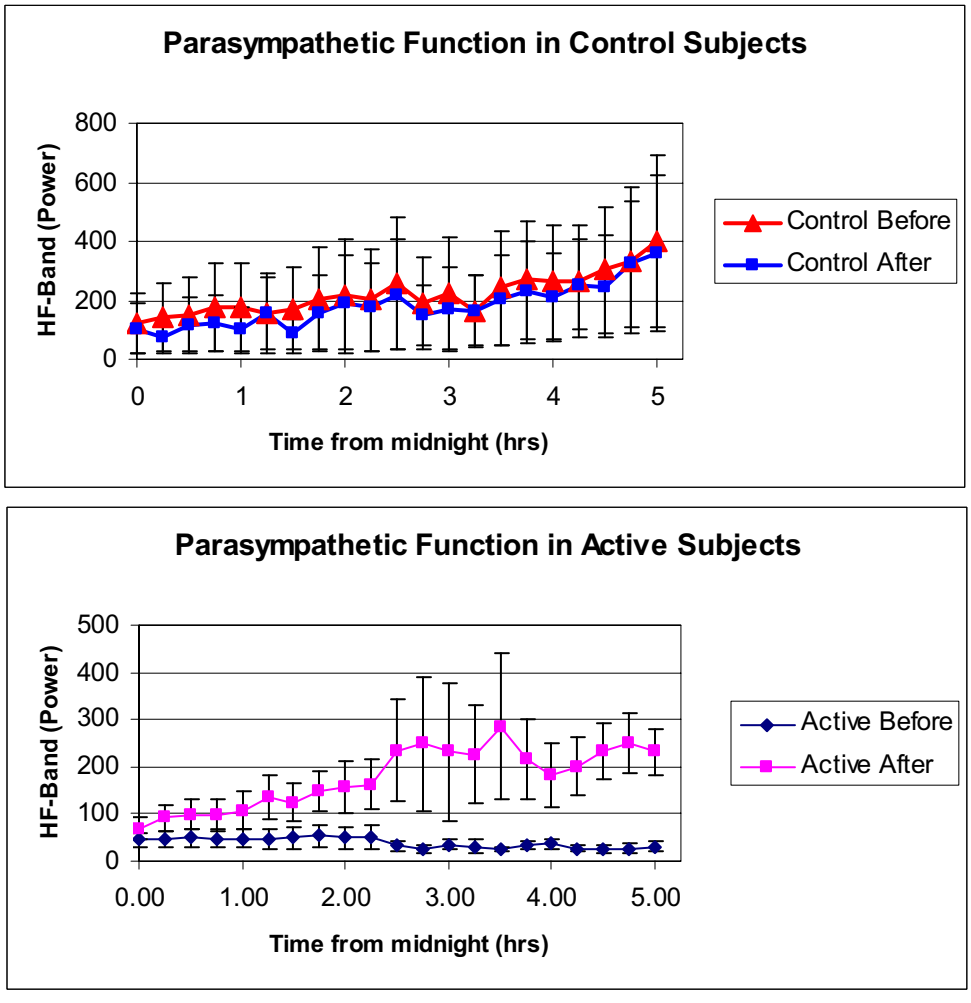
Figure 4: ***Effect of GABAdone and Placebo on Time to Fall Asleep (Sleep Latency) and on AM Grogginess (Restorative Sleep)***



Data from Physician Therapeutics, LLC

A separate cross-over clinical study of patients with fibromyalgia symptoms, including sleep disorders, used 24-hour ECG measurements and the High Frequency (HF) band in spectral heart rate variability analysis as a measure of the vagal parasympathetic activation. Seventy five percent of the patients with abnormal activation of the parasympathetic system during night showed a marked improvement in symptoms after the administration of *Sentra PM* at night (and a morning time administration of *Sentra AM*™).[22] The circadian patterns of activation of the parasympathetic nervous system in these patients approached the normal activation patterns after administration of *Sentra PM* as indicated in Figure 5.

Figure 5: Spectral Analysis of Heart Rate Variability in Control Patients and Active Patients (those with abnormal activation of the parasympathetic system during night-time) Before and After the Administration of Sentra PM and Sentra AM



Data from Physician Therapeutics, LLC

Physician Feedback

Dr. Lawrence May, a Diplomat of the American Board of Internal Medicine and Associate Clinical Professor at the UCLA School of Medicine, is currently the Medical Director for Physician Therapeutics LLC. In his experience, patients with sleep disorders, such as those who have early morning awakenings, snore, wake up once or twice in the night, or wake up tired in the morning benefit from the use of *GABAdone* and *Sentra PM*. "There are many side effects with conventional drugs that aid sleep such as trazadone, zolpiden (Ambien) or benzodiazepines such as Xanax®: the patients may be overly sedated, develop dependencies or have disturbed sleep architecture," says Dr. May. "With *GABAdone* and/or *Sentra PM*, patients wake up more refreshed, more invigorated, more functionally capable and these products have fewer side effects than conventional prescription drugs." According to Dr. May, the main side effect of *GABAdone* and *Sentra PM* is the tendency for patients to have more vivid dreams, but he has not encountered any serious adverse events or intolerance to the medical foods products.

Dr. May frequently prescribes *GABAdone* or *Sentra PM* as the first line of treatment for people with sleep disorders, and especially in older people who are already taking a number of prescription drugs. Most patients perceive improvements, some with the first dose, while others see a sustained benefit after a week or two. Dr. May's patients usually take *GABAdone* or *Sentra PM* for an extended period of time, since the symptoms can return if they stop taking the medical food. If the response to the medical food is inadequate, then a low dose of a pharmaceutical agent, such as trazadone or alprazolam can be added, but it is a lower dose than the dose that would have been used otherwise. Dr. May adds, "Medical foods are complementary to pharmaceutical agents. We have good sleep medications available, but the medical foods enhance the sleep architecture of patients by addressing the underlying nutritional requirements."

Dr. Allen Salick, a rheumatologist with offices at the Cedars Sinai Medical Towers, Los Angeles, prescribes *Sentra PM* to his fibromyalgia patients, and patients with chronic sleep disturbances. "On average, patients in my practice sleep 2 hours longer than they did before they started taking *Sentra PM*, and wake up 1-2 times less frequently per night. It increases not only the quantity of sleep they are getting, but also the quality, and without the daytime grogginess that often accompanies other sleep aids." Like Dr. May, Dr. Salick has also found that the time for the effect to occur is somewhat variable, "There are some patients who will call me up after the first night and say why didn't you ever give this to me before, because I have never slept this well in 20 years; while there are others who have to take this product for a couple of weeks before they see the effect."

Theramine™: A Medical Food for the Dietary Management of Pain and Inflammation

Pain pathways involve both the central and peripheral nervous systems, and multiple neurotransmitters and receptor subtypes. Substance P, a short peptide neuromodulator that

is found in both central and peripheral nervous systems, plays an important role in pain perception (*nociception*) and modulation of inflammatory and immune responses. GABA, the main inhibitory neurotransmitter in the spinal cord, can inhibit the activation of substance P containing neurons, thus dampening the transmission of the pain response and producing analgesia.[23] The activation of cholinergic and serotonergic pathways is known to inhibit the spinal nociceptive sensory transmission, and have analgesic effects.[24] Nitric oxide, a rapidly diffusible gaseous neurotransmitter, also plays a pivotal role in pain perception, especially in neuropathic pain.[25]

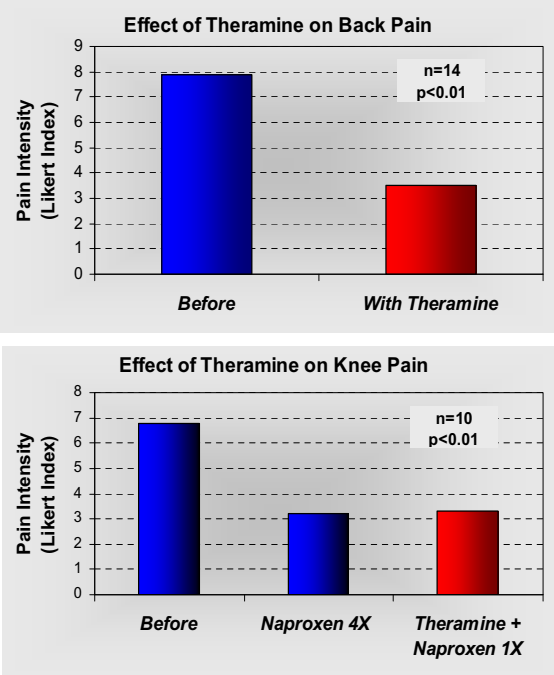
Pain disorders are associated with altered nutritional requirements for precursor amino acids, which are responsible for the production of neurotransmitters that modify pain pathways. For example, administration of L-arginine, a precursor to nitric oxide, has anti-nociceptive effects in disease states such as diabetes,[26] and the administration of choline, a precursor of acetylcholine, attenuates the perception of acute and inflammatory pain.[27] *Theramine* is a medical food formulated with precursors to all of the above-mentioned neurotransmitters involved in pain perception—it contains choline (a precursor to acetylcholine), arginine (a precursor to nitric oxide), glutamine (a precursor to GABA), as well as 5-hydroxytryptophan that can stimulate the serotonergic pathways and also GABA for activating the GABA receptors in pain pathways. In addition, it also has flavonoids and L-histidine to reduce inflammation. The indications for use of *Theramine* include acute and chronic pain, fibromyalgia, neuropathic pain, and pain due to inflammation.

Clinical Evidence

Several clinical studies have been conducted that demonstrate the efficacy of ***Theramine*** in managing pain. The data from two studies are shown in Figure 6. The first study deals with patients who had acute low back pain that had lasted at least 7 days. In this cross-over study, ***Theramine*** was added to their regimen, and pain was reassessed after 72 hours. As the figure shows, the administration of ***Theramine*** significantly decreased the perception of pain as measured on the Likert Index.

The second study examines the effect of *Theramine* as an adjunct to the Non-Steroidal Anti-Inflammatory Drug (NSAID), naproxen. The use of *Theramine* to manage the distinctive nutritional requirements associated with pain syndromes, along with a 250mg daily dose of naproxen provides significant analgesic effect.

Figure 6: Clinical Studies Showing that Administration of Theramine Reduces Pain Perception



Data from Physician Therapeutics, LLC

"On average, patients in my practice sleep 2 hours longer than they did before they started taking Sentra PM, and wake up 1-2 times less per night. It increases not only the quantity of sleep but also the quality and without the daytime grogginess that often accompanies other sleep aids"

- Dr. Allen Salick, Rheumatologist

Physician Feedback

Dr. Ismael Silva, a sports medicine specialist, initially used *Theramine* on some of his post-operative patients with pain, and patients who had pain due to injury. "We found that we got good analgesic effect with less medicine when we used *Theramine*. It appears as if managing the nutrient requirements of these patients helps to deal with their pain syndromes." Encouraged by these results, Dr. Silva currently prescribes the product to "hundreds" of his patients.

"A lot of the patients at our clinic were post-injury or post surgery, and requiring a very high dosage of the pharmaceutical agents, and in some, the pharmaceutical agents were starting to lose their effect. Our patients were lethargic due to the heavy medication, unable to work because of side-effects of the drugs, feeling tired, sleepy, and groggy." Co administration of once daily naproxen with *Theramine* allows patients to reduce the risks of developing side effects such as stomach ulceration. Therefore, many of the patients are able to return to work sooner and perform their routine tasks at a normal rate.

Dr. David Silver, Associate Clinical Professor of Medicine at UCLA school of Medicine, and former Clinical Chief of Rheumatology at Cedars-Sinai Medical Center, prescribes *Theramine* to "at least 20%" of his patient population, mainly for fibromyalgia, osteoarthritis and Reflex Sympathetic Dystrophy Syndrome.

Asked to describe a typical patient for whom he would prescribe *Theramine*, Dr. Silver said that a common patient type is one "who has pain from one of various conditions, say fibromyalgia, often one who has tried numerous pain medications on and off before they have seen me, who might be on narcotic analgesics or someone who doesn't want to take prescription medicines. Obviously, the older the patient, the more worried you are about side effects and what concomitant medications they are taking. But I will give *Theramine* to these patients—those who are not on any single prescription, and those who have a very complicated medical regimen. I have been surprised to recognize that many of these complex cases have an underlying nutritional requirement for amino acid precursors to neurotransmitters"

Dr. Silver finds that *Theramine* works as well as, if not better than, conventional pain medications because of the lower side effects and a better tolerability profile, and he frequently seeks it out as a first line option, especially in the case of chronic pain.

According to Dr. Silver, the physiologic effect of *Theramine* can be observed in less than 24 hours, and the safety profile of *Theramine* makes it a good candidate for long-term usage. The only adverse effect that Dr. Silver has observed is some patients complaining of an upset stomach, but other than that, it is well tolerated. Dr. Silver has written more than 8,000 prescriptions for *Theramine* over a three year period and has not observed adverse events other than initial nausea that responds to dose titration.

Pulmona™: A Medical Food for Dietary Management of Asthma and Pulmonary Hypertension

Nitric Oxide (NO) and NO pathophysiology underlie asthma as well as pulmonary hypertension.[28] Nitric oxide is involved in the dilation of pulmonary arteries thus reducing pulmonary artery pressure by dilation of bronchi and pulmonary arteries during bronchoconstriction. Decreased NO levels within the lungs may lead to pulmonary hypertension[29] The reduced activity of cNOS, the constitutive Nitric Oxide Synthase, one of the enzymes that produce NO, is one of the factors leading to bronchoconstriction in asthma. The reduction in cNOS activity is thought to be caused by an increase in arginase activity, depleting L-arginine levels which serve as a substrate for cNOS.[30]

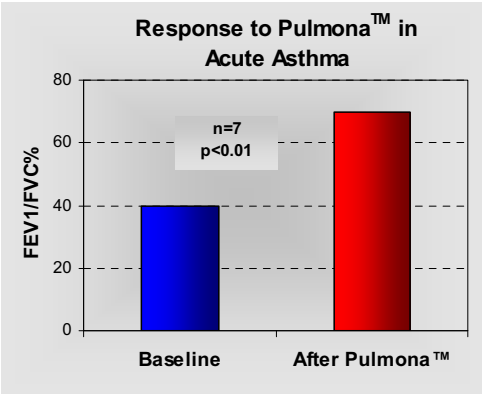
An increased nutritional requirement for L-arginine, the precursor to NO, in pulmonary hypertension has been medically established. Studies have revealed that plasma arginine levels in some disease states with pulmonary hypertension are lower than that for healthy individuals.[31] Administration of L-arginine enhances vasodilatation.[32] Acetylcholine is another vasodilator that acts through NOS dependent pathways.[33]

Pulmona is a medical food formulated to increase the production of nitric oxide and acetylcholine, for the dietary management of pulmonary hypertension and asthma. *Pulmona* maximizes the availability of these two neurotransmitters by providing the precursors to NO and acetylcholine, arginine and choline.

Clinical Studies

Clinical studies conducted on asthma patients have demonstrated that *Pulmona* can increase the flow rate of air as measured with FEV1 (forced expiratory volume in 1 second). Obstructive lung disorders such as asthma reduce FEV1 but not the total lung capacity, FVC (forced vital capacity), decreasing the ratio of FEV1/FVC. Studies performed on patients experiencing acute wheezing have shown that 15 minutes after administration of *Pulmona*, the FEV1/FVC volumes of these patients reached levels of approximately 70%, which are normal for healthy patients (Figure 7).

Figure 7: Clinical Studies Showing Pulmona Increases Pulmonary Flow Rate in Acute Asthma



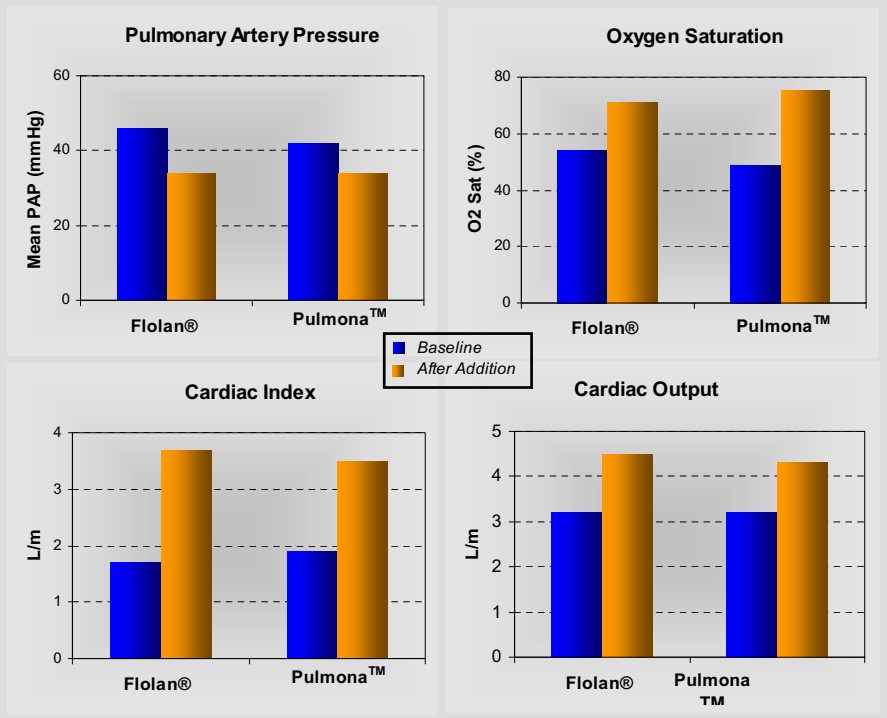
Data from Physician Therapeutics, LLC

"A lot of the patients at our clinic were post-injury or post surgery, and requiring a very high dosage of the pharmaceutical agents, and in some, the pharmaceutical agents were starting to lose effect. Our patients were lethargic due to the heavy medication, unable to work because of side-effects of the drugs, feeling tired, sleepy, and groggy"

- Dr. Ismael Silva, Sports Medicine

Patients with pulmonary hypertension are frequently prescribed potent vasodilators such as Flolan®, Tracleer, and sildenafil (Viagra) that relax blood vessels in the lung and increase cardiac output and oxygen saturation. A small open label, crossover study suggests that *Pulmona*, when given orally, can lower pulmonary artery pressures in patients with Class IV pulmonary hypertension. Clinical measures from representative patients are shown below (Figure 8).

Figure 8: Effects of Pulmona and epoprostenol (Flolan®) in patients with Class IV Pulmonary Hypertension as measured by Pulmonary Arterial Pressure, Oxygen Saturation, Cardiac Index and Cardiac Output



Data from Physician Therapeutics, LLC

Physician Feedback

Dr. Lawrence May prescribes *Pulmona* to patients who are chronically short of breath. "Many people with pulmonary disease have elements of bronchospasm, as in asthma; but also in cases that are neither asthma nor pulmonary hypertension. They may have increased arterial pressure due to right heart failure or intrinsic lung disease. This medical food product works well in all of them."

The tolerability and lack of side effects of *Pulmona* makes it safe for patients who have a relative contraindication to bronchodilators, such as those who have rapid heart rates and/or arrhythmias. Dr. May finds that his patients have reduced shortness of breath and are less dependent on rescue medications after taking *Pulmona*.

SIDE EFFECTS OF MEDICAL FOODS

Physician Therapeutics has maintained an adverse event log since 2003 with a toll free telephone number provided to physicians to report adverse events. To date, no serious adverse events have been reported. There have been several reports from patients of initial nausea that were resolved with dose titration. In addition, there have been anecdotal reports from physicians of a skin rash related to medical food products containing histidine. Physicians have reported that this rash clears upon discontinuation and does not require treatment.

In over 200,000 prescriptions for medical food products, some of which have been co administered with pharmaceutical agents in the customary practice of medicine, no serious adverse drug events have been observed or reported.

AVAILABILITY OF MEDICAL FOODS

Convenience Packed Medical Foods and Pharmaceutical Drugs

Medical Foods such as *GABAdone*, *Sentra PM*, *Theramine* and *Pulmona* can be used alone, or administered with pharmaceutical agents used conventionally in the practice of medicine. These medical foods, by managing the nutritional requirements associated with pain syndromes, sleep disorders, asthma, and other clinical conditions, can contribute to the medical management of these conditions. By addressing the underlying nutritional requirements of disease states, physicians can prescribe pharmaceutical agents at the lowest FDA approved dosage according to standard medical practice. By using low doses of pharmaceutical agents, patients can obtain relief from symptoms with fewer side effects. Physician Therapeutics markets medical food products with commonly used generic drugs in convenience packs. For example, *Theramine* is available in a convenience pack with the NSAID medication naproxen. *GABAdone* and *Sentra PM* are available with the frequently used sleep medication, trazadone and this convenience pack is used in many medical practices. Some physicians, like Dr. Silver, prefer to titrate their own dose of medical foods and pharmaceutical agents, while others like Dr. Silva prefer the convenience packs which allow them to prescribe the drug and the medical food at the same time.

Pricing and Reimbursement

Medical foods are economical as monotherapy or in convenience packs. These prescription products are covered under the Worker's Compensation Insurance plans, by many private health insurance plans and Medicare Part D. Products are readily available through pharmacies and through the offices of dispensing physicians.

FUTURE OF MEDICAL FOODS

Although medical foods are a distinct regulatory category and therapeutic class of products, general awareness of them in the medical community is low. "There is a lack of knowledge about medical foods and a high degree of skepticism in the field to everything new," explains Dr. May. "We need more clinical research in the area to help physicians

overcome this ignorance and to prove that these compounds work as well or better than traditional prescription drugs."

There is some confusion in the medical field around the differentiation between medical foods and dietary supplements. This can be overcome through increased dissemination of information to medical practitioners that outlines the distinguishing features of medical foods, such as their scientific basis, clinical efficacy as well as the statutory definition of this category and FDA regulation authorizing the use of medical foods for the dietary management of disease. The real challenge to the use of medical foods is in encouraging physicians to consider the nutritional status of patients, and enhance their understanding of the altered nutrient requirements inherent in disease states.

Adoption of medical foods will be driven largely by the efficacy of medical foods in managing the increased nutritional requirements imposed by, or associated with disease states. Wider utilization of medical foods that meet the distinctive nutritional requirements of commonly occurring disease states will improve outcomes for patients.

The tolerability and lack of side effects of *Pulmona* makes it safe for use in people who have a relative contraindication to bronchodilators, such as those patients who have rapid heart beats and arrhythmias, and may not be good candidates for any other therapy.

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