

# Medical Foods: Overview of an Emerging Science

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Medical foods offer physicians an additional tool for approaching and managing various medical conditions. They can help improve the symptoms and/or slow the progression of a specific chronic condition, and they are complementary to approved pharmacologic therapies. As the number of available medical food therapies increases, so must an understanding of their function and benefits to enable proper use. This article aims to provide a comprehensive overview of medical foods.

## Definition

As defined by the Orphan Drug Act (1988 Amendment), a medical food is "a food which is formulated to be consumed or administered enterally (orally) under the supervision of a physician, and which is intended for specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." These therapeutic agents are a heterogeneous group of formulations which comprise a relatively new category of medical protocols defined by Congress, and are subject to regulation by the U.S. Food and Drug Administration (FDA).

The distinctive nutritional requirements of medical foods towards a specific disease must be supported by solid laboratory and clinical data as well as by product performance. The clinical rationale of medical foods is thus subject to scrutiny by medical evaluations and objective determinations of efficacy. This increased surveillance of medical foods by the FDA is reflected in the requirements of the "Generally Regarded As Safe" (GRAS) designation, the highest FDA standard of safety given to foods which all components of the formulation must satisfy. Additionally, and unlike over-the-counter dietary supplements, they require the supervision and prescription of a physician to be obtained.

Medical foods and dietary supplements are discrete regulatory classifications and are not interchangeable. The former must be shown, by medical evaluation, to meet the distinctive nutritional needs of a specific, diseased patient population being targeted, prior to marketing. In contrast, dietary

supplements are intended for normal, healthy adults and require no pre-market efficacy tests. In addition, medical foods require *physician supervision* and a *prescription*. To summarize, medical foods are medical products for a specific nutritional purpose as opposed to dietary supplements which are a consumer product to supplement the diet and maintain good health and regular function.

In contrast, the efficacy of prescription drugs which make disease-specific claims must also be supported by clinical/scientific studies (e.g., animal toxicity, Phase I/II, large Phase III/IV, and post-marketing clinical studies) designed to highlight potential safety issues, while also being pre-approved by the FDA. This escalation of government supervision reflects the formal medical food claims, which refer to the "nutritional or dietary management of a specific disease or its metabolic processes," whereas a prescription drug claims "curing, treating, preventing or mitigating the effects of symptoms of a specific disease." Therefore medical foods represent a unique hybrid of therapeutics, and although sometimes prescribed in conjunction with conventional pharmaceuticals or supplements, nonetheless represent an entirely different scientific and medical approach to managing diseases.

Healthcare professionals may already be familiar with medical foods intended to support or even fully substitute the nutritional needs of hospitalized or critically ill patients who cannot meet them, such as those with malabsorption syndromes. These enterally administered therapeutics form an important subset of short-term therapies the inpatient clinician has at their disposal to acutely facilitate healing and improve outcomes. In the outpatient setting, however, medical foods are primarily aimed at slowing the progression of chronic, progressive diseases by modulation of the disease process via continuous, long-term administration. Given the wide array of possible targets for therapy, it is not difficult to envision that a significant number of diverse medical foods have been developed despite their relative novelty.

### **Examples of medical foods**

Medical foods are available for a wide number of common medical, neurological and psychiatric conditions. Many address the metabolic processes associated with a disease to help improve or slow progression.

#### ***Alzheimer's Disease***

Alzheimer's disease (AD) is the most common form of neurodegenerative dementia and it is predicted to reach epidemic proportions by the late 21st century. AD is an excellent model of a well-studied neurodegenerative disease with many severity-dependent potential targets of a medical food. A prominent feature in AD is the disturbance of the cerebral metabolic rate of glucose or regional cerebral hypometabolism. As this hypometabolism is an early and progressive event, it is reasonable to target this avenue in AD therapy. A first-in-class medical food for the clinical dietary management of the metabolic processes associated with mild-to-moderate AD was recently released. This represents the first new therapeutic agent in the AD market in over five years and helps to satisfy an unmet need for "targeted therapy" for AD patients.

Axona safely and effectively supports the nutritional requirements of patients with mild-to-moderate AD. The therapy is a proprietary formulation of medium-chain triglycerides (MCTs) (specifically caprylic triglyceride) that is digested and metabolized in the liver to produce ketone bodies. Ketone bodies are naturally occurring compounds produced by the body at low levels. After being metabolized in the liver and released into the bloodstream, these ketone bodies provide an alternative energy source for brain cells to help improve functioning.

Clinical studies have demonstrated that this novel approach to the management of AD can safely improve cognitive function and memory. On average, patients with AD who received Axona experienced significantly improved ADAS-Cog (Alzheimer's Disease Assessment Scale - Cognitive subscale) scores ( $P < 0.05$ ) at day 45, and in apolipoprotein E (ApoE4) genotype negative patients at day 45 and day 90 ( $P < 0.05$ ). Axona has also been studied in patients with age-related memory loss, and is currently being studied as a targeted therapy for improving quality of life measures for AD patients.

### ***Osteopenia and osteoporosis***

The nature of osteopenia and osteoporosis is one of the more clear-cut disease spectrums for the focus of medical food development. Elderly female patients are most often affected by the serious sequelae of this disease (predominantly fractures) and its associated disability can be quite limiting. The elderly often do not successfully meet the nutritional requirements of Vitamin D and calcium necessary for the prevention of osteopenia and osteoporosis. Fosteum has demonstrated a clinically effective combination of Vitamin D/calcium supplementation with soybean derivatives (known to partially simulate the protective effect of estrogen through mimicry). A randomized clinical trial performed in Italy with over 380 post-menopausal patients over two years demonstrated a significant reduction in bone turnover evidenced by statistically significant improvement in bone mass density (BMD) scores.

### ***Osteoarthritis***

Limbrel, another medical food, also places its focus in the musculoskeletal system by targeting the metabolic processes involved in osteoarthritis and joint degeneration. An interesting aspect of the therapeutic mechanism is its dual mode of action, which involves inhibition of the both inflammatory pathways well-defined in osteoarthritis (cyclooxygenase, lipoxygenase) as well as antioxidant properties which slow disease progression at the level of the involved joints themselves. In large, double-blind, placebo-controlled clinical studies in the United States and Japan, Limbrel administration has resulted in statistically significant improvement in all primary clinical endpoints (functional mobility, functional stiffness and functional joint discomfort). Open-label studies have also been performed with similar positive results. The endpoints were validated by the patient-scored Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), an established questionnaire designed to assess severity and patient disability due to knee and hip arthritis symptoms.

### ***Depression***

Deplyn (L-methylfolate) is an orally administered prescription medical food intended for the dietary management of suboptimal folate levels in depressed patients or hyperhomocysteinemia in schizophrenia patients. L-methylfolate can be used as adjunctive therapy for depressed patients with suboptimal folate levels in order to regulate the synthesis of trimonoamine neurotransmitters (serotonin, norepinephrine and dopamine). Studies have suggested that concomitant treatment along with selective-serotonin reuptake inhibitor (SSRI) medications may improve response to SSRI therapy.

### ***Central Nervous System Disorders***

Another related pair of medical foods branded Sentra AM & PM bridges the seemingly disparate indications between cognitive modulation and management of sleep and pain disorders. Acetylcholine, a ubiquitous neurotransmitter in humans and the target of the Sentra AM therapeutic, is thought to have an important role in memory formation and cognition, as well as in the arousal component of circadian

rhythm regulation. There is also casual, less-well studied links between acetylcholine deficiency and improper modulation of pain signaling in the central nervous system (CNS). In the peripheral nervous system (PNS), acetylcholine deficiency also has an implicated role in sustained muscle contraction, making its supplementation potentially useful in the management of chronic pain and fatigue syndromes.

Sentra AM is purely a cholinergic modulator, providing supplementation in choline and acetylcarnitine which are both acetylcholine precursors. Its claims include the ability to increase amounts of acetylcholine at the molecular level. Small double-blinded trials with emphasis on imaging data conducted by the manufacturer have demonstrated increased choline in the CNS of treated patients versus selected subjects. The indication thus spans entities as variable as fibromyalgia, sleep/arousal dysregulation syndromes and cognitive decline. Sentra PM focuses on the rebalancing of the excitatory/inhibitory axis of the neurotransmitter milieu, placing its indication within the realm of sleep onset and maintenance regulation. It provides a balanced ratio of precursors-to-neurotransmitters important in sleep onset (serotonin) and maintenance of normal sleep cycles (acetylcholine and glutamate). Eight open label trials demonstrating improved activation of the appropriate PNS (parasympathetic) response in symptomatic patients are reported by the company.

The role of neurotransmitter modulation by exogenous therapeutics is still a controversial one. However, spurred by the market need for adjunctive, non-addicting agents to assist patients with acute and chronic pain-related complaints, formulations have been developed which are intended to do just that. Theramine is a medical food engineered to stimulate production of neurotransmitters that are well-understood to inhibit CNS pain signaling, such as serotonin, GABA and norepinephrine. It also claims to facilitate PNS inhibition of inflammatory neuropeptides and Substance P, well-characterized signaling molecules for the perception of localized pain. The extrapolation of a possible improvement of the patient's baseline pain tolerance with Theramine administration makes this a consideration for healthcare practitioners that manage pain syndromes.

While medical foods are not as familiar to physicians as drugs, the potential benefits and risk/benefit ratio should be discussed with patients. These agents may provide a therapeutic complement to currently available pharmacologic therapies. It is likely that in the future, our knowledge about the underlying mechanisms and potential benefits of medical foods will be further elucidated. Additional well-designed, randomized, placebo-controlled studies are warranted in diverse areas.

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