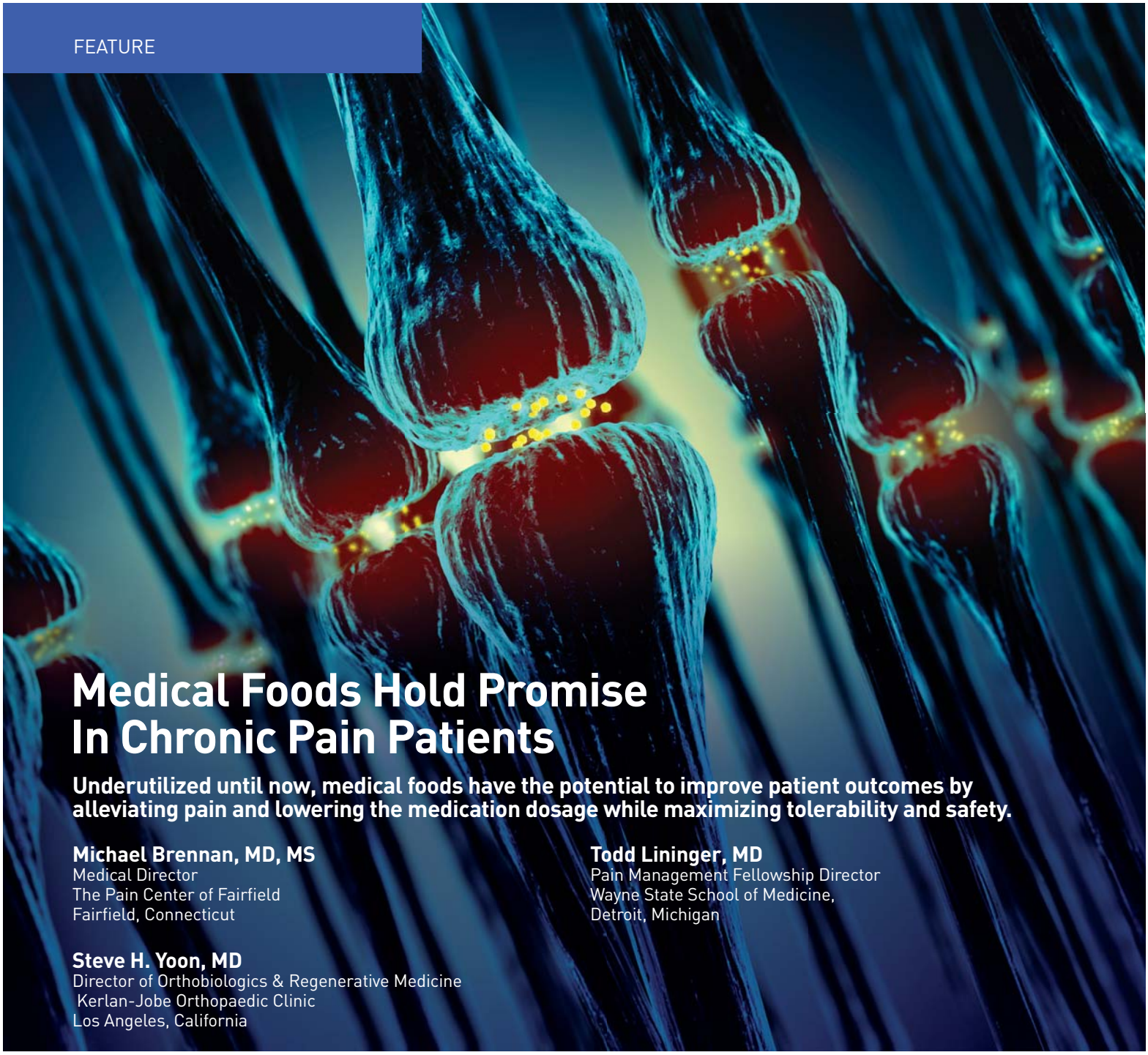

Medical Foods Hold Promise In Chronic Pain Patients

Underutilized until now, medical foods have the potential to improve patient outcomes by alleviating pain and lowering the medication dosage while maximizing tolerability and safety.

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The United States is in the midst of a public health challenge with regard to chronic pain. Given the intensifying focus on opioids, and the grim statistics on patient visits with regard to pain, practitioners throughout the spectrum of health care often feel overwhelmed by the challenges related to effective pain management.

Despite the inherent differences in patient populations and their pathologies, there are common approaches to the medical management of chronic pain. Chronic pain treatment generally relies on pharmacologic, and nonpharmacologic, therapies prescribed with a rationale that focuses on mechanistic synergies.[1,2] The clinician's goal is to maximize the patient's functionality by enhancing the analgesic response, and to minimize treatment-related side effects or toxicities. However, since most chronic pain conditions do not have any curative interventions, decisions as to any long-term pain management strategy must be considered together between clinician and patient. Further, the importance of comprehensive pain management that includes a biopsychosocial approach cannot be underestimated, and may help reduce clinical dependence on medication-based treatments. For the right patients, incorporating an inherently safe option with documented efficacy—like medical foods—into a regimen that includes active exercises, nonopioid and minimal opioid analgesic therapies, and cognitive and behavioral approaches can offer the most effective approach to pain of numerous etiologies. (See related article, page 65). Adding

medical foods into the pain management mix may enhance the ability to maintain or promote analgesia, reduce analgesic doses, and likely lessen actual and potential toxicities of analgesic and coanalgesic agents.

Limitations of Current Analgesic Therapies

Analgesic medications are a mainstay of chronic pain therapy, including nonsteroidal anti-inflammatory agents (NSAIDs), acetaminophen, opioids, and in certain pain states, adjuvant analgesics.[3] However, all of these medications have significant limitations, including questions concerning efficacy, the risk of significant adverse events, and drug-to-drug interactions. NSAIDs are commonly prescribed, but their analgesic efficacy is often modest and comes with a number of serious adverse effects.[4,5] The most frequent NSAID-related adverse effects are within the gastrointestinal (GI) tract, including ulceration, gastritis, and gastroesophageal reflux.

It has been estimated that NSAID-related GI bleeding is responsible for 100,000 hospitalizations and 16,500 deaths per year.[6,7] The annual risk of GI bleeds in patients over age 65 years is estimated to be 2.5%.[8,9] Hematopoietic toxicity (eg, bleeding) may occur, and hepatic, renal, and cardiovascular systems may be impacted.[7,10] NSAID-induced adverse events are dose-related, and elderly patients are at highest risk for these outcomes.[11] As a result of these risks, the American Geriatrics Society recommends that NSAIDs be restricted, or even eliminated, in individuals older than 65 years.[4] (See related article, page 72.)

Acetaminophen is another medication commonly relied on to manage chronic pain, but its efficacy is questionable, and it is associated with significant risk of adverse events.[12,13] For example, a Cochrane Database systematic review of trials evaluating acetaminophen versus placebo for the treatment of low back pain found that there was high-quality evidence of no benefit for acetaminophen (4 g per day) over placebo for reducing pain intensity at any time over 12 weeks of treatment.[12] The review also found that acetaminophen had no beneficial effect on quality of life, function, global impression of recovery, or sleep quality, at any time point.[12]

Another large study in patients with low back pain reported that neither a fixed dosage schedule nor an "as needed" regimen of acetaminophen were associated with any benefits.[13] The poor efficacy of acetaminophen, combined with the risk of severe liver toxicity, presents sufficient doubt about the near-universal reliance on this class of medications for the treatment of chronic low back pain.

With regard to opioids, emerging adverse effects, such as hormonal abnormalities, are becoming better understood.[14,15] Opioids are also associated with a number of well-known short- and long-term nutrition-related side effects, including constipation, nausea, sedation, an increased risk of falls and fractures, depression, and sexual dysfunction.[16] The current opioid crisis has escalated to a point where Surgeon General Vivek Murthy, MD, MBA, has taken the unprecedented step of writing a letter to every single physician in the United States to highlight the grave concern with regard to opioid safety.[17]

In addressing the escalating use of opioids, Dr. Murthy wrote, "The results have been devastating. Since 1999, opioid overdose deaths have quadrupled and opioid prescriptions have increased markedly—almost enough for every adult in America to have a bottle of pills. Yet the amount of pain reported by Americans has not changed. Now, nearly 2 million people in America have a prescription opioid use disorder, contributing to increased heroin use and the spread of HIV and hepatitis C."

Imploring all of us to reconsider our prescribing habits, Dr. Murthy recommends better patient education that relies on a more rational approach to opioids, starting with the recognition that they are potentially addictive. Given the limited efficacy and substantial risk of treatment-related toxicities, there is a clear unmet need for alternative analgesic therapies that are safe, and that have demonstrated efficacy in the treatment of chronic pain. Medical foods are an appealing option given their strong safety profile, and their design to target the underlying neuronal pathways that generate chronic pain syndromes.

Medical Foods: Meeting An Unmet Need

Medical foods fall into a distinct FDA regulatory category that differs from both pharmaceutical agents and dietary supplements. Medical food is defined by the FDA as "a food which is formulated to be consumed or administered enterally 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."[18]

The FDA identifies that medical foods are intended for specific dietary requirements of a condition, and "are specifically formulated and processed (as opposed to naturally occurring foodstuff) for a patient who requires use of the product as a major component of a disease or condition's specific dietary management."[18]

With regard to pain, medical foods are intended to meet the potential needs of unique nutritional requirements, resulting from a specific disease

Table 1. Medical Food versus Dietary Supplement

Characteristic	Prescription Drug	Medical Food	Dietary Supplement
Intended for use under medical supervision	Yes	Yes	No
Labeled for the management of a specific medical disorder, disease, or condition	Yes	Yes	No
Includes a package insert	Yes	Yes	No
Requires a prescription	Yes	No	No

Table 2. Neurotransmitters Involved in the Modulation of Pain and Pain-Related Syndromes

Amino Acid Precursor	Neurotransmitter	Physiological Effect
Choline	Acetylcholine	Decreased pain perception; pain inhibition; sleep modulation
L-Histidine	Histamine	Inflammation inhibition
5-hydroxytryptophan	Serotonin	Inflammation inhibition; modulation of pain processing, mood, and sleep cycle
Serine	D-Serine	Increased sensitivity to opioids
Arginine	Nitric oxide	Stimulation of production of natural opioids
Glutamine	Gamma-aminobutyric acid	Modulation of sleep and anxiety
L-glutamic acid	Glutamate	Stimulation of the mind

Summarized from references: 4, 8, 22
GABA, gamma-aminobutyric acid

or condition as determined by medical evaluation. Medical foods must be prescribed by a physician after a diagnosis has been made, yet they are not regulated as drugs, and are not subject to any regulatory requirements that specifically apply to drugs. They are also exempt from food labeling requirements pertaining to health claims under the Nutritional Labeling Act.[18] Medical foods are also distinct from nutritional supplements (Table 1), although they do resemble nutritional supplements in terms of regulation.

The ingredients in medical foods must contain substances that are recognized by qualified experts to be safe under the conditions of its intended use (ie, generally recognized as safe [GRAS]). Because of their positive safety profile, medical foods may help minimize the number of the concerns typically associated with conventional analgesics.

The rationale for using medical foods in the treatment of chronic pain syndromes arises from an understanding that the metabolic process is disrupted, leading to a depletion of neurotransmitters and an associated synaptic fatigue that results from an increase in precursor turnover and dietary deficiency of the precursors. A number of neurotransmitters are involved in the modulation and sensation of pain, particularly in conditions such as sleep dysfunction, mood disorders, and fatigue (Table 2). Abnormalities in neurotransmitter levels also have been documented in fibromyalgia.[19]

The goal of medical foods is to restore the homeostasis of these neurotransmitter levels.[4,19] Thus, medical foods that correct nutritional deficiencies may be an appropriate target for patients who experience poorly managed pain.

Two randomized double-blind studies have evaluated an amino acid formulation (AAF) that contains the neurotransmitter precursors choline, L-histidine, 5-hydroxytryptophan, serine, and arginine (Theramine, Targeted Medical Pharma LLC).[4,20] This AAF formulation has been developed as a medical food for the dietary modulation of the metabolic processes associated with pain and inflammation. These studies demonstrated that the AAF is both safe and more effective than low-dose NSAIDs for the treatment of low back pain.[4,20] In 1 study, 129 adult patients with back pain lasting more than 6 weeks were randomized to 1 of 3 groups for 28 days: naproxen only (250 mg/day), AAF only (2 capsules twice daily), or

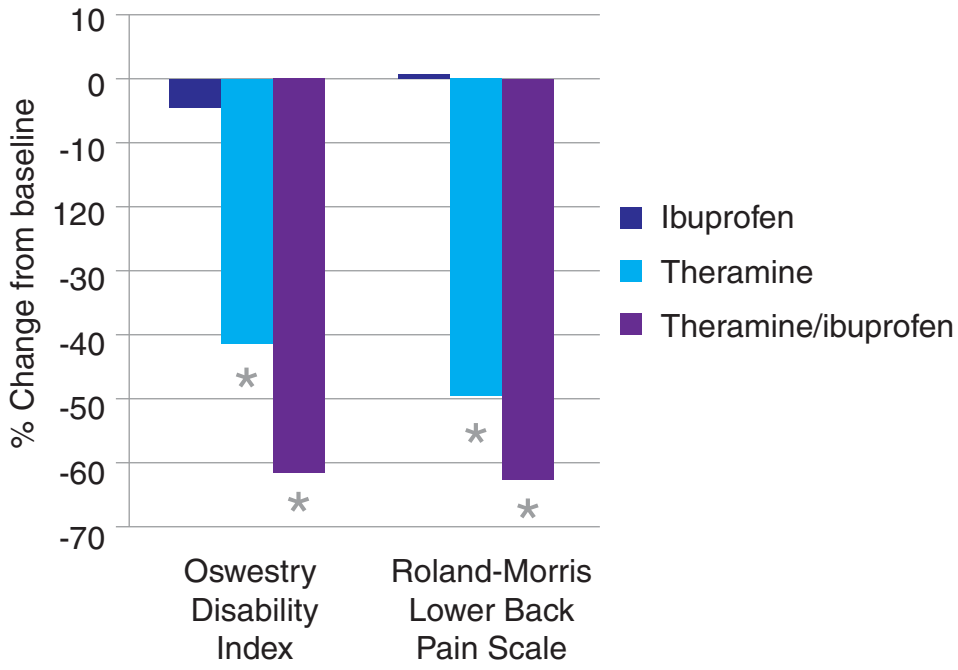

Figure 1. Percent change from baseline to day 28 in Oswestry Disability Index and Roland Morris Disability Index in patients with chronic back pain; *$P<0.05$[4]

an AAF/naproxen combination.[20]

The primary efficacy endpoint of these studies was the change in participants' awakening stiffness and pain scores as assessed by the Roland-Morris Lower Back Pain Scale and the Oswestry Disability Index.[4,20] Those receiving AAF alone achieved a statistically significant reduction from baseline in the Oswestry Disability Index (–33%) and Roland-Morris Lower Back Pain Scale (–44%) compared to no change for those receiving naproxen only. Those in the AAF/naproxen combination group achieved even greater reductions in these pain indices (–60% and –65%, respectively).

Inflammation, as measured by C-reactive protein (CRP), was also significantly reduced in the AAF (–17%) and AAF/naproxen (–79%) groups, while those receiving naproxen had a 185% increase in CRP. All treatments were well tolerated with no adverse events reported; however, those in the naproxen-only group experienced significant increases in hepatic transaminases (ALT, AST), indicative of hepatocellular inflammation, while those in the AAF or AAF/naproxen groups had no significant increase.[20]

Comparable results were seen in a similarly designed study, involving 122 patients with chronic back pain who were randomized to 1 of 3 groups: ibuprofen alone (400 mg/day), AAF alone, or a combination of the 2 for 28 days.[4] Patients receiving AAF or AAF/ibuprofen achieved significantly greater reductions from baseline to day 28 in the Oswestry Disability Index and Roland-Morris Lower Back Pain Scale compared with those receiving ibuprofen alone (Figure 1). Notably, this study also documented that amino acid precursor levels were more than 2 standard deviations (SDs) below the mean for normal subjects at baseline. Measurements over the 4-week study showed that treatment with AAF was associated with a significant increase in these precursors.[4]

In contrast, patients treated with ibuprofen monotherapy did not show an increase in amino acid concentrations.[4] The study also showed that AAF, alone or in combination with ibuprofen, was associated with reductions in CRP (–47% and –36%, respectively) and interleukin-6 (IL-6; –24% and –43%, respectively), while the ibuprofen-only group was associated with increases in both CRP (60%) and IL-6 (13%).[4] These differences were highly statistically significant ($P<0.001$ for all comparisons). Overall, these results suggest that AAF, alone or in combination with low-dose NSAIDs, restores plasma amino acid levels and produces measurable improvements in pain as well as demonstrated decreases in inflammation.

Patients with chronic pain often have sleep disturbances that can impact the perception of pain.[21]

Neurotransmitters, such as serotonin and acetylcholine, modulate the sleep cycle; their adequate supply is important for the production of sleep cycles, including phase IV delta and REM sleep.[22] A double-blind, placebo-controlled trial in 111 adult patients with a history of sleep disturbance evaluated the effect of another AAF-containing acetylcholine and serotonin precursors (Sentra PM, Physician Therapeutics) on sleep parameters.[23] The sleep disturbances were required to last at least 6 weeks, and were defined by perceived lack of restorative sleep. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) and a Leeds Sleep Evaluation Visual Analogue Scale (LSEQ). The patients were randomly assigned to 1 of 4 groups: AAF, trazodone 50 mg, AAF/trazodone combination, and placebo. The results indicated that AAF shortened sleep latency and improved sleep quality without morning grogginess compared with placebo, while trazodone alone had no significant effect.[23]

In particular, those receiving AAF and AAF/trazodone experienced a 3.86- and 6.48-point improvement, respectively, in sleep quality (10-point scale) and a 41- and 56-minute reduction in sleep latency compared to no improvement for either parameter in the trazodone and placebo groups ($P<0.001$ for both).[23] The enhanced benefit of AAF when used in combination with trazodone may be related to the fact that AAF and trazodone affect cholinergic and serotonergic pathways in different and potentially synergistic ways.

Medical Foods in Perspective

Growing concerns about prescribing ever-increasing doses or combinations of analgesics, and an apparent lack of evidence demonstrating any lasting improvement in long-term clinical outcomes, has created heightened urgency for safer, more effective therapies to better manage chronic pain conditions. The efficacy of traditional pharmacologic agents tends to diminish while the risk of serious adverse events increases.[24] This is particularly true for the elderly who are more susceptible to adverse events and drug interactions because they are commonly taking multiple medications. This creates enhanced risk for NSAID-induced GI bleeding, and the CNS depressant effects of opioids can enhance disorientation, confusion, and mental "fogginess," increasing the risk for falls or accidents.[25]

Medical foods provide a new alternative to traditional medication therapies. The GRAS ingredients of medical foods present no concerns for drug interactions and no risk of long-term complications. In addition, because medical foods have a unique mechanism of action (ie, replacement of amino acids that are essential for the synthesis of neurotransmitters responsible for transmitting pain signals and mediating their perception), medical foods may also be used in combination with traditional pharmaceuticals, producing enhanced efficacy and the potential to reduce the dose of the concomitant medication.

Relying on medical foods for pain management will maintain efficacy safely, while reducing the risk of adverse events. This was evidenced in the AAF/NSAID combination trials where the low doses of NSAIDs used in combination with AAF were associated with a low rate of adverse events.[4] Indeed, while NSAIDs alone were associated with a slight increase in liver transaminases, the AAF/NSAID combination was not.[4]

Medical foods must meet strict FDA safety and efficacy standards, within stringent therapeutic guidelines. This differentiates medical foods from nutritional supplements, such as vitamins and essential minerals, which are not federally regulated for safety or efficacy.[18]

Because medical foods have such a benign safety profile, they have the potential to be more cost-effective than standard analgesic medications. For example, consider the costs that come with treating medication-related adverse events (eg, NSAID-related GI bleeding). This point was highlighted by a pharmacoeconomic analysis that evaluated the costs of NSAID-related GI bleeding, laboratory monitoring, and clinical evaluation—the use of an AAF over generic NSAIDs in elderly patients was found to be less costly.[8]

In summary, medical foods have been an underutilized option for the treatment of chronic pain. In an era focusing on the patient-centered approach, physicians should have at least an interest in, and at appropriate times, a preference for alternative, non-traditional therapies. Medical foods provide clinicians with a unique therapeutic modality that has the potential to improve patient outcomes by alleviating pain, and at the same time maximize tolerability and safety. ■

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