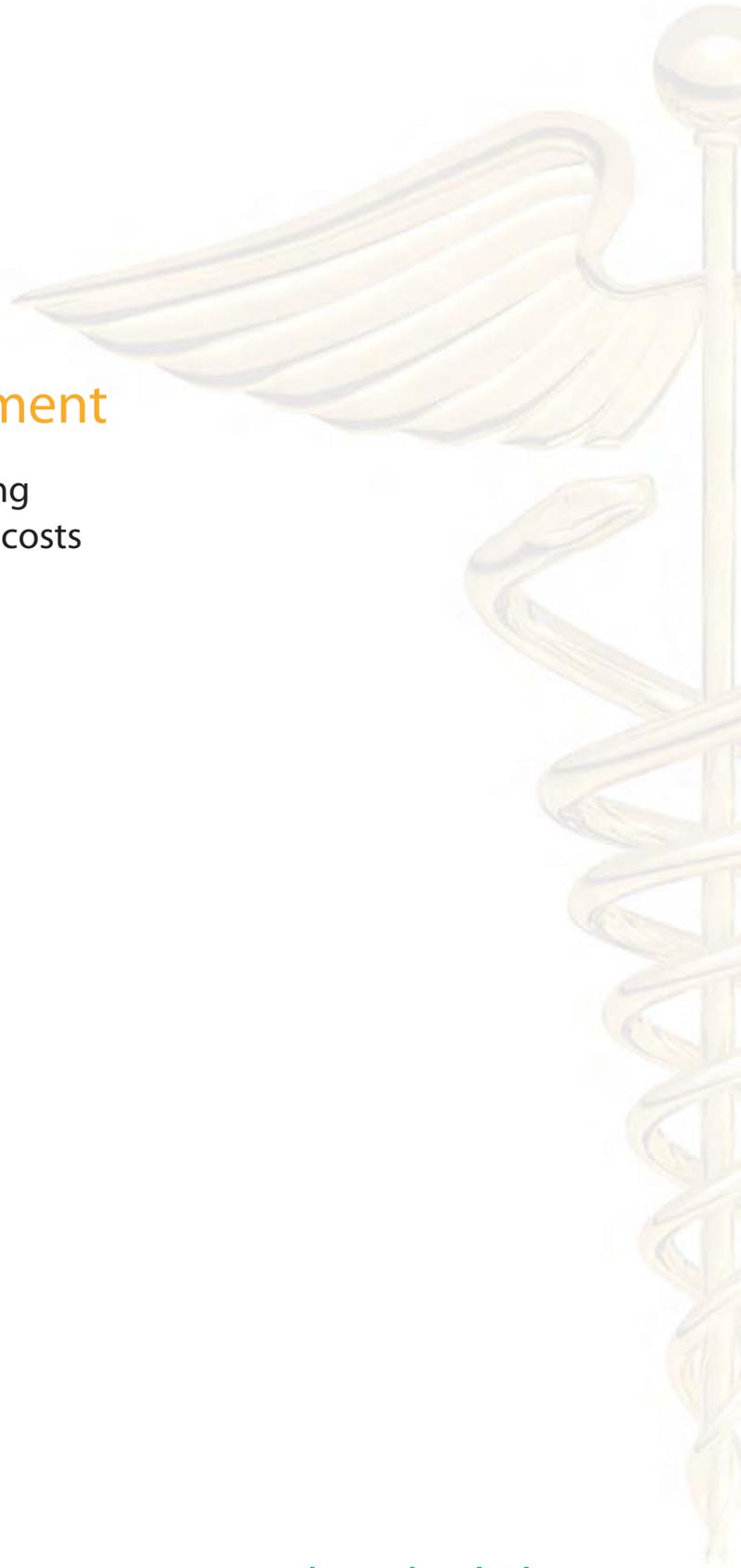




## Innovations in Pain Management

The potential of medical foods for improving clinical outcomes and reducing healthcare costs



Targeted Medical Pharma  
White Paper

## The Treatment of Pain

Pain and the treatment of pain affect every sector of our society. From over the counter non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen and others, to long acting narcotic analgesics, the treatment of pain is not without risk. While NSAIDs have a familiar black box warning for gastrointestinal problems, the FDA has recently required a black box warning for acetaminophen (tylenol and others), citing the risk of severe liver injury. All medications including NSAIDs (cox-2 inhibitors included), acetaminophen, oral steroids, narcotic drugs, muscle relaxants and antidepressants have some benefits for treating pain, but also have associated risks.

The proliferation of pain in the United States has resulted in a sharp increase over the past decade in the use and overuse of narcotics. Prescribing narcotics has become a popular option for the treatment of chronic pain associated with back injuries, headaches, arthritis and fibromyalgia. Opioid prescriptions alone are up 33% from 181.7 million in 2001 to 240.9 million in 2012. This trend has given rise to a host of unanticipated medical, legal and social costs.<sup>1</sup>

Physicians have many choices for the treatment of pain; however acetaminophen, NSAIDs and narcotic analgesics are not always suitable for patients that need long term therapy or belong to a high risk group. Finding a treatment for pain that is both effective and safe for long term use is an imperative for the millions of affected patients as well as the healthcare community which seeks to contain the costs of this prolific epidemic.

## The Pain Gap

### PAIN FACTS

**Headache Pain, Back Pain, and Neck Pain are the Leading Cause of Recurrent Pain in America**

**Adults with Back Pain Spend Almost 200 Million Days in Bed a Year**

**More Than Half of Americans Live with Chronic or Recurrent Pain**

**40% of Americans Say Pain Interferes with Their Mood, Sleep, and Day to Day Life**

Millions suffer from acute or chronic pain every year and the effects of pain exact a tremendous toll on our country in health care costs, rehabilitation and lost worker productivity, as well as the emotional and financial burden it places on patients and their families. The costs of unrelieved pain can result in longer hospital stays, increased rates of re-hospitalization, increased outpatient visits, and decreased ability to function fully, leading to lost income and insurance coverage.

In 2011, at least 100 million adult Americans suffered from common chronic pain conditions, a conservative estimate because it does not include acute pain or children. The number of Americans in pain has resulted in a significant public health problem that costs society at least \$560-\$635 billion annually (an amount equal to about \$2,000.00 for everyone living in the U.S.)<sup>2</sup>

Chronic pain takes an enormous personal toll on millions of patients and their families, and leads to increased health care costs. Reducing the burden of treating chronic pain is a societal necessity, a medical challenge and an economic requirement.

1) IMS Health Data, California Workers' Compensation Institute, 2012

2) Institute of Medicine of the National Academies Report. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, 2011. The National Academies Press, Washington DC.

## The Cost of Pain

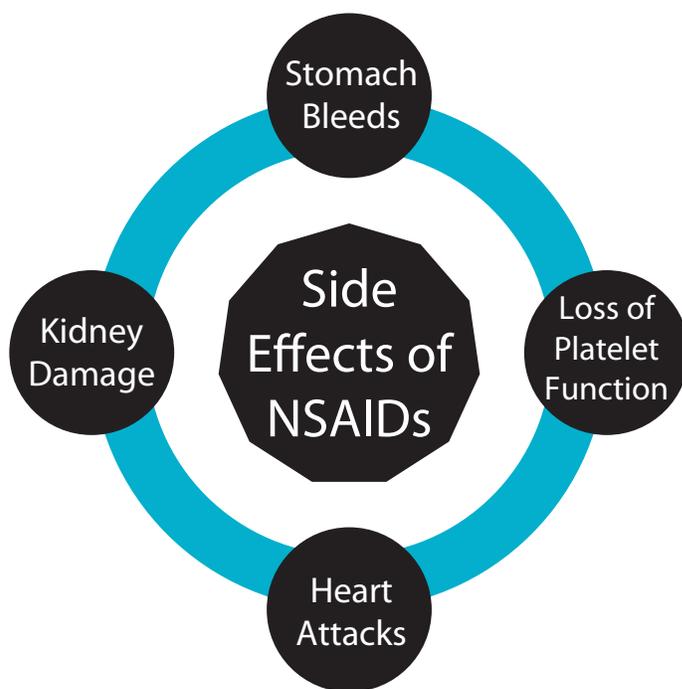
The prevalence of pain has a tremendous impact on business, with a recent report by the Institute of Medicine indicating that the annual value of lost productivity in 2010 dollars ranged between \$297.4 billion to \$335.5 billion. The value of lost productivity is based on three estimates: days of work missed (ranging from \$11.6 to \$12.7 billion); hours of work lost (from \$95.2 to \$96.5 billion); and lower wages (from \$190.6 billion to \$226.3 billion). This billion dollar annualized price tag will likely climb as the U.S. population ages.

The cost of pain also includes the cost of treating side effects. The most commonly prescribed drug for pain are non-steroidal anti-inflammatory drugs (NSAIDs). Approximately 98 million prescriptions for NSAIDs were filled in the United States in 2012 (IMS 2012). Although effective for treating pain and inflammation, NSAIDs are linked to adverse side effects which make them inappropriate for use in many patient populations.

There are several serious side effects and toxicity related to the use of traditional NSAIDs which can lead to costly hospitalizations or death.

Treatment of GI problems alone caused by the use of NSAIDs is estimated to add over 40% to the cost of arthritis care.<sup>3</sup>

Patients with chronic pain have more hospital admissions, longer hospital stays, and unnecessary trips to the emergency room. Such inefficient and even wasteful treatment for pain is contributing to the rapid rise in health care costs in the United States.



Traditionally, physicians have had to balance the risk of side effects such as GI bleeds and addiction versus the benefits in treating pain and chronic painful conditions. Neither NSAIDs nor narcotics are suitable alternatives for patients that need long term therapy and there has long been an unmet medical need for the safe and effective treatment of pain. Clinical studies have determined that managing the increased nutritional requirements of pain with medical foods such as Theramine® can be a safe and effective alternative for the treatment of pain and inflammation without the risks of addiction, adverse reactions or additional medications to prevent side effects. All of the ingredients in Theramine are GRAS (Generally Recognized as Safe) and do not require FDA pre-market approval because the safety of the ingredients has been established.

3) Bloom, BS. Direct medical costs of disease and gastrointestinal side effects during treatment for arthritis. Am J Med. 1988; 84(2A): 20-24

## Patients at Risk

There are several patient populations that particular care should be taken when prescribing an NSAID or narcotic medication for pain. There is no current NSAID or narcotic regimen available for treatment of pain and inflammation that does not carry a high risk of adverse side effects. There are large segments of the population that should not take NSAIDs or suffer from chronic conditions for which a narcotic or an NSAID is not indicated. NSAIDs and narcotics are not indicated for long term use, for use in high risk groups or for the treatment of chronic non-malignant pain. There are also several patient populations that should avoid entirely the use of NSAIDs and narcotics for pain relief due to the very high risk of adverse side effects.

Unfortunately, all NSAIDs, including aspirin at low doses, have been associated with both minor gastrointestinal (GI) side effects such as dyspepsia and abdominal discomfort, and major side effects such as ulcers, perforation, and bleeding.

Any of the risk factors listed in the figure to the right contraindicate a patient for the use of an NSAID and are considered to be very high risk factors for complications associated with NSAIDs. The risk of drug induced nephrotoxicity which can lead to severe kidney damage is also very real and should be assessed within the high risk groups.

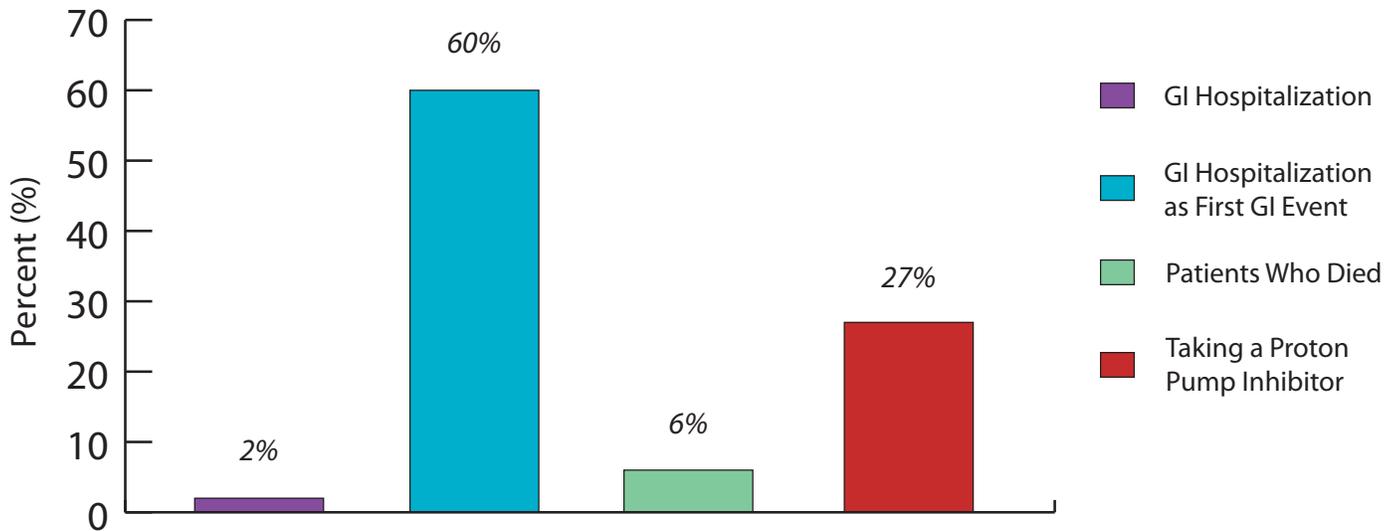
### Patients at Risk for NSAID Induced Ulcers

- 65 Years of Age or Older
- History of Peptic Ulcer Disease or Previous GI Bleed
- History of Cardiovascular Disease
- History of Hepatic or Renal Impairment
- Currently Taking Corticosteroids, Anticoagulants, or Aspirin

### Patients at Risk for Nephrotoxicity

- 65 Years of Age or Older
- History of Renal Insufficiency
- History of Hypertension
- History of Hepatic Cirrhosis
- Congestive Heart Failure
- Concurrent Diuretic
- ACE Inhibitor Use
- History of Atherosclerotic Disease

## NSAID Induced Adverse Side Effects in the Elderly<sup>6</sup>



A study on the effects of NSAID induced side effects in the elderly reflected the average direct costs of GI side effects per patient-day on NSAIDs were 3.5 times higher than those of a patient-day not on NSAIDs. Seventy percent of the cost was attributed to GI events resulting from NSAID treatment.<sup>6</sup>

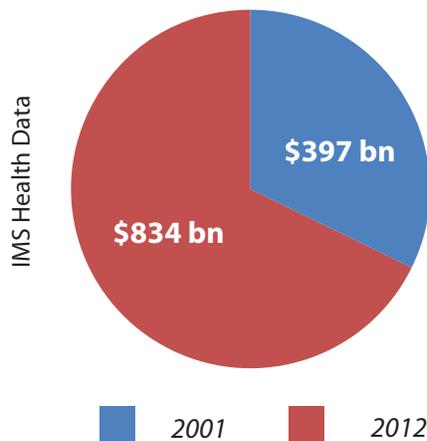
Severe GI events associated with NSAIDs have received a significant amount of attention from clinicians and healthcare policy decision-makers because they are costly, require hospitalization, and may be fatal. However, from the perspective of the healthcare system, minor GI side effects and prophylactic gastroprotection against NSAID-related side effects may consume more healthcare resources than do more severe events because of their high prevalence.

Use of opioids in the treatment of pain also comes at a high price. Opioid use has resulted in increased hospitalizations, increased spending on opioid addiction and increased workplace costs. The cost of the average lost time workers' compensation claim when long acting opioids are prescribed is 900% higher than the average claim without the use of opioids. U.S. emergency room visits have also increased. The number of cases in which an opioid other than heroin was cited as a reason for an emergency room treatment in 2004 was 299,498, and in 2011 was 885,348, an almost 300% increase.<sup>7</sup>

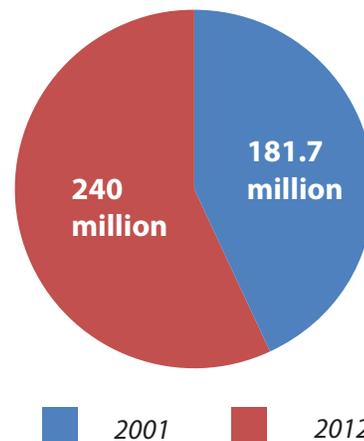
6) Br J Clin Pharmacol. 2001 August; 52(2): 185–192. Cost of prescribed NSAID-related gastrointestinal adverse events in elderly patients

7) IMS Health Data, California Workers' Compensation Institute

## Sales of Opioids



## Opioid Prescriptions



A considerable amount of money is spent every year to protect against or manage adverse events induced by NSAID and narcotic pain therapies. The need for safe and effective therapies in addition to appropriate patient risk management strategies is a potential means of reducing the rapidly expanding drug related healthcare resource costs.

## Safe and Effective Option for Pain

Simply treating the symptoms of pain have not proven to be effective or cost saving in the long run. As previously discussed, use of NSAIDs or narcotics is not without risk and certain patient populations should avoid use altogether.

Use of NSAIDs and narcotics for non-malignant pain has an adverse effect on both patients and payers:

- Patient safety is compromised
- Risk of addiction
- Delay of return to work
- Higher risk of on the job injury
- Increased cost of medication and treatment

The use of medical foods for the treatment of pain disorders, sleep, obesity and fatigue is a growing trend in medicine. Patients, payers and physicians are looking for safe alternatives to manage disease effectively without the harmful side effects associated with certain pharmaceuticals.

Incorporating the use of medical foods such as Theramine® into a clinical pain management protocol, allows physicians the flexibility to use less of a narcotic or NSAID pain reliever and potentially eliminate their use all together. Reducing the burden of adverse side effects of these drugs while improving clinical outcomes is critical for overall patient care and a return to normal activities of daily living. While the initial costs of shifting away from certain generic medications may seem high, the benefits of long-term savings and reductions in other health related costs could prove enormous.

## The Promise of Medical Foods

Medical foods are used by many healthcare professionals to treat the underlying pathophysiology of pain syndromes rather than just the symptoms alone. They are a class of medications that address the specific nutrient, amino acid, and other nutritional needs of adults who have different or altered physiologic requirements due to the maladaptive nature of pain syndromes. Pain perception is coordinated by a complex network of neurons, neurotransmitters, peptides and hormones connected together by the central and peripheral nervous systems. Pain perception involves the coordinated responses of numerous ascending excitatory and descending inhibitory pathways. Pain reduction is accomplished by moderating responsiveness of the nociceptors to noxious stimuli, regulating the transmission of pain signals over the neural pathways of the peripheral and central nervous system, and controlling inflammation, which sensitizes the nociceptors to noxious stimuli.

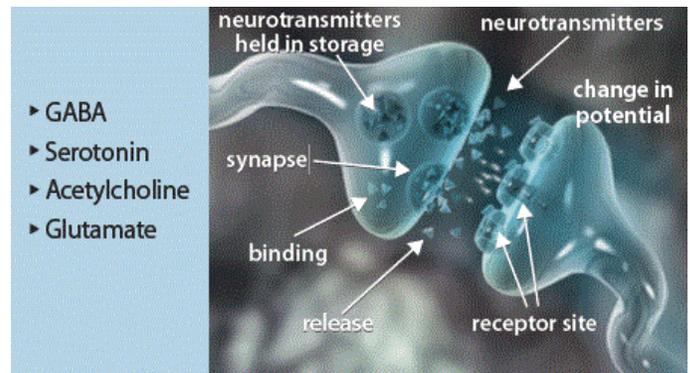
Ingredient	Role in Pain Management
5-HTP	<ul style="list-style-type: none"><li>• Precursor to Serotonin</li><li>• Decrease pain signals in spine and brain</li><li>• Inhibit release of substance p</li></ul>
Arginine	<ul style="list-style-type: none"><li>• Precursor to Nitric Oxide</li><li>• Inhibits transmission of afferent pain signals</li><li>• Inhibits NMDA receptor activity</li></ul>
Glutamine	<ul style="list-style-type: none"><li>• Precursor to Glutamate, GABA, Glutathione</li><li>• Inhibits NMDA receptors by activating GABAergic receptors</li><li>• Prevents the oxidative damage of inflammation</li></ul>
Choline	<ul style="list-style-type: none"><li>• Precursor to Acetylcholine</li><li>• Activates parasympathetic controls</li><li>• Inhibits NMDA receptor activity</li></ul>

Patients with pain disorders and inflammatory conditions are known to have increased nutritional requirements for tryptophan, choline, arginine, GABA, flavonoids and certain oxidants. The amino acids in the medical food, Theramine®, are precursors of neurotransmitters which modulate pain processes and inflammation. Theramine provides specific amounts of arginine, choline, GABA, glutamine, histidine, 5-hydroxytryptophan, and serine to address increased metabolic demand for the neurotransmitters associated with modulation of pain and inflammation. Under normal physiological conditions, glutamine, arginine, serine, and choline are considered nonessential because endogenous synthesis is sufficient to satisfy metabolic demand. When needs are altered by conditions that increase metabolic demand, such as pain, the usual rate of synthesis is no longer sufficient and these nutrients become conditionally essential, requiring that additional amounts be consumed. These nutritional requirements are such that they cannot safely be achieved by the modification of the normal diet alone, or by supplementing the diet.

Clinical evaluations demonstrate that patients with pain disorders show decreased blood levels of specific amino acids despite having a sufficient intake of protein indicating that the need for these amino acids are selectively increased in these patients.<sup>9</sup> The pain process can be modulated by providing the amino acid precursors of neurotransmitters that are involved in the transmission and mitigation of pain and inflammatory signals. By addressing the pathophysiology of the pain process with a medical food, a physician can significantly reduce and eventually eliminate the dose of an NSAID or narcotic pain reliever and replace it with twice daily dose of a medical food without loss of efficacy. Depending on the nature and the severity

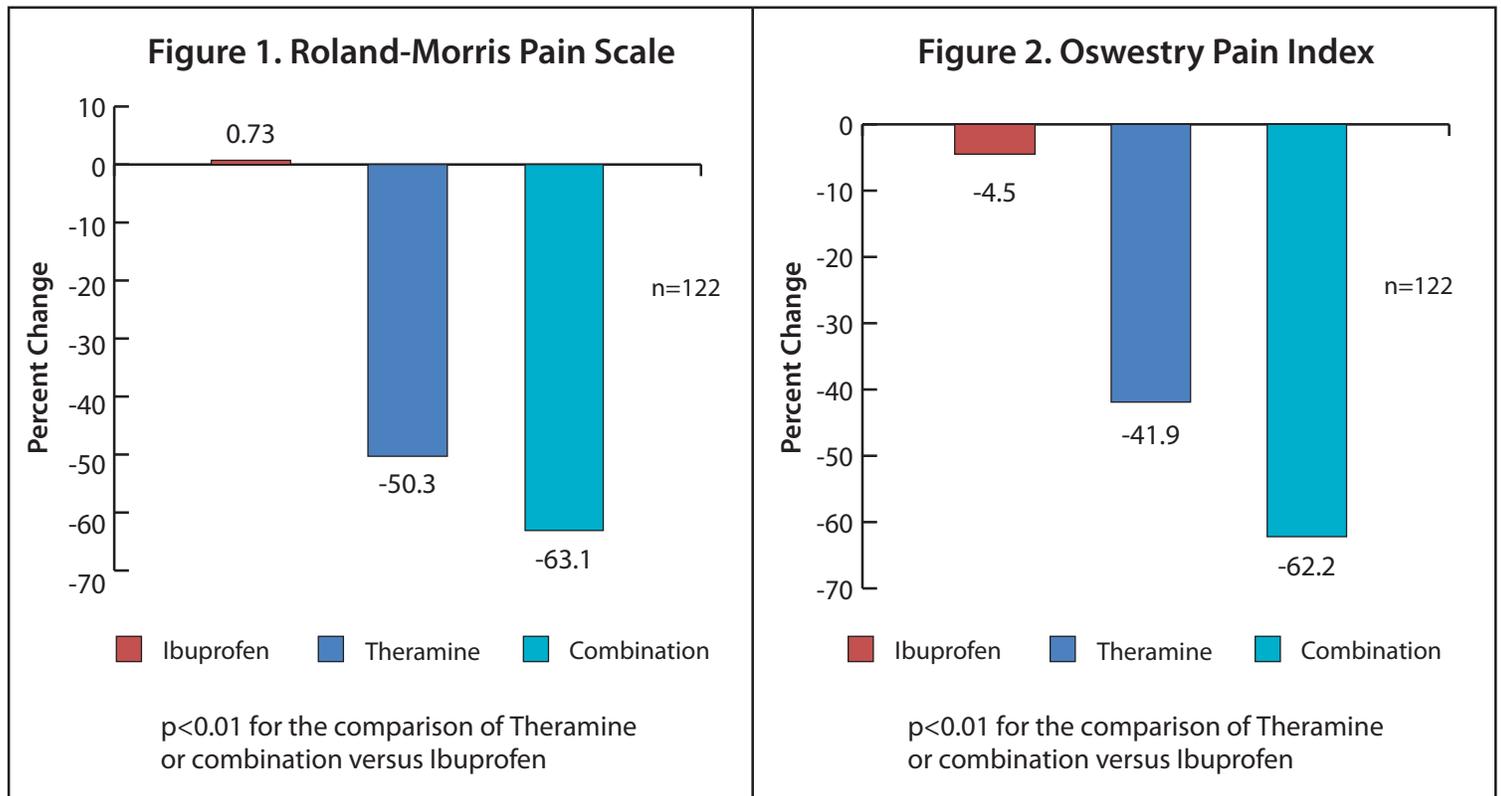
of pain, a physician may choose to use a medical food alone or as adjunct to an NSAID or other analgesic. Co-administration of a medical food with an analgesic medication allows the physician to titrate the dose of the pharmaceutical medication to the specific needs of the patient, resulting in an overall lower dose of medication.

There is no current NSAID or narcotic regimen available for the treatment of pain and inflammation that does not carry a high risk of adverse side effects. As noted previously, there are large segments of the population that should not take NSAIDs or suffer from chronic conditions for which a narcotic or an NSAID is not indicated. NSAIDs and narcotics are also not indicated for long term use. Theramine is an appropriate therapy for use in high risk populations or on a long term basis because of the superior safety profile. The only reported side effects associated with the use of Theramine are benign and include dry mouth, headache and upset stomach. These side effects are short lived and may be addressed by dose titration and hydration.



Medical foods provide the precursors to the neurotransmitters responsible for modulating pain, inflammation, and nervous system activity.

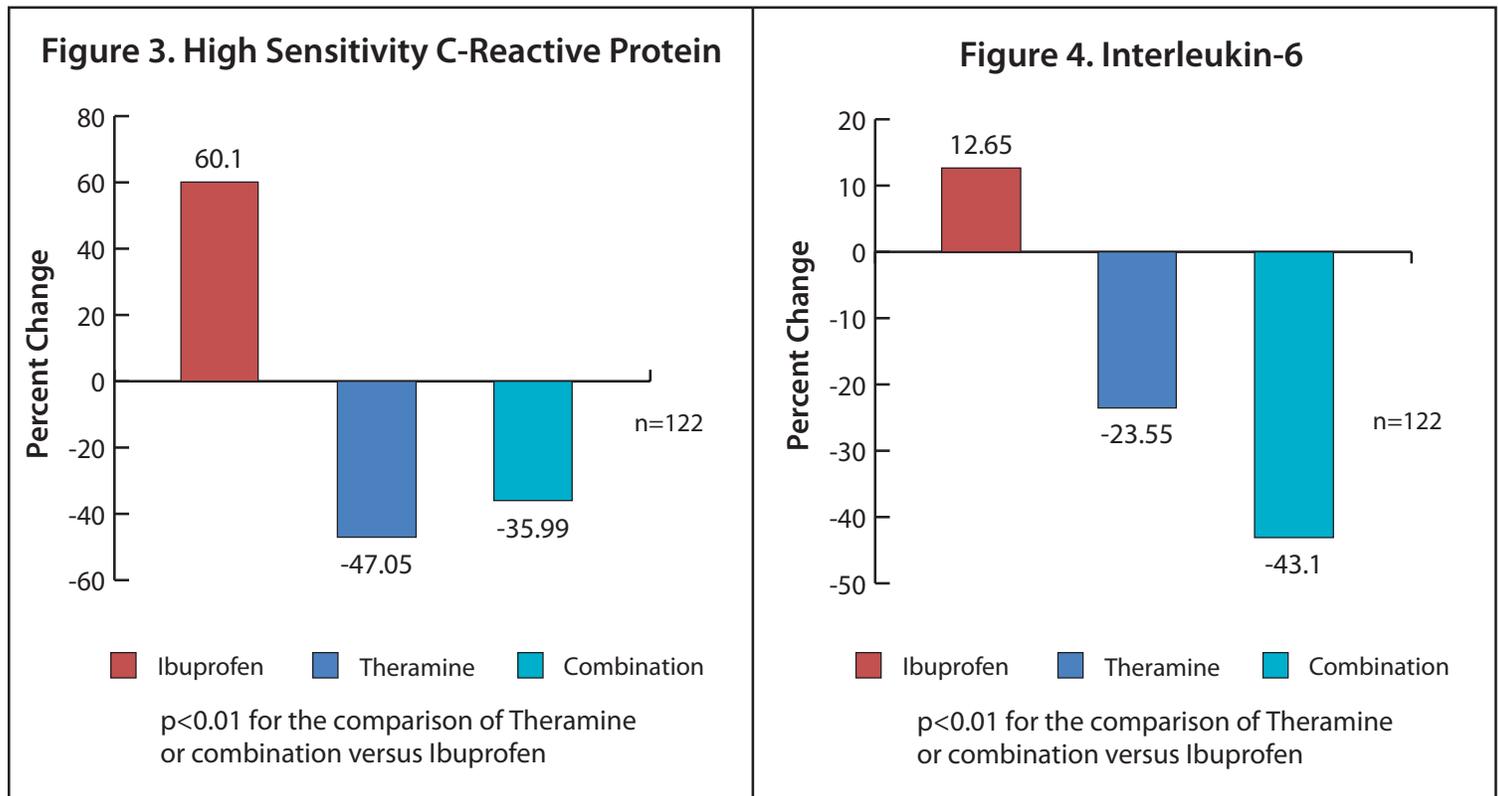
9) Larson AA. Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways. 2000 August.



In two clinical studies comparing the medical food Theramine® and a non-steroidal anti-inflammatory medication, Theramine was shown to be more effective than low dose NSAIDs in treating low back pain. Clinical data indicate significant reduction in back pain with the administration of Theramine alone and as an adjunct therapy to a low dose NSAID, while administration of a low dose NSAID had no appreciable effect on pain. The use of Theramine as either a standalone or adjunct therapy can significantly improve pain perception.

Theramine is encapsulated with a patented technology that promotes the rapid cellular uptake and conversion of milligram amounts of amino acids and nutrients into the specific neurotransmitters responsible for modulating nociception and inflammation. This patented technology allows Theramine to be effective without attenuating over time. Two multicenter double blind trials have established the efficacy of Theramine in the treatment of chronic back pain.

As indicated in **Figure 1** and **Figure 2**, pain fell by 63% with administration of Theramine and an NSAID as measured by the Roland-Morris Index, and by 62% as measured by The Oswestry Disability Index.



A reduction in inflammatory markers was also noted with the administration of Theramine®. C-reactive protein (CRP) and interleukin-6 decreased with the administration of Theramine (**Figure 3, Figure 4**). Reduction of C-reactive protein (CRP) levels was noted with the administration of Theramine alone as well as when used with an NSAID. Conversely, studies reveal that the administration of an NSAID alone elevated CRP.

The current advice of the American Geriatrics Society is to restrict or even eliminate the use of NSAIDs for people over the age of 65. This demographic has the highest incidence of osteoarthritis, back pain, and spinal stenosis and is the most susceptible to adverse events associated with NSAIDs. The therapeutic options for many of these patients are very limited and do not reduce inflammation or address inflammatory processes. In many cases the available therapeutic options are associated with a host of co-morbidities such as addiction, depression and weight gain.

In one pharmacoeconomic analysis published in the *Journal of Pharmacy Research* in 2012, It was established that the use of the medical food, Theramine, resulted in an overall cost reduction which would be beneficial to both patient and payer.

<b>Associated Effect or Need</b>	<b>Cost of Theramine Per 3,000,000 pts/year</b>	<b>Cost of NSAIDs Per 3,000,000 pts/year</b>
<b>GI Bleeds</b>	0	\$225,000,000
<b>Protective Medication</b>	0	\$432,000,000
<b>Lab Tests</b>	\$1,000	\$75,000,000
<b>GI Bleeds</b>	0	\$144,000,000
<b>Death/100 pt. years</b>	0	0.4
<b>Deaths/300,000 pt. years</b>	0	1,200

Theramine® has been designed using Targeted Cellular Technology (TCT), an integrated molecular system that facilitates the uptake and utilization of the neurotransmitter precursors that are used in the modulation of pain, by target cells within the nervous system. TCT allows for the production of neurotransmitters from precursors in milligram quantities not gram quantities. Targeted Cellular Technology allows for ingestion of smaller amounts of amino acids to elicit the same response as larger amounts, making daily dosing more feasible and reducing the potential for tolerance. Unlike pharmaceutical agents that are not innate components of the pain process, and thus may lose their effectiveness in a relatively short period of time, the effectiveness of Theramine is not attenuated.

Traditional pain medication will always have its place in therapeutic treatment, and when used properly, is effective. However, physicians, payers and patients are requesting safer, more effective alternatives to treat pain without harmful and costly side effects. The rapidly increasing population of patients 65 years of age and older is a major concern for both physicians and payers as the pain related costs to overall U.S. health care expenses are likely to rise proportionally as well. The economic impact of pain is certain, as are the physical, emotional, and social impact for millions of people.



2980 Beverly Glen Circle, Suite 301  
Los Angeles, CA 90077  
Tel: (310) 474-9809  
Fax: (888) 652-3017  
[www.tmedpharma.com](http://www.tmedpharma.com)  
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