The High Cost of Side Effects

In the late 1800 and early 1900's, Dr. William Osler referenced the nutritional requirements associated with diseases such as tuberculosis and asthma and the importance of certain nutrients in the treatment of some illnesses, as mentioned in his book, "The Principles and Practices of Medicine." This treatment approach was widely accepted by medical science for the next several decades. In the 1940's, with the development and distribution of penicillin, pharmaceutical companies began to strongly influence the practice of medicine. In the 1960's, the pharmaceutical industry dominated the treatment of most diseases through the use of synthetic drugs.

Although drugs can be effective in treating illness and in some cases can be life saving, some drugs have undesirable and even deadly side effects. They can cause illness, toxicity and death. Side effects can be more costly than the disease itself. In the United States, adverse drug reactions are the leading cause of illness and account for 106,000 deaths annually. In one year over two million hospitalized patients suffered serious drug reactions. This is because a single prescription drug can disrupt multiple cell functions.

In 1999, the Centers for Disease Control reported more than 600,000 hospital admissions and 700,000 emergency-room visits resulting from medications that were correctly administered but nonetheless produced serious side effects - from intestinal bleeding to seizures to even death. Because the elderly take the most drugs, they are at the greatest risk. On average, Americans who are 65 or older take six different medications every day, including prescription and over-the-counter drugs. For residents of nursing homes and other long term care facilities, that average drug burden rises to eight. Very often a second drug is prescribed to alleviate the side effects caused by the first, and then a third drug to alleviate the symptoms caused by the first two, and so on.

One of the most commonly used types of medicines, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), are associated with side effects and increased cost to the healthcare system in general and to health insurance companies in particular. It is estimated that over $4 billion is spent on medical costs related to complications from NSAID use. Over 40% of the cost in treating arthritis is attributed to side effects from NSAID use. NSAIDs can cause a variety of secondary issues, including GI discomfort, GI bleeding, anemia, ulceration and perforation of the gastrointestinal tract and liver and kidney disease (1). NSAIDs can also cause toxicity in patients taking other medications such as lithium.

NSAIDs are associated with an increased risk of adverse cardiovascular events, including heart attack, stroke, and new onset or worsening of pre-existing hypertension. The cardiovascular risk may be increased with duration of use of NSAIDs or pre-existing cardiovascular risk factors or disease.

There are several NSAIDs currently on the market, some sold directly to consumers as over the counter drugs (OTC) and others that are available by prescription. NSAIDs inhibit specific types of cyclooxygenase ((COX)-1 and (COX)-2) enzymes and it is common to divide NSAIDs into two groups, nonselective and selective. Nonselective NSAIDs inhibit both enzymes where

selective NSAIDS inhibit the COX-2 pathway. Examples of nonselective NSAIDs include aspirin, ibuprofen, naproxen, diclofenac and Piroxicam. Selective NSAIDs (also called COX-2 inhibitors) include celecoxib (Celebrex), which is the only selective NSAID currently available in the United States. Rofecoxib (Vioxx) and valdecoxib (Bextra) were removed from the market in 2004 due to the increase in heart attacks and strokes in patients taking these medications.

Acid suppressive medications, such as proton-pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are often used in conjunction with NSAIDS to protect the lining of the GI tract. However, the use of these agents increases the cost of treatment by 68%. Recent studies have shown a 30% increase in hip fractures in patients taking acid suppressive medications for two years. An increased risk was also seen in people taking these medications for one year. In patients 50 to 59 years of age, the risk of hip fracture was doubled. Risk is increased with duration of use, larger doses and advancing age. Acid suppressive medications are also responsible for a 30% increase in hospital acquired pneumonia. PPIs and H2RAs also interfere with the utilization of the Cytochrome P450 enzyme, which is used drug metabolism and excretion.

It is estimated that more than 100,000 Americans are hospitalized each year as the result of NSAID use and between 15,000 and 20,000 Americans die each year from ulcers and gastrointestinal bleeding linked to NSAID use (2). Many patients taking NSAIDs are asymptomatic even though gastrointestinal effects from NSAID use can be serious and often life threatening (3). In fact, nearly 60% of patients who develop ulcers of life-threatening GI complications had no previous symptoms. A patient hospitalized for a GI bleeding is quite costly, averaging approximately $50,000 per admission. ??

The treatment of arthritis with NSAIDs increases the cost of care by 46% due to the treatment of adverse events. This was demonstrated in several studies, including a two year study analysis done by Medicaid in 1983. Since then, NSAID use has continued to rise, increasing the percentage of adverse events in arthritis patients treated with NSAIDs. Similar results were found for a more recent study in the Netherlands, where (COX)-1 and (COX)-2 NSAIDs caused 2823 hospitalizations in one year, 165 dying as a consequence (6). In a Dutch observational study, it has been estimated that for every dollar spent on NSAIDs, an additional 0.68 is spent just on gastro protective agents (7). A separate Canadian study found for each dollar spent on NSAIDs, an additional $0.73 was spent on the prophylaxis and treatment of NSAID-related GI events. (8)

The treatment of the elderly is especially concerning as this demographic group is increasing rapidly and utilize a greater number of medications than younger age groups. With advancing age physiological changes occur, GFR (glomerular filtration rate) declines, oxidative metabolism through the Cytochrome P450 system decreases resulting in a decreased clearance of drugs. Many drugs interfere with this enzyme at any age and worsen with multiple medications. In addition, total and functional hepatic blood flow decreases after the age of 50 and drops significantly after the age of 75. The widespread use of polypharmacy and NSAIDS in these patients can be very risky yet is ubiquitous.

Proteins are the building blocks for important physiologic and biologic functions, and their functions include regulation of neurotransmitters, hormones, antibodies and tissue repair. The malabsorption of proteins can quickly lead to a variety of diseases and conditions. Proteins have many different functions in the body and are necessary for virtually every activity in the body.

NSAID use is known to induce acute renal failure in some patients. Treatment of renal failure can include costly treatments such as kidney dialysis or kidney transplant. Kidney dialysis costs $44,000 per year per patient with a life expectancy of 5 years. The estimated total cost per patient over 5 years is $220,000. Cost of a kidney transplant can reach $90,000 with a $16,000 per year treatment cost. The life expectancy for a kidney transplant patient is 17 years and would cost approximately $362,000 during this time.

Drug induced liver disease is the leading cause of liver transplants (10). Liver transplants costs approximately $400,000 and have a low success rate, with patients extending life for an average of 2.5 years. Liver transplantation is the only curative treatment in patients with decompensated liver disease.

Recently, a black box warning has been placed on the product information sheet of all NSAIDs due to the increased risk of cardiovascular disease (CVD), which includes an increase incidence of congestive heart failure, myocardial infarction, hypertension and stroke.

BLACK BOX WARNING

Cardiovascular Risk

- **NSAIDs** may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

- **Naproxen sodium** is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

- **NSAIDS** cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Stroke is the leading cause of disability among adults in the U.S. A patient taking NSAID s may have a 60% to 70% increased risk to cardiovascular disease. The estimated total cost of CVD in 2009 is $475 billion, affecting approximately 80,000,000 people, with $43 billion associated with the treatment of stroke.

Addiction from opioid use is a side effect of pain killers such has opioids. The National Institute on Drug Abuse (NIDA) Director Nora Volkow has stated that up to 7% of patients who are

prescribed narcotic or opioid analgesics to treat chronic pain will become addicted. From the National Substance Abuse Treatment Services Survey (N-SATSS), the average cost for inpatient programs was about $7,000 per month. Treatment regimes longer than 30 days produce a higher recovery rate, but are more costly to the system. Rehabilitation from prescription drug addiction can cost $10,000 to$40,000. It is estimated today that there are more than 4.7 million Americans dependent on prescription painkillers, which represents up to 2% of the US adult population overall, and this number continues to grow every year.

Neurotransmitters are intimately involved in disease. Neurotransmitters are chemical messengers found in large concentration in the brain but also throughout the body and are released during a nerve impulses to either excite or inhibit nerve impulse. In fact, most pharmaceuticals work by blocking or manipulating a neurotransmitter pathway, such as selective serotonin re-uptake inhibitors (SSRIs). Unfortunately, these drugs quickly deplete the cells of neurotransmitters by prohibiting re-uptake of neurotransmitters. This forces the cells to release their neurotransmitter stores without replacing them. This becomes a vicious cycle for the patient because the disease itself is causing an increase in the requirements of specific nutrients. In addition, other factors contribute to the depletion of neurotransmitters, such as pharmaceutical drug use, poor diet, stress and chemical exposure.

It is possible to restore neurotransmitter levels back to a healthy level. This can be done through a unique technology found in specific medical food products. This technology allows for neurotransmitters to be produced from precursors in milligram quantities of amino acids and other necessary molecules. Cell specificity is also achieved through this technology. Pairing a low dose pharmaceutical drug with a medical food product, that is produced by Physician Therapeutics, allows for a significant reduction in the pharmaceutical dose, shifting the dose response curve to the left and side effect profile to the right. What this means is the same therapeutics response is achieved with a lot less drug and the side effects are far less or nonexistent when compared to the same dose of pharmaceutical when not paired with a specific medical food formulation.

The modulation of neurotransmitters, particularly for treatment of pain syndromes will alter the function of NSAIDS thereby reducing the required dose of the NSAID. Reduction of drug dose leads to a reduction of side effects. Theramine is a Medical Food designed to augment neurotransmitter function through the management of the nutrient requirement for neurotransmitter precursors associated with the metabolic needs of the pain syndromes. The utilization of a Medical Food treatment of pain syndromes can lead to a substantial cost savings by reducing dose and side effects of pain treatments such as NSAIDS.

Theramine™

Indication

Theramine is intended for use in the management of pain syndromes including acute pain, chronic pain, fibromyalgia, neuropathic pain, and inflammatory pain. ***Theramine*** is a medical food that must be used under the active or ongoing supervision of a physician. Medical foods are

developed to address the different or altered physiologic requirements that may exist for individuals with distinctive nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions, and drug therapies.[1]

Pain is a complex process that is mediated by neurotransmitters which transmit signals originating from a pain-inducing stimulus to specific centers in the brain where it is perceived. Pain is exacerbated by the presence of inflammation which increases sensitivity to pain-inducing stimuli. Patients with pain syndromes benefit from increased availability of the specific neurotransmitters involved in modulating the pain process complemented by antioxidants and anti-inflammatory agents that reduce inflammation. ***Theramine*** is designed to provide a balance of neurotransmitters with well-defined roles in the modulation of pain and a blend of antioxidants, anti-inflammatory agents, and immunomodulators to moderate the effects of inflammation on the pain response.

Ingredients

Theramine is a proprietary formulation of neurotransmitter precursors (L-arginine, L-glutamine, L-histidine, choline bitartrate, 5-hydroxytryptophan), neurotransmitters (gamma-aminobutyric acid [GABA]), and a neuromodulator (L-serine); polyphenolic antioxidants (grape seed extract, cinnamon bark, cocoa); anti-inflammatory and immunomodulatory peptides (whey protein hydrolysate); and adenosine antagonists (cocoa, metabromine). Each of these ingredients has been specifically selected based on scientific support for their roles in the physiological processes involved in reduction of pain. These roles are summarized in this monograph in the section, *Scientific Support for Use of* ***Theramine*** *in Management of Pain Syndromes*. The Ingredients in Theramine are GRAS/GRAS/E.

All of the ingredients included in ***Theramine*** are classified as generally recognized as safe (GRAS) by the United States Food and Drug Administration (FDA). To qualify for GRAS status, a substance that is added to a food, including a medical food, has to be supported by data demonstrating that it is safe when consumed in amounts from these foods as they are typically ingested or prescribed.

Targeted Cellular Technology™

Theramine has been formulated using *Targeted Cellular Technology*, an integrated molecular system that facilitates the uptake and utilization of neurotransmitter precursors by target cells within the nervous system. This 5-component system consists of (1) specific neurotransmitter precursors; (2) a stimulus for the neuronal uptake of these precursors by specific neurons; (3) an adenosine antagonist that blocks the inhibitory effect of adenosine on neuronal activity

[1] As defined in the guidelines issued by the Center for Food Safety and Nutrition, United States Food and Drug Administration (FDA).

(adenosine brake); (4) a stimulus to trigger the release of the required neurotransmitters from targeted neurons; and (5) a mechanism to prevent attenuation of the precursor response, a well known phenomenon associated with precursor administration.

Use of *Targeted Cellular Technology* improves the metabolic efficiency of neurotransmitter synthesis, thereby reducing the amounts of amino acid precursors needed to correct neurotransmitter imbalances. Use of *Targeted Cellular Technology* also insures that the appropriate amounts of neurotransmitter precursors are delivered to the target neurons with the appropriate timing. As such, *Targeted Cellular Technology* synchronizes the fluctuating demand for neurotransmitters with the availability of the precursor supply, which is especially important for processes that are controlled by circadian rhythms such as utilization of arginine for the production of nitric oxide.

Previous attempts to provide an exogenous source of precursor amino acids in the quantities required to support neurotransmitter synthesis for individuals with specific needs necessitated that large amounts of these amino acids be added to the formulations. For patients whose requirements were considerably higher than normal, the amounts of exogenous amino acids that were needed were not practical to consume on a daily basis. In addition, ingestion of large amounts of amino acids increased the risk of adverse effects and the potential for attenuation of the response. Improving metabolic efficiency in uptake and utilization of neurotransmitter precursors by target neurons with *Targeted Cellular Technology*™ allows ingestion of smaller amounts of amino acids to elicit the same response, thus making daily dosing more feasible and reducing the potential for tolerance. Unlike pharmaceutical agents which are not innately involved in the pain process, and thus may lose their effectiveness in a relatively short period of time, the effectiveness of ***Theramine*** is not attenuated.

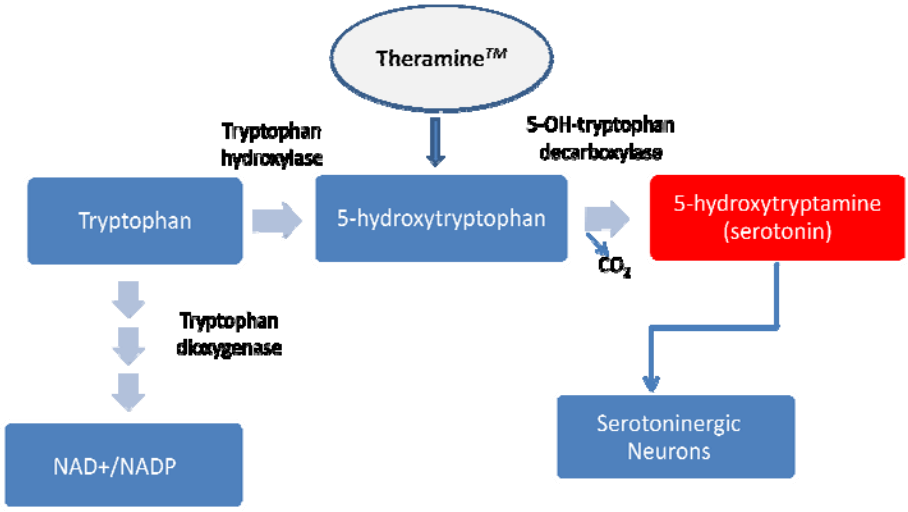
Metabolism

Theramine is a source of amino acids for patients with certain types of pain syndromes. These patients require additional amounts of tryptophan, arginine, glutamate, choline, and histidine to support synthesis of the neurotransmitters serotonin (5-hydroxytryptamine), nitric oxide, gamma-aminobutyric acid (GABA), histamine, and acetylcholine, respectively, which are active in the processes that mediate pain. Under normal physiological conditions, glutamate, arginine, and choline are metabolized as nonessential amino acids because endogenous synthesis is sufficient to satisfy metabolic demand. When needs are altered as in some types of pain syndromes, the usual rate of synthesis is no longer sufficient and these amino acids become conditionally essential, requiring that a supplemental amount be consumed. Histidine has also been considered nonessential for adults because it can be obtained from breakdown of skeletal muscle and hemoglobin; however, there is no evidence of histidine de novo synthesis in mammalian tissues

and therefore an exogenous supply is important during times of increased needs to preserve muscle mass and plasma hemoglobin concentration.

In contrast to the amino acids which are nonessential under normal conditions, tryptophan is an essential amino acid that must always be consumed from exogenous sources, as the enzymes required for its synthesis are absent in humans. Because it is an essential amino acid, the amount of tryptophan consumed determines the amount available to be divided among multiple pathways of utilization. Tryptophan is a precursor not only of serotonin, but also of the coenzymes nicotinamide adenine dinucleotide (NAD+) and nicotinamide adenine dinucleotide phosphate (NADP) (Figure 1). The competition between these and other metabolic pathways for a limited supply of tryptophan restricts the amount of serotonin that can be produced from supplemental amounts of the amino acid. To overcome this limitation, ***Theramine*** provides 5-hydroxytryptophan, which is the immediate precursor of serotonin in the conversion pathway (Figure 1). The availability of this intermediate circumvents the limiting step in serotonin synthesis and lessens the dependence of serotonin levels on the amount of tryptophan consumed. By facilitating production of serotonin without requiring large amounts of tryptophan as a precursor, ***Theramine*** conserves the existing supply of the amino acid for other uses, thus improving metabolic efficiency.

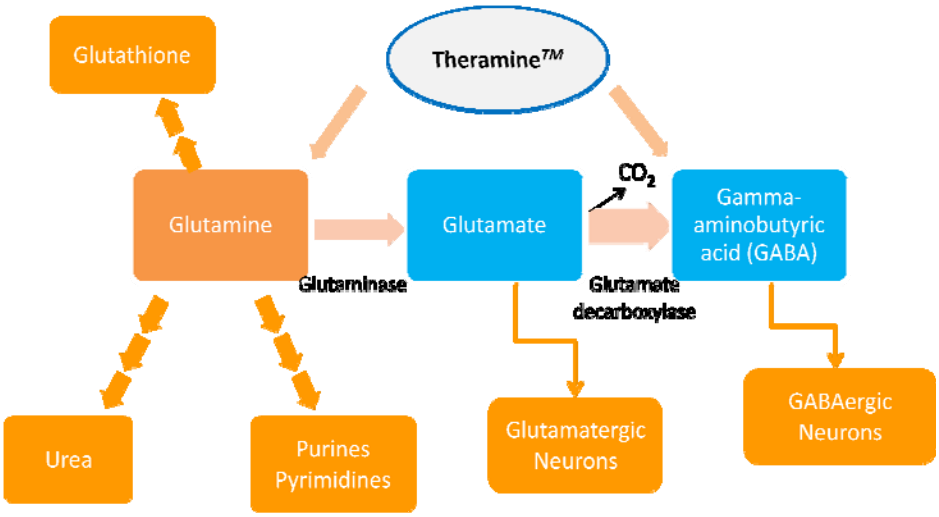
Figure 1. Competing Pathways of Tryptophan Metabolism



In contrast to tryptophan, glutamate is not normally dependent on exogenous sources and thus metabolic competition for glutamate will develop only under conditions of increased demand. For individuals with pain syndromes, the requirement for glutamate is higher than normal because additional amounts are needed to support GABA synthesis and to function as a neurotransmitter. Under normal physiological conditions, glutamate can be supplied by several sources including deamination of glutamine; however, glutamine is also utilized for synthesis of other compounds such as glutathione, purines, pyrimidines, and urea (Figure 2). These

competitive demands for glutamine limit the amount of glutamate, and thus the amount of GABA available to function as neurotransmitters. ***Theramine*** improves metabolic efficiency by increasing the available supply of both glutamine and GABA. Additional glutamine insures that there is sufficient glutamate to function as a neurotransmitter and as a precursor for GABA synthesis without compromising other glutamine-dependent pathways. Additional GABA further insures that there is a sufficient amount of this neurotransmitter while conserving the available supplies of both glutamate and glutamine.

Figure 2. Competing Pathways of Glutamine Metabolism



The metabolic pathways which generate arginine are also normally sufficient to insure an adequate supply of this amino acid. Arginine is utilized as a precursor of nitric oxide, in addition to creatine phosphate and urea (Figure 3). When demand for nitric oxide is increased, arginine is diverted from synthesis of these other compounds. To compensate for the resulting decrease in arginine available to these pathways, glutamate is mobilized as a substrate for synthesis of additional amounts of arginine. ***Theramine*** improves metabolic efficiency by insuring that there is a sufficient amount of arginine available to satisfy the competitive demands which will otherwise deplete the glutamate body pool and upset neurotransmitter balance (nitric oxide, glutamate and GABA), and that there is additional glutamine to conserve the existing supply of glutamate.

Figure 3. Competing Pathways of Arginine Metabolism

Dosage

The recommended dose of ***Theramine*** is 1 or 2 capsules, taken 1 to 4 times daily as directed by a physician. As with any medical food, the best dosing protocol should be determined by assessment of individual needs. The amounts of each ingredient provided by ***Theramine*** at the doses recommended for pain reduction are provided in Table 1.

Table 1. Ingredients in *Theramine*

Ingredient	mg/kg body weight[1]
δ-aminobutyric acid (GABA)	1.5 – 12.0
choline bitartrate	1.0 – 7.7
L-arginine	0.6 – 4.6
Whey protein hydrolysate	0.6 – 4.6
L-histidine	0.4 – 3.1
L-glutamine	0.4 – 3.1
metabromine	0.4 – 3.1
5-hydroxytryptophan (griffonia seed, 95%	0.2– 1.9

Ingredient	mg/kg body weight[1]
w/w)	
grape seed extract	0.2 – 1.5
L-serine	0.2 – 1.5
cinnamon bark	0.2 – 1.5
cocoa powder	

[1]Over dosing range of 1 to 4 capsules

Theramine can be taken with pain medications such as once daily low dose aspirin (32 mg) or other nonsteroidal anti-inflammatory drugs (NSAIDs) such as low dose naproxen (250 mg) or tramadol (50 mg daily). If pain relief is obtained when ***Theramine*** is taken in combination with other pain medications, then the drug dosage may be further tapered to lower levels under medical supervision.

Theramine can also be used to manage the effective dose and dose-related side effects of pain medications. A randomized crossover study of patients with pain syndromes who were given ***Theramine*** in combination with naproxen demonstrated that the effective dose of naproxen required to achieve pain reduction was decreased 75% from 4 times daily prior to use of **Theramine** to once daily after use. This study is described in greater detail in this monograph in the section, *Clinical Support for the Use of* ***Theramine*** *in Pain Syndromes.*

Side Effects

As with any amino acid therapy, headache, upset stomach, or dry mouth may be experienced in some people after beginning treatment with ***Theramine***. These symptoms are mild and temporary, and readily managed by increasing fluid intake. The development of side effects from ***Theramine*** can be minimized by careful titration of the dosage. The ingredients in ***Theramine*** are regularly consumed in amounts similar to those obtained from the normal food supply; therefore, adverse reactions associated with administration of ***Theramine*** are not expected to occur.

GI side effects associated with ***Theramine*** occur in less than 6,000,000 daily doses even when administered with a daily single dose of NSAIDS.

Nutritional Requirements of Pain Disorders

The nutrient requirements of most interest for patients with pain syndromes are the amino acids which function as neurotransmitters in the transmission of pain signals or which are utilized for synthesis of neurotransmitters involved in this process. The concept that nutrient requirements

are modified in disease has long been recognized, and is supported by studies which have shown changes in plasma, urinary, and tissue levels of nutrients associated with changes in physiological endpoints reflective of the disease pathology. These requirements can be estimated by determining the level of intake at which a physiological response is normalized, indicating that the balance between intake and metabolic demand has been restored. For example, improvement in perceived intensity of back pain following consumption of supplemental amounts of 5-hydroxytryptophan, arginine, and glutamine from ***Theramine*** suggests that an additional allowance for tryptophan, arginine, and glutamate is needed by individuals with pain syndromes.

A large body of peer-reviewed published data supports the basis for increased requirements of arginine, tryptophan, choline, glutamine, serine, and histidine in pain syndromes. Patients suffering from different types of pain syndromes show decreased blood levels of these amino acids despite having a sufficient intake of protein indicating that the needs for these amino acids are selectively increased in these patients. This observation may be explained by the competitive demands for these amino acids by different metabolic pathways which decrease the supply available to function in the pain process. Low blood levels of tryptophan accompanied by altered tryptophan metabolism have been frequently reported in patients with pain disorders. These patients also commonly exhibit reduced blood levels of 5-hydroxytryptophan, arginine, choline, GABA, histidine, and serine. Moreover, they also respond to oral administration of amino acid formulations by showing favorable changes in physiologic endpoints and improvements in clinical symptoms associated with pain, thus supporting a need for increased amounts of those amino acids which are reduced in the blood of patients with pain disorders.

A summary of the scientific support for increased requirements of specific amino acids for found in ***Theramine*** in patients with pain disorders is found in accompanying monograph.

Cost Analysis Summary from Side Effects

More than 215,000 one month treatment courses of ***Theramine*** and related co-packs have been administered in the last two years. This represents more than 12,000,000 individual doses of Theramine. There has not been a single symptomatic or asymptomatic gastrointestinal hemorrhage detected. Thus, the incidence of significant gastrointestinal hemorrhage in association with Theramine appears to less than 1 in 12,000,000 doses. This compares to an expected rate of approximately 500 symptomatic events from NSAIDS in a similar patient set. Substantial cost savings can be generated to the cost of care by eliminating the prevention and treatment of GI effects of NSAIDS.

In the underlying analysis we have considered only the patients with osteoarthritis taking prescription NSAIDS. If you analyze only the patients with osteoarthritis who take prescription. NSAIDS and not over the counter preparations, the number of patient estimated as 20,000,000. The side effect cost is outlined in the table below. The total estimated cost of the GI effects of NSAIDS in this population is $328,300,000 per year.

# of patients	20,000,000.00
Drug b Cost	
GI	
incidence per 1000 pt years	2.45
# of Gi bleeds per year	49,000
% asymtpmatic	0.5
%mild	0.4
% severe	0.1
number of asymp	24500
number of mild	19600
number of severe	4900
cost asymp	1000
Cost mild	3000
cost severe	50000
cost per year asymp	$24,500,000
cost per yaar mild	$58,800,000
cost per year severe	$245,000,000
tota gi Cost	$328,300,000

If you assume that the cost of Theramine is $160 per month and the cost of a prescription NSAIDS is $360 per month (including the drugs to prevent the side effects), the yearly cost is in the table below.

Cost of Drug						
	monthly cost	months	yearly cos	users	yearly cost	
drug a Theramine	160	12	1920	20,000,000	$38,400,000,000	cpost of a
drug b NSAIDS-GI drug	360	12	4320	20,000,000	$86,400,000,000	cost of b
					$0	benit of a
					$328,300,000	benefit of b
Population analyzed is the osteoarthritis population who use prescription NSAIDS						

The assumption of this analysis is that the entire cost of the GI side-effects can be eliminated at a savings of $328,300,000.

The ICER, ICER reciprocal and ICER$ is listed below.

ICER	$146.21
reciprcol	$0.01
ICER $	$1.93

The cost effectiveness analysis is in the table below:

Qaly assuption is that there is no difference in quality of the response --drug a provides the same response as b			
savings per QALY GI alone	$2,924,154.74		
gastrointesintal cost			
Number of events	49,000		
gi cost	$328,300,000		
amount saved per gi avoided	$6,700.00		
gi			
cost of theramine	$38,400,000,000		
cost of nsaids with gi pro	$86,400,000,000		
savings with theramine	$328,300,000		
Savings with theramine	-$48,328,300,000		
savings per patient	-$2,416.42		
savings per qaly	-$2,416,415.00		

The saving per patient is -$2,416.42 and the savings per Qaly is -$2,416,415. The cost saving to eliminate gastrointestinal hemorrhage is quite large and cost effective.

A similar analysis could be performed for the cost saving for addiction and cost saving of kidney-liver disease.