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Theramine (A Medical Food) Versus Non-Steroidal Anti Inflammatory Agents in Elderly Patients: A Pharmacoeconomic Analysis

***David S. Silver MD,Elizabeth H. Charuvastra RN,Lawrence May MD,Stephanie L. Pavlik CRA,William E. Shell MD**

Targeted Medical Pharma,2980 N. Beverly Glen Circle,Suite 301,Los Angeles, CA 90077, USA

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ABSTRACT

Non-steroidal anti-inflammatory drugs are the leading cause of drug induced morbidity and mortality in the United States. Gastrointestinal hemorrhage is the most common concern, with hypertension, edema, renal complication and cardiovascular risk other considerations. These complications occur at higher rates in elderly patients. Strategies to reduce these risks have had mixed results. Theramine, a prescription only medical food, is used to treat pain and inflammation without risk of gastrointestinal or other side effects. We undertook a pharmacoeconomic analysis of Theramine versus NSAIDs in elderly patients; specifically examining the additional cost burden of the strategies to prevent GI side effects and complications. The higher acquisition costs for Theramine are offset by the reduction in side effects and need for testing and other protective medications in patients over the age of sixty-five taking NSAIDs. Theramine should be the preferred choice over NSAIDs in elderly patients.

Key words: Theramine, NSAIDs, Side effects, Cost Analysis, Elderly population, Pain management

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a mainstay treatment of pain from a variety of inflammatory and non-inflammatory conditions. They are a recommended treatment for a wide variety of disease states such as, rheumatoid arthritis, systemic lupus erythematosis, and osteoarthritis, as well as nonsystemic acute and chronic muscle, joint and ligament discomforts. With more than 100 million prescriptions annually, NSAIDs are the most commonly prescribed drug class (1). Concerns regarding safety have led to reduced use in older and high-risk patients, who are often the patients most in need of pain relief. Billions of dollars are spent each year on NSAIDs, the majority over the counter purchases with approximately 10% by prescription.

NSAIDs are associated with significant drug induced morbidity and mortality. In the late 1990's it was estimated 16,500 died and over 100,000 were hospitalized from NSAID induced GI bleeds (2). This complication accounted for a third of the total cost of arthritis care (3, 4). Patients over the age of 65, with concomitant medications and disease states are the most likely to suffer serious consequence side effects (5).

Table 1. Risk factors for NSAID induced upper gastrointestinal bleed

- Age of 65 years and over.
- Previous history of gastroduodenal ulcer and gastrointestinal bleeding.
- Concomitant use of medications that are known to increase the likelihood of upper-gastrointestinal adverse events (anticoagulants, aspirin, including low-dose aspirin, and corticosteroids).
- Presence of serious co-morbidity, such as cardiovascular disease, renal or hepatic impairment, diabetes, or hypertension.
- Prolonged duration of NSAID use.
- Use of the maximum recommended doses of NSAIDs.
- The presence of Helicobacter pylori infection.
- Alcohol use.
- Smoking.

***Corresponding author.**
David S. Silver MD,
Targeted Medical Pharma,
2980 N. Beverly Glen Circle,
Suite 301,Los Angeles,
CA 90077, USA

The introduction of COX-2 inhibitors in the late 1990's was intended to reduce the incidence of NSAID induced bleeds while preserving equivalent efficacy (6,7). Although COX-2 inhibitors did show a reduction in gastrointestinal side effects, the incremental cost and concerns about cardiovascular safety have limited their use (8,9). Two popular agents (Vioxx and Bextra) were voluntarily withdrawn from the market. Further investigation revealed that the COX-2 inhibitors were probably no different from non selective NSAIDs in terms of cardiovascular risk (10, 11, 12). Physician and public awareness of the potential toxicity of the class was increased. These drugs simply provide symptomatic relief making the search for alternative agents imperative.

NSAIDs are associated with other toxicities as well. Patients with impaired renal or hepatic function must exercise caution when taking NSAIDs or should not take them at all. NSAIDs precipitate blood pressure elevation and fluid retention. Approximately a fifth of the population cannot tolerate NSAIDs due to esophageal reflux, dyspepsia or diarrhea and GI side effects independent of hemorrhage (5,13).

The addition of proton pump inhibitors to NSAIDs has been shown to decrease GI bleeds and dyspepsia by up to 50% (14). However, the additional cost and other potential complications such as pneumonic reduced calcium absorption, resulting in osteoporosis, (15) and B12 deficiency from changes in gut flora are problematic (16, 17). Reduced compliance occurs due to the number of pills taken and frequency in dosing (18-20). New agents combining a NSAID with a Nitric Oxide moiety reduce GI bleeds by 20-30% and lower the risk of hypertension, but have yet to be approved by the FDA and will be costly if they reach the market (21).

Alternatives to NSAIDs for pain management also have challenges. Narcotic analgesics, although effective, are sedating, cause constipation, urinary retention and have potential for addiction. Tricyclic antidepressants, dual reuptake inhibitors, anti epileptics, and others have a separate set of side effects and can also be costly.

Theramine

Theramine is intended for use in the management of pain syndromes including

fibromyalgia, acute and chronic, neuropathic or inflammatory pain. Theramine is a medical food that must be used under the active or ongoing supervision of a physician. Medical foods address the altered physiologic requirements and distinctive nutritional needs resulting from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions or drug therapies. (22)

The nutrient requirements that are most crucial for patients with pain syndromes are the amino acids which are essential for the synthesis of neurotransmitters which transmit pain signals and mediate their perception. (23) The concept that nutrient requirements are modified in disease has long been recognized, and is supported by studies of plasma, urinary, and tissue levels of nutrients associated with changes in physiological endpoints, symptoms or decreases. (24). 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 an additional need for tryptophan, arginine, and glutamate in individuals suffering with pain syndromes. (25-28) Many peer-reviewed publications support increased requirements of arginine, tryptophan, choline, glutamine, serine, and histidine in pain syndromes. Patients suffering with pain syndromes have decreased blood levels of these amino acids despite sufficient protein intake indicating amino acid needs are selectively increased in pain patients. (29 -31) This observation may be explained by the competitive demands for these amino acids by metabolic pathways which decrease the supply available to moderate the pain process. Low blood levels of tryptophan and/or altered tryptophan metabolism are reported in patients with pain disorders. (32) These patients also exhibit reduced blood levels of 5-hydroxytryptophan (5-HTP), arginine, choline, GABA, histidine, and serine. (33 - 35) Moreover, they respond to oral administration of amino acid formulations by showing favorable changes in physiologic endpoints and improvements in clinical symptoms supporting a need for increased amounts of those amino acids which are reduced in the blood of patients with pain disorders. (36,37).

Theramine Clinical Trials

Two double blind multicenter randomized trials which compared Theramine to low dose Naproxen and Ibuprofen respectively have been performed (38,39). Each study involved 120 patients in 12 centers around the US. Patients were randomized to receive Theramine alone, 2 capsules twice daily, NSAID, or a combination of both. In both studies, Theramine showed statistically significantly greater pain relief than either Naproxen, 250mg daily or Ibuprofen 400mg daily. The combination of Theramine and NSAID produced better pain relief than either alone. Importantly, Theramine lowered CRP while increased CRP was seen in the Naproxen and Ibuprofen groups. No side effects from Theramine were reported in either trial.

Observational reporting after over 60,000,000 doses of Theramine revealed no GI bleeds. Although underreporting may have occurred, the data implies GI risk in patients taking Theramine is unlikely. Therefore, an increased risk of gastrointestinal bleeds based on the formulation would not be expected.

Cost Analysis

Pharmacy and therapeutic formulary committees are charged with balancing efficacy and safety concerns versus cost of medication acquisition. Analysis of economic factors is necessary before placing a more expensive medication on formulary. In an ideal world, only safety and efficacy would drive decisions. The burden of escalating health care costs and limited resources demand a pharmacoeconomic analysis. The costs of side effects can be challenging to quantify but must be undertaken to determine cost benefit rates of Theramine compared to a generic NSAID.

The available clinical data estimates 1-4% of patients over the age of 65 taking NSAIDs will experience a GI bleed annually (40-42). A significant percentage of patients in this age group will take aspirin 81mg every day or every other day for cardiovascular prophylaxis, further increasing the risk (43). The estimated cost of hospitalization for a GI bleed is $50,000 (44). It is recommended that high risk patients take proton pump inhibitors (PPIs) with the NSAID to prevent GI events (45-47). This includes patients over the age of 65 or patients with a previous history of ulcer or GI hemorrhage which represent over half of all chronic users of NSAIDS. The costs of additional PPIs are approximately $120 per month. Compliance with combination therapy, especially in populations with already complicated medical regimens, is diminished. Most commonly, if patients are asymptomatic, they will continue to take the NSAID for pain relief and not take the PPI, although a preparation that combines naproxyn with prilosec is available in a single pill. Alternatively, the use of Celecoxib, the only available COX-2 selective inhibitor, would cost approximately $200.

These costs do not account for the other complications including renal, hepatic, and others associated with the use of NSAIDs. Biannual blood screening to monitor potential side effects of NSAIDs is estimated at $100 and must be considered as well. Finally, evaluation costs for patients who present with dyspepsia and undergo gastroenterological workup. Estimates range from 25-50% of all patients taking NSAIDs will have evidence of endoscopic ulceration in the stomach or duodenum, but only a fraction of them will be scoped in clinical settings (48,49).

The following assumptions are based on clinical evidence available with an implied bias in favor of NSAIDs, as they are presently the preferred treatment.

1. The annual risk of GI bleed in patients over the age of 65 taking regular NSAIDs is 2.5%.
2. Theramine does not cause gastrointestinal bleeds.
3. The cost of generic NSAID is $10 per month. The insurance reimbursement of Theramine averages $176 per month at the most commonly and clinical trial dose. The dollar amount is based on the average insurance reimbursement for Theramine.
4. Laboratory screen of complete blood count (CBC) and complete metabolic panel semi-annually costs $100 total per year.
5. Estimate of 40-65% of NSAID users are considered at high GI risk for bleed and should receive a PPI or COX-2 inhibitor. All patients in the 65 and older age group are considered at high risk. It is recommended that high risk patients should be either on a COX-2 inhibitor or a PPI with a standard NSAID. The average cost estimate would be $40 to $120 per month per patient and will prevent 50% of all NSAID induced GI bleeds.
6. Assume 10% of patients taking NSAIDs will require GI work up for dyspepsia costing $1200 for upper endoscopy, Helicobacter Pylori testing, consultation and endoscopies.
7. Mortality for upper gastrointestinal bleed is approximately 16% in high risk patients (2,49).
8. Calculations of cost per 100 patients treated per year will be performed as well as cost per life saved. The additional costs of cardiovascular, renal and hepatic toxicity due to NSAIDs may be substantial but have not been calculated.
9. The figures do not include patients in whom NSAID therapy is contraindicated, specifically patients with renal insufficiency, previous history of GI bleed, congestive heart failure, peripheral edema, hepatic failure, poorly controlled hypertension and aspirin sensitivity. These patients now have an option for non-narcotic pain relief.

MATERIALS AND METHODS

Risk data and rates of gastrointestinal bleeding, morbidity and mortality data were derived from the Medicare database and peer reviewed literature. Medication acquisition costs were determined based on listed average wholesale pricing (AWP). Procedural and hospitalization rates were obtained from the Medicare fee schedule.

RESULTS

The annual cost of Theramine for 100 patients treated is $211,200. A generic NSAID for 100 patients would be $12,000 if all patients were given generic NSAID's; the cost of branded prescription NSAIDs would obviously add to this cost. The additional costs include: $75,000 for costs of GI bleeds per 100 patients treated per year, medication acquisition costs of $144,000 for high risk patients, laboratory testing of $10,000 for all patients, cost of GI evaluation of symptomatic patients $14,500. Excluding cost of treatment for hepatic, renal and cardiovascular side effects generic NSAIDs will cost $241,500 per 100 patients treated. When examining actual costs, Theramine is cost savings when comparing total impact of NSAIDs. Cost per life saved analysis was not performed as there is no incremental overall cost increase to use of Theramine.

DISCUSSION

NSAIDs are the most commonly utilized drug class. Despite efficacy in treating symptoms of inflammatory and non inflammatory conditions, their use has been reduced greatly due to the side effect profile. Physicians must make difficult decisions either accepting the risk or prescribing as needed with therapeutic efficacy reduced. Patients are either exposed to significant side effects or suffer with inadequate pain relief. Recent guidelines for pain management in the elderly have recommended only rare use of NSAIDS, despite the fact that over 50% of individuals over the age of 65 suffer from chronic pain (50).

Efforts to diminish the GI side effects of NSAIDs include co-administration of a PPI or use of COX-2 inhibitor increase cost. They do not eliminate the gastrointestinal effects or impact hepatic, renal and cardiovascular toxicities at all.

Theramine, a prescription only medical food, has been shown to be an effective and safe anti-inflammatory pain reliever without the concerning side effects of NSAIDs. Although more expensive than generic NSAIDs, the use of Theramine is cost neutral using conservative estimates of the economic impact of NSAID side effects based on best care practice guidelines. Cost neutrality favors the use of Theramine because of the reduction in morbidity and mortality.

Theramine, unlike generic NSAIDs plus a PPI or COX-2 inhibitors, eliminates all NSAID induced side effects. Despite the initial upfront costs, even when low risk patients are included, Theramine lowers cost of care, and there is no risk of GI bleed, renal or hepatic toxicity, hypertension, peripheral edema or heart attack. Based on this analysis, Theramine should be preferred in all cases instead of NSAIDs. If Theramine does not provide adequate therapeutic response, use of NSAIDs can be considered and administered at the lowest dose and for the shortest time when added to Theramine. The economic reducibility or likely cost saving in addition to the reduced burden of morbidity and mortality make Theramine preferred over NSAID for treatment of pain syndromes.

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Conflict of Interest

The authors of this manuscript are owners, employees or consultants of Targeted Medical Pharma, Inc. (TMP). TMP has been the sponsor for all data compilation and preparation related to this manuscript.

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