

# **Non-narcotic Analgesics: Renal & GI Considerations September 1998**

by

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## **INTRODUCTION**

Pain occurs frequently in all societies and is the most common symptom for which patients seek medical assistance. Defined as an unpleasant subjective sensation, which results from a noxious stimulus, pain alerts the body to possible or actual organ damage.<sup>1</sup> More than 75 million people in the United States have some form of persistent or recurrent pain.<sup>2</sup> General advances in the management of pain have provided a scientific rationale for more effective use of non-narcotic and narcotic analgesic drugs, more selective anesthetic and neurosurgical approaches, and the integration of behavioral approaches to pain control. Despite these treatment measures, however, the effective management of pain for the majority of patients remains inadequate. In a 1994 Harris poll, one sixth of the adult population reported experiencing chronic pain and 57% of these individuals expressed dissatisfaction with the way their healthcare provider was managed their pain. Other studies have shown that attitudes and beliefs of patients about their chronic pain management may dictate the degree of their disability.

The most frequently prescribed treatment for chronic pain is nonsteroidal anti-inflammatory drugs (NSAIDs), which account for almost 4% of all prescriptions filled in the United States, at a cost in excess of \$2 billion per year.<sup>3</sup> Parallel with the beneficial anti-inflammatory and analgesic effects of NSAIDs are associated gastrointestinal (GI) and renal morbidity. An estimated 500,000 persons are likely to develop some degree of NSAID-related renal functional abnormality during 1 year,<sup>4</sup> and the Food and Drug Administration (FDA) estimates that 2% to 4% of chronic NSAID users will develop upper GI bleeding, a symptomatic ulcer, or an intestinal perforation each year.<sup>5</sup> Furthermore, as many as 20,000 deaths may occur annually as a result of NSAID-induced GI injury.<sup>5</sup>

In recognition of this public health issue and the unsuspected medical, social, and economic consequences of the use of NSAIDs and other non-narcotic analgesics, it is important for the practicing clinician to have an accurate understanding of the diagnosis, pathogenesis, and treatment of analgesic-induced nephropathy and gastropathy. Additionally, knowledge of

specific risk factors will help physicians choose appropriate alternative therapies as options for patients in whom NSAIDs are inappropriate and, ultimately, help them manage their patients more effectively.

## THE ANALGESIC DILEMMA

Typically, physicians have had a number of therapeutic options when treating a patient with chronic pain, including acetaminophen, opioid analgesics, and NSAIDs, including aspirin. While all these drugs are effective in controlling pain, both opioids and NSAIDs are associated with use-limiting adverse effects. Opioids are associated with tolerance and physical dependence; NSAIDs are associated with GI bleeding and ulceration, which can be fatal.

The needs of a patient in chronic pain include comfort, freedom from therapeutic adverse reactions, the ability to perform the functional activities of daily living, psychological reassurance, and a satisfying quality of life. Patients are often presented with a choice of medications that are effective in controlling pain but may have side effects that impact other organ systems. For example, in some patients taking NSAIDs for chronic pain, the incidence of GI-related complications may offset the analgesic benefit of these agents.<sup>6</sup> Balancing the beneficial analgesic action of pain relievers with their potential adverse effects is a decision debated by millions of physicians and patients every year.

## THE ROLE OF PROSTAGLANDINS IN NORMAL GI AND RENAL FUNCTION

In the GI tract, prostaglandins inhibit acid ( $H^+$ ) secretion, enhance the restitution of denuded epithelium, increase the secretion of epithelial protectants (bicarbonate [ $HCO_3^-$ ] and mucus), and promote mucosal blood flow in injured tissues. Providing adequate blood flow to GI mucosa is considered the most important,<sup>5</sup> as it supports epithelial regrowth across denuded areas. In the absence of prostaglandins, ischemic areas take longer to heal, thus facilitating ulcer development.

The effects of various classes of prostaglandins in the kidney include modulation of renal blood flow and glomerular filtration rate (GFR), the stimulation of the release of renin, the reabsorption of water, and the excretion of sodium and potassium (Table 1).

**Table 1**

### **Renal Effects of Prostaglandins**

Prostaglandin  $E_2$

vasodilation; diuresis and natriuresis; NaCl/water excretion

Prostaglandin F

NaCl and water excretion; vasoconstriction

Prostaglandin I<sub>2</sub>  
vasodilation; renin release

Prostaglandin D<sub>2</sub>  
vasodilation in resistance vessels

## THE EFFECT OF NSAIDS ON PROSTAGLANDINS

The ability of NSAIDs to exert analgesic and anti-inflammatory effects is mediated by two mechanisms. The first is through suppression of prostaglandin synthesis at sites of tissue injury. The second is through the modulation of the neutrophil intracellular signaling function, which decreases the migration of neutrophils to inflammatory sites and minimizes the release of free radicals and destructive enzymes at those locations.<sup>5</sup>

The anti-inflammatory properties of NSAIDs appear to result from their ability to inhibit cyclooxygenase (COX), an enzyme involved in the biosynthesis of prostaglandins. The major drawback of NSAIDs appears to be the adverse GI and renal effects associated with this suppression of prostaglandin synthesis.

Although prostaglandins are key mediators of inflammation, they also play critical physiologic roles in tissue homeostasis and function. The body depends on these compounds to regulate gastric mucosal protective function, renal blood flow, and platelet activation. However, when NSAIDs block inflammation and pain by inhibiting COX, they also block the normal functions of prostaglandins, producing potentially serious side effects.

The side effects that are associated with NSAID use include GI injury due to the loss of the protective action of prostaglandins in gastric mucosa, hypertension and/or edema due to the decrease in renal blood flow and the increased retention of salt and water, and prolonged bleeding time due to interference with platelet function. These side effects are responsible for such serious adverse effects as GI bleeds, hyperkalemia, and renal insufficiency, especially in the elderly.

These adverse effects, especially in the GI mucosa, cause significant morbidity, occasional mortality, and substantial increases in cost of therapy. It has been estimated that among the 17 million NSAID users in the United States, up to 200,000 hospitalizations from complicated ulcers and 20,000 deaths occur each year due to NSAID-related GI events.<sup>7</sup>

It has been shown that NSAIDs may raise blood pressure, necessitating treatment in patients who already have borderline hypertension, and that NSAIDs may increase blood pressure in patients taking beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and loop diuretics.<sup>3</sup> Patients taking these agents should be closely monitored for signs of increased blood pressure and peripheral edema. If these occur, it may be appropriate to consider an alternative analgesic that does not interact with antihypertensives, such as acetaminophen or

tramadol. Alternatively, an antihypertensive that does not interact with NSAIDs, such as a thiazide diuretic, may be considered.

In the elderly, NSAID-induced inhibition of renal prostaglandin production can lead to sodium and water retention, manifesting as peripheral edema, and may exacerbate chronic congestive heart failure in susceptible individuals. In the clinical setting of significant preexisting reduction of renal perfusion, the use of NSAIDs, including use of over-the-counter (OTC) recommended doses, may induce acute reversible renal failure.

## **THE EFFECT OF NSAIDS ON THE GASTROINTESTINAL SYSTEM**

It is well established that NSAIDs are associated with an increased risk of adverse GI effects.<sup>8</sup> GI toxicity resulting from the use of NSAIDs is the major type of adverse drug reaction reported to the FDA,<sup>5</sup> and NSAID-associated GI side effects represent as much as one fourth of all drug side effects reported.<sup>9</sup> GI toxicity includes nausea, heartburn, and dyspepsia, gastric or duodenal ulcers, and also potentially life-threatening complications such as bleeding and ulcer perforation (Table 2)(Figure 1A & 1B). Mechanisms responsible for GI injury from NSAIDs include inhibition of prostaglandin synthesis and direct mucosal injury. Impairment of platelet function may contribute to GI bleeding due to an increased bleeding time.

**Table 2**

### **Adverse GI Events Associated With NSAID Use**

- Nausea
- Heartburn
- Dyspepsia
- Gastric ulcers
- Duodenal ulcers
- Perforations
- Bleeding complications

There are two types of mucosal lesions that may be encountered in patients taking NSAIDs. The first is acute damage characterized by cell shedding and mucosal hemorrhages, and the

second is chronic ulceration. Although studies have shown that mucosal hemorrhages are present in most subjects taking NSAIDs on a regular basis,<sup>9</sup> erosions in the mucosal lining are dose-related,<sup>9</sup> and may be asymptomatic in as many as 60% of cases.<sup>9</sup> Other clinical and epidemiological evidence indicates that the relative risk of gastric ulcer increases as the dose of aspirin and other NSAIDs increase, although the causal relationship to duodenal ulcers is as yet undetermined.<sup>9</sup>

Patients at the greatest risk for ulcer complications include the elderly, those with a previous history of ulceration, and those on corticosteroids or oral anticoagulants. Although higher NSAID doses are associated with a greater risk of ulcer complications, even OTC NSAIDs are known to cause ulcers. In fact, the absolute number of ulcer complications may be greatest from OTC NSAIDs because of the widespread use of these agents. Therefore, it is especially important to be aware of any OTC NSAIDs that the patient may be taking, since the effects would be additive to prescription NSAIDs, increasing the risk of side effects.

The risk of developing clinically important GI complications caused by NSAID treatment was evaluated in a large case-control study that included 684 patients with ulcer perforation and GI hemorrhage, and 1268 control subjects. This study showed a linear increase in estimated relative risk of complications with an increasing dose of NSAIDs and increasing age. The results also showed an additive risk when NSAIDs were used in combination with aspirin, or when either NSAIDs or aspirin alone or together was taken with significant amounts of alcohol.<sup>10</sup>

The relative risk of peptic ulcer disease associated with the use of non-aspirin NSAIDs was also evaluated in nearly 1500 patients over the age of 65 years who had been hospitalized for confirmed peptic ulcer disease. Results showed that the development of peptic ulcer disease increased with increasing dose of the NSAID (Figure 2).

The frequency and nature of NSAID-related damage to the stomach and small intestine were investigated in a postmortem analysis of the stomach, duodenum, and small intestine of 713 patients.<sup>13</sup> Of these patients, 249 had NSAIDs prescribed to them in the 6 months prior to death and 464 did not. The prevalence of nonspecific small intestine ulcers and ulcers of the stomach and duodenum was compared in the two groups of patients.

Results demonstrated that the patients who were prescribed NSAIDs had an increased prevalence of nonspecific ulceration of the small intestine mucosa. Nonspecific small intestine ulceration was found in 8.4% of the users of NSAIDs as compared to 0.6% of the nonusers ( $P < 0.001$ ). Three patients died as a direct consequence of peritonitis from perforated, nonspecific small intestine ulcers.

NSAIDs can cause strictures of the small intestine and colon with pathological configurations that range from nonspecific broad-based strictures to obstructive luminal diaphragms. The histology of the diaphragms reveals submucosal fibrosis with normal overlying epithelium. NSAIDs can also cause diffuse intestinal inflammation and increased intestinal mucosal permeability, known as NSAID enteropathy. This condition is characterized clinically by occult blood loss, iron deficiency anemia, malabsorption, and protein-losing enteropathy.

The pathophysiology of NSAID enteropathy is believed to be a disruption of the small

intestine mucosal barrier. This disruption causes increased permeability to luminal bacteria, which invade the intestinal mucosa and incite inflammation.

NSAIDs have also been reported to induce a variety of types of colitis such as eosinophilic, collagenous, pseudomembranous, and nonspecific colitis. Rectal administration of NSAIDs has frequently been associated with inflammation, ulcers, and strictures of the rectum and anus.<sup>11</sup> NSAIDs have also been suggested to exacerbate symptoms in subjects with preexisting colonic diseases such as diverticulitis and inflammatory bowel disease.<sup>12</sup>

### **ARAMIS Database Findings Support the Association Between GI Disease and NSAIDs**

The Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) is a federally funded study that has followed individuals with chronic rheumatic diseases for 25 years. The patients studied include more than 6500 persons with rheumatoid arthritis and approximately 5000 persons with osteoarthritis. The database is used to evaluate the effectiveness and toxicity of various medications taken to treat these illnesses.

The ARAMIS database shows that 98 of 6500 rheumatoid arthritis patients, and 35 of 5000 osteoarthritis patients, will have a life-threatening GI complication requiring at least 1 day of hospitalization every year, and that 10% to 15% of these patients with a life-threatening GI complication will die.<sup>8,14</sup> The data also demonstrate that patients with rheumatoid arthritis are about 5\_ times as likely to develop a serious GI complication to NSAIDs as compared to patients who do not take these medications.<sup>8</sup> Additionally, the use of prophylactic medications, such as H<sub>2</sub>-antagonists, is ineffective in preventing GI-related symptoms.<sup>8</sup> Of note is that GI-related symptoms are silent in more than 80% of individuals taking NSAIDs.

ARAMIS data indicate that the risk of NSAID-related GI bleeding remains constant over time and that the GI tract does not seem to acclimate to the injury that occurs with the use of NSAIDs. The increased risk of bleeding associated with NSAID use was also reported in a case-control study of 57 patients hospitalized for GI bleeding who used NSAIDs on a regular basis. This study suggested that bleeding was associated with the use of aspirin, may be increased with other NSAIDs, and was not associated with acetaminophen.<sup>15</sup>

### **New Class Labeling Developed for NSAIDs Regarding the Risk of GI Complications**

The studies and reports validating the potentially life-threatening GI-related complications associated with the use of NSAIDs, and recommendations from an FDA advisory panel convened to discuss these issues, have prompted the FDA to recommend new labeling for NSAID package inserts and for patient information regarding these medications. The proposed new labeling of the package insert emphasizes several points: 1) Serious and fatal events "can occur at any time" in patients chronically treated with an NSAID; 2) Mucosal lesions can occur without being associated with symptoms, and thus more serious events can occur without warning; and 3) Patients with previous gastric lesions, debilitating diseases, or advanced age (>65 years) appear to be most susceptible to gastric complications. Therefore, it is recommended that NSAIDs be used at the lowest effective dose for the shortest duration of time necessary, especially in patients over the age of 65 years, those taking oral corticosteroids, and those treated with anticoagulants.

## **CLINICAL EFFECTS OF NSAIDS ON**

# RENAL FUNCTION

NSAIDs are capable of inducing a variety of renal function abnormalities, particularly in patients at risk due to decreased renal perfusion such as the elderly; those with heart disease, liver disease, diabetes; or patients taking diuretics. In light of the number of patients who take NSAIDs on a prescription or OTC basis, the absolute number of at-risk patients is relatively large. Patients who depend on prostaglandin synthesis to maintain renal function are at increased risk of developing renal complications associated with NSAID use. The triad of side effects associated with NSAID usage in high-risk individuals includes fluid and electrolyte disturbances, acute renal failure, and nephrotic syndrome with acute interstitial nephritis. (Table 3)

## Table 3

### NSAID-Induced Renal Syndromes and Associated Risk Factors

<u>Renal Syndrome</u>	<u>Risk Factors</u>
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Sodium retention and edema NSAID therapy (most common adverse event)
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Hyperkalemia Renal disease
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Heart failure
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Diabetes
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Multiple myeloma
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Potassium therapy
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Potassium sparing diuretic
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Acute failure  
Liver disease

Renal disease

Heart disease

Diuretics

Old age

Nephrotic syndrome with interstitial nephritis  
Fenoprofen

Papillary necrosis  
Phenacetin abuse

(?) Aspirin-acetaminophen combination

Massive NSAID overdose

## **THE EFFECT OF ANALGESICS ON LIVER FUNCTION**

Nearly all analgesics currently in use are associated with hepatic injury. Because of its central role in drug metabolism, the liver is involved in 3% to 10% of all adverse drug reactions. Even though the incidence of hepatotoxicity with NSAIDs is low, the widespread use of these drugs actually accounts for 9% of all hepatotoxicity cases and, therefore, represents a significant health impact. Two NSAIDs, sulindac and diclofenac, may have a higher incidence of toxicity

and should be monitored for hepatotoxicity.

The risk of developing hepatotoxicity is increased in elderly patients with rheumatic diseases who may be predisposed to injury because of underlying alterations in hepatic function. Patients with alcoholic cirrhosis are especially susceptible to NSAID toxicity, due to the increased risk of bleeding complications, and, if drinking actively, to acetaminophen hepatotoxicity. The daily use of both acetaminophen and NSAIDs in patients with alcoholic cirrhosis is not recommended unless the benefits outweigh the risks.

## CLINICAL IMPLICATIONS

### **Nonpharmacologic Treatment Options for Chronic Pain**

A common cause of chronic pain in the United States is osteoarthritis, and nonpharmacologic methods should be the keystone in treating these patients. The American College of Rheumatology (ACR) recommends nonpharmacologic methods as the first step in the treatment of osteoarthritis of the hip and knee. Nonpharmacologic therapeutic approaches can be used alone or in combination with analgesic drugs and include physical therapy, certain behavioral approaches, and use of anesthetics. Because chronic pain is commonly associated with reduced physical activity, a graded physical therapy program, including range-of-motion and muscle strengthening exercises, can play a pivotal role in reestablishing the functional status of the patient. Behavioral approaches that may improve the patient's coping mechanisms include strategies to integrate pain symptoms into a functioning lifestyle, breathing exercises to increase relaxation, and therapy to improve control over the psychological factors of anxiety, fear, and the demoralization associated with chronic pain. Anesthetic procedures for pain management include neuroablative, neurostimulatory, and neuropharmacologic procedures that are typically used at a specific pain site.<sup>16</sup>

### **Pharmacologic Treatment Options**

#### *NSAIDs*

NSAIDs are one of the most commonly prescribed classes of drugs for the treatment of pain (Table 4). They are available in both OTC and prescription form and are used safely and effectively by millions of patients. At low doses, NSAIDs act as pure analgesics by inhibiting peripheral prostaglandin synthesis; at higher doses, NSAIDs act as anti-inflammatory drugs. Not all pain has an inflammatory component, so it is not always necessary to use NSAIDs at anti-inflammatory doses. However, higher doses may be beneficial in the treatment of true inflammatory diseases such as rheumatoid arthritis.

#### **Table 4**

#### **Commonly Used NSAIDs**

#### **NSAID**

#### **Availability**

aspirin  
OTC

diclofenac  
Prescription

diflunisal  
Prescription

etodolac  
Prescription

fenoprofen  
Prescription

ibuprofen  
OTC, Prescription

ketoprofen  
OTC, Prescription

nabumetone  
Prescription

naproxen  
OTC, Prescription

oxaprozin  
Prescription

piroxicam  
Prescription

sulindac  
Prescription

tolmetin  
Prescription

The frequent incidence of polypharmacy in the elderly complicates the therapeutic management of pain. The poor absorption, distribution, and excretion differences characteristic of the elderly make potential drug interactions even more of a hazard (Table 5). Based on these observations, pain prescribing guidelines for the elderly should include a careful assessment of the etiology of the patient's pain, frequent reassessment of the patient's total medication list (especially the OTC medications), and the administration of the mildest, simplest regimen possible to achieve the desired effect.

**Table 5**

## Some Possible NSAID-Associated Drug Interactions in the Elderly

### Agent/Drug Class Effect

#### *Antihypertensives*

beta-blockers  
ACE inhibitors  
Loop diuretics  
increase blood pressure  
edema  
hyperkalemia

#### *Anticonvulsants*

Phenytoin  
Sodium valproate  
increase plasma levels of anticonvulsants

#### *Oral hypoglycemics*

Sulfonylureas  
increase plasma levels resulting in hypoglycemia

#### *Oral anticoagulants*

Warfarin  
increase anticoagulant effect

#### *Others*

Digoxin  
increase digoxin levels

Adapted from Conaway DC. Using NSAIDs safely in the elderly. *Hosp Med.* May 1995;1-9.<sup>5</sup>

#### *Propoxyphene*

Propoxyphene is one of the most common narcotic analgesics used worldwide, and it has been

used as an alternative analgesic for patients who cannot tolerate NSAIDs. It is a centrally acting non-opiate with efficacy similar to aspirin or acetaminophen. Common side effects include dizziness, sedation, and constipation. At therapeutic doses, side effects such as dizziness are generally minor in nature, although in the elderly, they may be of concern due to the increased potential of falls. Additionally, chronic use of propoxyphene may cause dependence. These adverse effects preclude propoxyphene from use as a first-line agent in most chronic pain states.

### *Acetaminophen*

Acetaminophen is effective in the treatment of mild to moderate pain and does not produce GI side effects such as those associated with aspirin and other NSAIDs. This low incidence of GI side effects makes acetaminophen particularly useful in patients at risk for NSAID-associated GI adverse events, such as the elderly. Additionally, acetaminophen is recommended by the National Kidney Foundation as the first drug of choice for patients with preexisting renal disease, and it is recommended by the American College of Rheumatology as the first drug of choice when pharmacologic treatment is required for osteoarthritis of the hip or knee.

Acetaminophen has been shown to be as effective as ibuprofen in the treatment of patients with osteoarthritis of the knee.<sup>17</sup> In order to maximize its benefits, acetaminophen should be used at a dose of 1000 mg every 4 to 6 hours (not to exceed 4000 mg per day). The key to optimizing acetaminophen therapy in patients with osteoarthritis is to use it at an adequate dose for an adequate duration. Acetaminophen has been associated with hepatotoxicity, most commonly at massive overdose levels. If a patient normally consumes three or more alcohol-containing drinks per day, clinicians should attempt to reduce this consumption before recommending chronic use of any analgesic, including acetaminophen.

### *Tramadol*

Tramadol is not an NSAID. It is a non-narcotic analgesic with two mechanisms of action. The first is a low-affinity binding to the mu-opioid receptors (6000 times less than morphine), and the second is the inhibition of norepinephrine and serotonin reuptake by the nerve cells.<sup>18</sup> Tramadol is indicated for the treatment of moderate to moderately severe pain.

Clinical studies have shown tramadol to be effective in controlling chronic joint pain associated with osteoarthritis (OA).<sup>19,20</sup> In a randomized, double-blind, parallel study of 293 subjects, tramadol (200 - 400 mg/day) and ibuprofen (1200 - 2400 mg/day) were found to be comparable in the reduction of chronic joint pain of OA (Figure 3)<sup>20</sup>.

The side effects associated with tramadol include nausea, somnolence, constipation, and vomiting. These side effects are generally transient, and anecdotal reports suggest that these symptoms may be reduced by slow titration to the target dose. Even though tramadol binds to the opioid receptor, ongoing epidemiological studies in the United States show an extremely limited abuse potential. This finding is additionally supported by 20 years of use in Europe. Tramadol does not inhibit prostaglandin production and is therefore not associated with any GI and renal prostaglandin-inhibiting side effects.

### **Treatment Algorithm for the Management of Mild to Severe Pain**

In the treatment of patients with chronic pain, acetaminophen may be the most appropriate first choice for mild to moderate pain, due to its low incidence of side effects (Figure 4). Low-dose

ibuprofen is an alternative option for those patients without risk factors for NSAID complications. In cases of moderate pain, 50 to 100 mg of tramadol may be given every 4 to 6 hours, or the lowest effective dose of an NSAID for the shortest duration of time should be administered. Moderate to severe pain can be treated with tramadol, 50 to 100 mg every 4 to 6 hours, or opioids for the shortest duration at the lowest effective dose. Once the pain is controlled, the goal of therapy should be to work back toward the beginning of the algorithm to the milder agents.

## CONCLUSION

Chronic pain management calls for a comprehensive multidisciplinary approach that includes analgesic and adjunctive medications, psychoeducational tools, occupational medicine, some minimally invasive procedures, even nonconventional therapies, and, much less often, surgical intervention.

NSAIDs are one of the most common classes of drugs used in the treatment of pain. While they are generally safe when used as directed, NSAIDs are not without substantial risk. It is estimated that up to 200,000 people are hospitalized and 20,000 people may die each year due to NSAID-induced GI bleeding. As such, it is important that alternative analgesics are available for patients who are NSAID-intolerant or inappropriate candidates for NSAIDs. Other analgesics available for patients at risk for NSAID-induced complications include acetaminophen, tramadol, and propoxyphene.

The patient's attitude also plays an important role in the management of chronic pain. As such, treatment regimens can benefit from the availability of psychosocial support, stress management, and other physician-mediated interactions. A comprehensive multidisciplinary approach to chronic pain management that meets physiologic, psychological, and economic needs can help patients become pain free and enable them to resume the activities of daily living.

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## Figures

Figure 1A  
Endoscopic View of  
a Gastric Ulcer

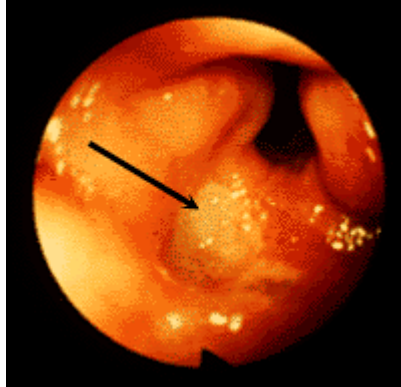


Figure 1B  
CT Scan of  
a Gastric Perforation

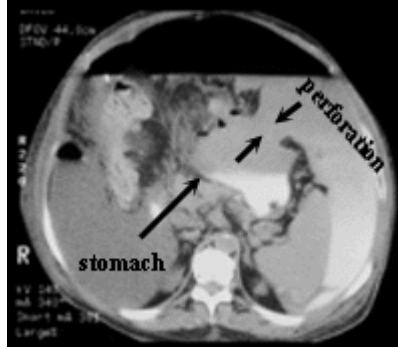
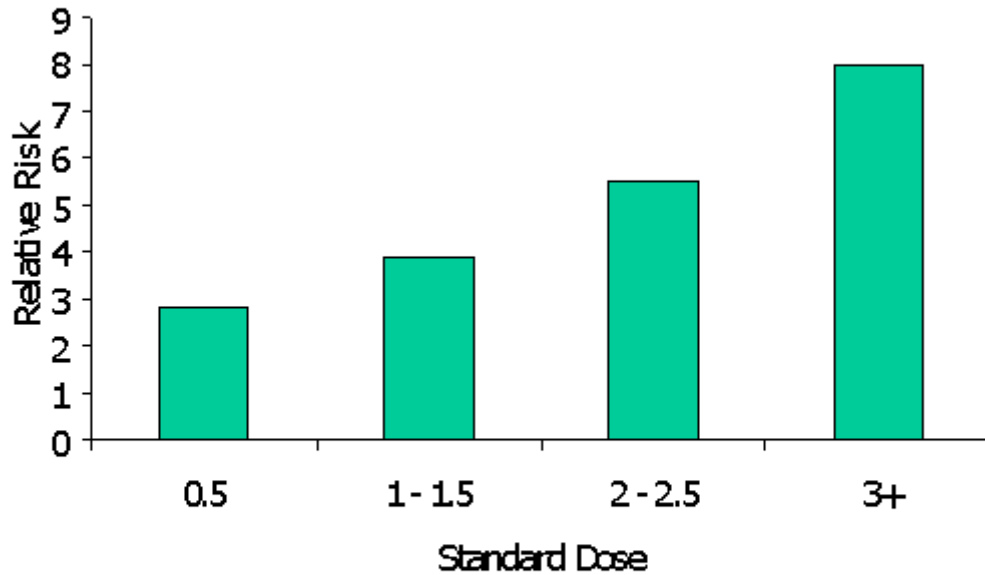


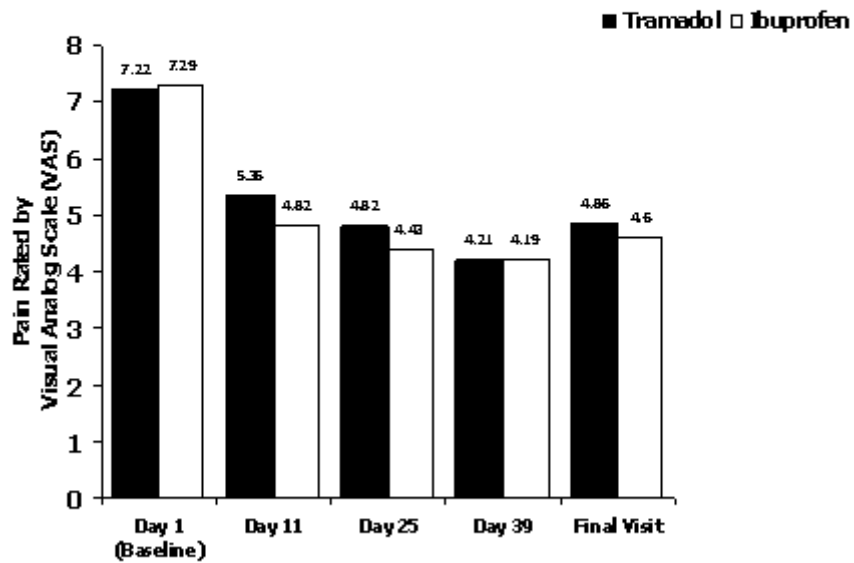
Figure 2: Relative Risk for the Development of Peptic Ulcer Disease in the Elderly by Standard Dose Among Current Users



% of Patients (N=1415)	0.5	1-1.5	2-2.5	3+
	9%	74%	14%	2%

Adapted from Griffin MR, Piper J, Daugherty JR, et al. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med.* 1991;114:257-263.

**Figure 3**  
**Tramadol vs Ibuprofen in the**  
**Treatment**  
**of Chronic Knee Pain**



Dalgin PH. Comparison of tramadol and ibuprofen for the chronic pain of osteoarthritis. [abstract] *Arthritis Rheum.* 1997;40(suppl):S86. <sup>21</sup>

**Figure 4**

**Suggested StepWise Approach to the Management of Osteoarthritis Pain**

