

# ASHP Therapeutic Position Statement on the Safe Use of Oral Nonprescription Analgesics

## Statement of Position

Nonprescription oral analgesics are extensively used for the management of headache, fever, and mild to moderate aches and pains. When taken as directed for short-term use, these agents are generally safe and effective. However, there are a number of considerations regarding the optimal choice for a given patient and condition. Recent media coverage has highlighted controversies about the relative efficacy and safety of the various available agents, increasing the potential for public confusion about the appropriate choice of a nonprescription analgesic.

ASHP encourages the appropriate selection and use of nonprescription analgesics. Selection should include an assessment of the patient's condition; concurrent diseases and medications; patient characteristics and preferences; the safety, efficacy, and cost of nonprescription analgesics; and the patient's response to therapy. ASHP encourages health care providers, especially pharmacists, to take an active role in helping to ensure that patients make the best use of these medications. ASHP recognizes the role of patients in taking responsibility for their own care and encourages consumers to follow the instructions on the label and consult with a health care provider, particularly if they have a chronic condition or are taking other medications, so that potentially harmful drug effects or interactions can be avoided.

## Background

Approximately 2% of the U.S. population consumes an analgesic, antipyretic, or nonsteroidal anti-inflammatory drug (NSAID) each day.<sup>1</sup> Between 1991 and 1995, sales of nonprescription analgesics increased by \$370 million to \$2.62 billion, indicating widespread use of these agents.<sup>2</sup> More than 150 nonprescription products containing aspirin, nonacetylated salicylates, ibuprofen, naproxen sodium, ketoprofen, or acetaminophen, either alone or in combination with other medications, are currently available for purchase by the U.S. public.

A number of epidemiologic studies have characterized the association between the consumption of the ingredients contained in nonprescription analgesics and toxicity to the kidney, liver, and gastrointestinal (GI) tract.<sup>3-10</sup> Annual U.S. costs associated with the toxicities of prescription and nonprescription use of acetaminophen, aspirin, and nonaspirin NSAIDs are estimated to be about \$51.5 million, \$458.6 million, and \$1.35 billion, respectively.<sup>7</sup> Excessive consumption of analgesic ingredients on an ongoing basis without medical supervision is clearly not in keeping with the labeled use of nonprescription analgesic products. The availability of analgesics as single-agent products and as combination products not primarily marketed for pain relief underscores the need to guard against inadvertent or intentional excessive use.

Several types of nonprescription analgesics are available, each with different pharmacologic properties and toxicities. The introduction of several agents in the NSAID class to the nonprescription market has contributed to public

confusion about the relative safety and efficacy of nonprescription analgesics. Recent media coverage has focused on the nephrotoxic effects of nonsalicylate NSAIDs and the hepatotoxic effect of acetaminophen in combination with ethanol. Warnings for people who consume three or more alcoholic drinks per day are now required by the Food and Drug Administration for all nonprescription drugs containing internal analgesics, including cough and cold remedies.<sup>11</sup> The potential for unintentional overdose is enhanced by the increasing number of combination products with brand names that the public would not recognize as products containing an analgesic. These issues heighten the importance of consumers seeking the assistance of a health care provider, such as their pharmacist, when selecting a nonprescription product.

## Pain Responsive to Nonprescription Analgesics

Pain occurs when an organ or musculoskeletal or skin structure is injured by trauma, disease, muscle spasms, or inflammation. Pain-evoking stimuli have in common the ability to cause cells to release proteolytic enzymes and polypeptides that stimulate nerve endings and initiate the pain impulse. Prostaglandins sensitize nerve endings to polypeptide-induced stimulation.<sup>12</sup>

Pain is categorized, according to its origin, as somatic, visceral, or neuropathic. Somatic pain arises from the musculoskeletal system or the skin. Visceral pain originates in the organs of the thorax and the abdomen. Neuropathic pain occurs from injury to the somatic sensory pathways.

Conditions producing visceral pain include ischemia of organ or tissue (e.g., angina), spasm of visceral smooth muscle, and physical distention of an organ or stretching of its associated mesentery.<sup>13</sup> Unlike somatic pain, visceral pain may not be localized by the brain as coming from a specific organ and is often interpreted as coming from various skin or muscle segments (referred pain).

Nonprescription analgesics are very effective for mild to moderate somatic pain from skeletal muscle (myalgia), joints (arthralgia), osteoarthritis, and soft tissue and for dysmenorrhea and headache. They are less effective against visceral pain.<sup>12</sup> Nonprescription analgesics are commonly used for acute pain and are frequently used as adjunctive therapy in the management of chronic malignant or nonmalignant pain. It is unclear whether neuropathic pain is relieved by nonprescription analgesics.

## Nonprescription Analgesics

Three classes of nonprescription analgesics are currently available: the para-aminophenols, which currently include only acetaminophen; the salicylates, which include aspirin (acetylsalicylic acid) and the nonacetylated salicylates (sodium salicylate, choline salicylate, and magnesium salicylate); and the propionic acid derivatives (ibuprofen, naproxen

sodium, and ketoprofen). Because they have similar pharmacologic properties, the salicylates and propionic acid derivatives are collectively recognized as NSAIDs. These agents are available as brand-name and generic products and are often found in combination with one another as well as with analgesic adjuvants such as caffeine. Nonprescription analgesics are also frequently found in remedies promoted for the relief of cough, cold, and flu symptoms.

**Pharmacologic Properties.** NSAIDs have pharmacologic properties that include analgesic, antipyretic, and anti-inflammatory effects.<sup>12</sup> With the exception of choline salicylate and magnesium salicylate, NSAIDs also have antiplatelet effects. Analgesic effects of NSAIDs occur at lower dosages than those required for anti-inflammatory effects. At nonprescription dosages, most NSAIDs do not have significant anti-inflammatory effects.<sup>14</sup> Acetaminophen has analgesic and antipyretic activity; it has no clinically significant anti-inflammatory or antiplatelet activity.

The primary mechanism of action of NSAIDs is peripheral inhibition of cyclooxygenase, the enzyme responsible for synthesis of prostaglandins from arachidonic acid. Aspirin irreversibly inhibits cyclooxygenase, whereas other NSAIDs act reversibly on this enzyme.<sup>15</sup> The resulting decrease in prostaglandin synthesis reduces the sensitivity of peripheral pain receptors to pain impulses at the site of inflammation and trauma. Acetaminophen may inhibit prostaglandin synthesis centrally, which could account for the difference in adverse effects seen between acetaminophen and NSAIDs.

Prostaglandins have a variety of functions in the kidney, including vasodilation, diuresis, and natriuresis; thromboxane A<sub>2</sub> is a vasoconstrictor.<sup>15,16</sup> Blood pressure, blood volume, and electrolyte balance are some of the functions regulated by prostaglandins. Prostaglandins are also involved in maintaining the integrity of the stomach lining and the functional activity of platelets. Inhibition of prostaglandin synthesis by NSAIDs can therefore result in decreased renal perfusion, electrolyte imbalance, and gastric irritation. With the exception of choline salicylate and magnesium salicylate, platelet dysfunction with resultant bleeding can also occur.

**Comparative Efficacy.** Numerous clinical trials have compared the relative efficacy of nonprescription analgesics. A majority of these trials have been conducted for headache, dysmenorrhea, or pain associated with dental procedures, osteoarthritis, episiotomy, or athletic injury. Most of these studies did not demonstrate a significant difference in the analgesic efficacy of these agents at standard analgesic dosages. Clinical studies have shown superior pain control with one agent versus another, but many of those studies were single-dose studies, which often provide different outcomes than multiple-dose studies.

Nonsalicylate NSAIDs are superior to acetaminophen and salicylates for dysmenorrhea and pain from metastatic bone disease. They also may be more effective than salicylates or acetaminophen for pain associated with inflammation (e.g., dental pain, sunburn, gout, rheumatic disorders) when used at anti-inflammatory dosages.<sup>12</sup> However, pain relief is a subjective endpoint that is influenced by a host of factors, including prior experience and a belief that the pain will be relieved. Thus, individuals may perceive that a particular nonprescription analgesic is more effective than another for a specific type of pain.

## Safety Considerations in Nonprescription Analgesic Selection

**Renal Disease.** Because of the previously described functions of prostaglandins in the kidney and the vascular system, patients taking nonprescription analgesics may be at risk for fluid and electrolyte disturbances, acute renal failure, acute interstitial nephritis, chronic renal failure, and analgesic-associated nephropathy (AAN).<sup>4,5,17</sup> While a majority of these effects are more commonly associated with use of nonsalicylate NSAIDs, AAN has been attributed to the long-term use of all nonprescription analgesics.<sup>18</sup> Combination analgesic products (those containing two or more nonnarcotic analgesics with or without caffeine, codeine, or another narcotic analgesic), particularly products containing phenacetin before its removal from the U.S. market in 1983, have been most commonly implicated in AAN.<sup>18</sup> However, the actual risk of non-phenacetin combinations continues to be debated.<sup>19</sup> Certain patient risk factors increase the potential for adverse renal effects, such as preexisting renal insufficiency, congestive heart failure, hypertension, liver disease, diabetes, atherosclerotic cardiovascular disease, and diuretic therapy.<sup>17</sup> Dehydration also increases the risk of drug-induced renal effects.<sup>17</sup>

**Cardiovascular Disease.** In addition to the increased risk of adverse renal effects, there are other reasons for patients with cardiovascular disease to be cautious of using NSAIDs. Regular use of NSAIDs may impair blood pressure control.<sup>1</sup> Further, patients with significant cardiovascular disease may have impaired ability to tolerate serious GI complications resulting from regular use of NSAIDs.<sup>20</sup> Although low-dose aspirin (50–325 mg per day) is now recommended for treatment of some cardiovascular diseases (e.g., ischemic stroke, acute myocardial infarction) and for use in conjunction with specific revascularization procedures, these indications require the advice and supervision of a health care provider to ensure safe, appropriate use.<sup>21</sup>

**Diabetes Mellitus.** It has been suggested that patients with diabetes mellitus may constitute a population at high risk for adverse effects after the ingestion of NSAIDs. Diabetic patients have lower pain tolerance than control subjects and thus may be more likely to require nonprescription analgesics.<sup>22</sup> Diabetes can alter the normal mechanisms for regulating vascular pressure, and these alterations may be further exacerbated by NSAIDs. Patients with diabetes have a high rate of end-stage renal disease<sup>23</sup> and are at increased risk of NSAID-induced nephropathy.<sup>17</sup> Although some uses of NSAIDs may be appropriate in the diabetic patient (e.g., the medically supervised use of low-dose aspirin for prevention of cardiovascular events<sup>24</sup>), the aforementioned concerns are arguments against indiscriminate use of nonprescription dosages of NSAIDs in this population.

**Gastrointestinal Disease.** Nonprescription NSAIDs can cause GI complications—dyspepsia, gastritis, ulcer formation, GI bleeding, and perforation—by the mechanisms of direct mucosal damage and systemic prostaglandin inhibition.<sup>12,25-29</sup> These complications are generally dose related. Gastritis is a local effect that can occur at low dosages and without the risk of ulcer formation.<sup>12</sup> Ulceration generally results from systemic prostaglandin inhibition and is most often initially

asymptomatic. However, symptoms may not correlate with the presence or absence of ulceration.

Patients at highest risk for development of serious NSAID-associated ulcer complications (ulcer, bleeding, or complications from bleeding) include those with a history of GI disease, those older than 60 years of age, and those concomitantly using corticosteroids, anticoagulants, or nicotine.<sup>7,30</sup> Additional risk factors include cardiovascular disease, use of aspirin and other NSAIDs in combination, and concomitant use of aspirin or other NSAIDs with alcohol.<sup>20,28,31</sup> Patients with any of these risk factors should use NSAIDs cautiously and only after consulting a qualified health care provider. Acetaminophen has not been associated with GI toxicity and may be preferred for patients with GI risk factors.

**Hepatic Disease.** Although relatively uncommon, adverse hepatic effects ranging from mild to fatal have been associated with nonprescription analgesics taken for therapeutic purposes. Salicylates may cause acute, intrinsic hepatotoxicity when blood levels are high, especially in patients with preexisting hepatic impairment, juvenile arthritis, or rheumatic fever.<sup>32</sup> There have also been occasional reports of hepatic injury associated with ibuprofen and naproxen, but the relative risk for nonsalicylate NSAID-induced hepatotoxicity is considered to be low.<sup>8,9</sup>

Chronic alcohol abuse may increase the risk of liver toxicity from excessive acetaminophen use (i.e., the use of dosages exceeding the recommended daily dosage).<sup>10,33</sup> The proposed mechanism is that chronic alcohol ingestion concomitantly induces cytochrome P-450 enzymes and depletes glutathione, through both the effects of the alcohol and the malnutrition associated with alcoholism, leading to accumulation of acetaminophen's toxic metabolite. FDA recently issued a final rule that all nonprescription analgesics carry the warning that people who generally consume three or more alcoholic drinks per day should consult their physicians for advice on taking pain relievers and not exceed the recommended dosage of analgesic.<sup>11</sup>

**Asthma.** Approximately 20% of patients with asthma have potentially life-threatening hypersensitivity reactions after aspirin ingestion.<sup>34</sup> Many aspirin-intolerant patients are sensitive to other NSAIDs and to chemicals such as preservatives and food dyes (e.g., tartrazine yellow). Although the exact mechanism of aspirin or NSAID intolerance is unknown, it is postulated that aspirin-mediated inhibition of cyclooxygenase causes arachidonic acid to be metabolized through the lipoyxygenase pathway rather than the cyclooxygenase pathway.<sup>35</sup> The end result is accumulation of leukotrienes, which can cause bronchospasm and anaphylaxis. Patients with a history of nasal polyps or aspirin-induced disorders such as severe rhinitis, sinusitis, urticaria, angioedema, bronchospasm, and anaphylaxis should avoid most NSAIDs. Choline salicylate, sodium salicylate, and acetaminophen are generally considered acceptable alternatives for most patients.

**Coagulation Defects.** Patients with coagulation defects such as von Willebrand's disease, hemophilia, thrombocytopenia, uremia, and cirrhosis should avoid NSAID-containing products.<sup>36</sup> Older adults and those who consume alcohol regularly or take anticoagulants may have prolonged bleeding time and should use nonprescription NSAIDs with care. Although all NSAIDs have the potential to prolong bleeding time, nonacetylated salicylates do not have as great an effect

on platelet function and may be used with appropriate medical supervision. Although a possible interaction with warfarin has been noted, acetaminophen is generally considered the preferred agent for most patients with underlying conditions that affect coagulation.<sup>37</sup>

**Hyperuricemia.** Many patients with gout self-medicate with nonprescription analgesics in an attempt to relieve the pain associated with this condition. Salicylates at daily dosages of 1–2 g inhibit tubular secretion of uric acid and elevate plasma urate concentrations, which may worsen hyperuricemia.<sup>12</sup> In addition, salicylates antagonize the uricosuric effects of sulfipyrazone and probenecid.<sup>12</sup> Therefore, salicylates should generally be avoided in patients with gout or hyperuricemia.

Not all patients with gout or hyperuricemia would be expected to have adverse effects with NSAIDs, particularly if they used the products infrequently at the recommended nonprescription dosages. However, patients with gout or hyperuricemia should seek the advice of a qualified health care provider when selecting nonprescription analgesics.

**Special Populations.** Safety issues associated with nonprescription analgesics are especially important in certain patient groups, including older adults, infants and children, and pregnant or lactating women. Older adults who suffer from arthritis, muscle aches and pain, headaches, and cold symptoms frequently self-medicate with nonprescription analgesics, using either single-agent or combination products. In a survey of patients 76 to 96 years of age, nonprescription analgesics and anti-inflammatory agents represented 35% of nonprescription drugs used.<sup>38</sup> Because geriatric patients commonly take prescription cardiovascular agents, diuretics, and anti-inflammatory medications, concomitant use of nonprescription analgesics should be closely monitored to prevent drug interactions.<sup>38</sup> In addition, older patients tend to be more sensitive to the effects of medications, may have decreased renal clearance, and often require dosage adjustment to minimize adverse effects.

In the pediatric population, the safe and effective use of nonprescription analgesics depends on proper dosing. Dosage should ideally be based on weight, and the medication should be administered with an appropriate measuring device. Age may be an alternative dosage guide for pediatric patients who are an appropriate weight for their age. Dosage adjustments will be required throughout the infant and toddler years because weight changes significantly during this developmental period. Appropriate attention to the concentrations of various liquid products is important to ensure safe dosing. Salicylates are not recommended as analgesics or antipyretics for children with symptoms of influenza or chickenpox because of the risk of Reye's syndrome.<sup>39</sup> Because the early symptoms of influenza and chickenpox may be difficult to distinguish from those of other illnesses, it may be prudent to avoid salicylates in children unless these are specifically prescribed by a physician. Both acetaminophen and ibuprofen<sup>40</sup> have been shown to be safe and effective for short-term use in children.

Maternal ingestion of nonprescription analgesics may affect the fetus, neonate, or breast-fed infant. In pregnant women, aspirin may affect maternal or fetal homeostasis, and high doses may cause birth defects, intrauterine growth retardation, or stillbirth. Administration of NSAIDs during the third trimester has been associated with premature closure of the patent ductus arteriosus.<sup>41</sup> In most circumstances,

acetaminophen is considered the analgesic of choice for pregnant women. The American Academy of Pediatrics has determined that both acetaminophen and ibuprofen are compatible with breast-feeding.<sup>42</sup>

Patients scheduled for elective surgery constitute a special population in whom the bleeding risks associated with aspirin and NSAIDs must be considered. The decision to avoid use of NSAID-containing products before elective surgery depends on the bleeding risks associated with the surgery, the indication for NSAID therapy, patient risk factors, the specific agent and dosage employed, and the availability and appropriateness of alternative analgesics.

**Drug Interactions.** Drug interactions with aspirin, other salicylates, and NSAIDs number more than 100 and can be found in reviews and standard textbooks on drug interactions. Most reported interactions between salicylates or NSAIDs and other drugs are pharmacokinetic. However, pharmacodynamic interactions appear to be more important clinically in that it is largely the effect of these agents on arachidonic acid metabolism that renders patients more susceptible to adverse effects from concomitantly administered medications.<sup>43</sup> Interactions with salicylates and NSAIDs range from those of minor clinical importance to those with potentially life-threatening implications (e.g., increased risk of bleeding with oral anticoagulants).<sup>43</sup> Although some drug interactions have been noted only with specific agents, in many instances the pharmacologic and pharmacokinetic properties of salicylates and NSAIDs make it likely that nearly all the agents in these classes will interact similarly with another drug or class of drugs. Patients and their health care providers should be aware of any medication (prescription or nonprescription) that the patient is taking on a regular basis, because this may influence selection of a nonprescription analgesic. Few clinically important drug interactions with acetaminophen have been reported but include alcohol in excessive amounts, isoniazid, and rifampin.<sup>10,44</sup>

### Other Considerations

Additional factors should be considered in the selection of nonprescription analgesics. The patient's pain should be assessed for its responsiveness to nonprescription analgesics and the need for physician referral. Nonprescription analgesics are indicated for self-treatment of mild to moderate pain and should be taken for no longer than 7–10 days. More severe pain or pain of longer duration requires evaluation by a physician. When these products are used as antipyretics, use should generally be limited to three days. Febrile infants younger than three months and older patients with a high fever or constitutional symptoms suggestive of a serious underlying infectious disease should be referred to a physician.<sup>12</sup>

When nonprescription analgesics are appropriate, drug selection should take into account not only the comparative safety and efficacy of available drug products but also available dosage forms and costs of therapy. These factors should be considered along with the patient's prior response to therapy, certain patient characteristics (e.g., allergies or physical impairment that may limit the ability to take medications), and patient preference.<sup>12</sup>

Appropriate use of nonprescription analgesics requires adherence to the instructions on the label. Patients should understand the limits of nonprescription therapy and the

importance of seeking medical attention should symptoms persist. Because pharmacists are often accessible at the point of purchase of nonprescription products, they are in a unique position to assist patients in the selection and optimal use of nonprescription analgesics.

### Summary

Nonprescription analgesics are generally safe and effective when used correctly for mild to moderate pain or fever. However, these agents do have risks, and selection of the best agent for a given patient requires consideration of a number of medication and patient factors. Consumers are encouraged to read and follow label instructions and to consult with a qualified health care provider, such as their pharmacist, for help in sorting out these factors and ensuring the best possible outcomes from nonprescription analgesic therapy.

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