# Nonprescription Analgesics: Misunderstood and Abused

Illness from failure to comply with the labeling of over-the-counter analgesics containing acetaminophen or a nonsteroidal anti-inflammatory drug is as inevitable as their use is ubiquitous. The author discusses the characteristics of high-risk users, the signs of possible misuse, how to treat toxic effects, and what to tell patients to prevent recurrence.

**By Kennon Heard, MD**

The availability of nonprescription, or over-the-counter, analgesics allows patients to treat their symptoms without having to visit a health care provider. Both that availability and the perceived safety of these products likely contribute to their widespread use by more than 50 million people in the US each week (with millions more using prescription medications that contain a nonprescription analgesic combined with an opioid).[1] They can be purchased at convenience stores, gas stations, and even from vending machines. It is hard to imagine a household where some type of nonprescription analgesic is not available.

When the manufacturer's instructions are followed, adverse effects from acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and naproxen are very rare. However, product labeling provides explicit dose and duration limits and recommends that patients with several common medical conditions should discuss the use of these medications with a health care provider. The United States Food and Drug Administration now requires that all OTC analgesics carry explicit warnings about the risk of bleeding (NSAIDs) or liver injury (acetaminophen) when these products are misused.

This article will review the potential toxicities of nonprescription analgesics, the reasons for their misuse, the appropriate treatment of adverse effects from excessive doses, and ways to help patients use these medications safely.

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## ADVERSE EFFECTS OF NONPRESCRIPTION ANALGESICS

Patients can develop symptoms or toxicity from any of the nonprescription analgesics. Therapeutic doses of acetaminophen are rarely associated with adverse events. There are reports suggesting that renal injury and hypertension may occur in long-term users, meaning those who take acetaminophen regularly over a period of years.[2] Recent studies have found that some patients develop asymptomatic aminotransferase elevation with more than 5 days of treatment, but there are no published prospective studies that report clinically significant liver injury from therapeutic doses of acetaminophen.[3]

Accidental acetaminophen overdose with therapeutic intent has been documented in numerous reports.[4] This may result from using excessive doses of a single product, using appropriate doses of multiple nonprescription acetaminophen products, or combining nonprescription analgesics with prescription products containing acetaminophen. The net effect is repeated ingestion of high doses that produce liver injury.

**>>FAST TRACK<<**

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The adverse effects of aspirin and other NSAIDs are familiar to most clinicians. The greatest risk from these medications is gastrointestinal (GI) tox-

icity.[5] Up to 20% of NSAID users will have some GI symptoms while taking them, mostly minor effects that do not prompt discontinuation. The risk of more serious GI toxicity varies with the pattern of use and the population. Short-term use of nonprescription doses of ibuprofen, for example, has minimal risk of GI toxicity.[6] However, regular use of nonprescription doses doubles the risk of upper GI bleeding.[7] There may also be subgroups that are more vulnerable to GI toxicity. For example, older patients, patients on low-dose aspirin, and patients with a history of ulcers are at increased risk for NSAID-induced GI bleeding.[8]

Renal injury from NSAIDs is less common than GI toxicity, but a significant number of users will develop some form of it.[9] Given the mediation of glomerular blood flow by prostaglandins and the prostaglandin antagonist property of NSAIDs, these drugs obviously must be used with caution in the presence of renal insufficiency. The risk of renal failure increases with common medical conditions such as hypertension and diabetes, as well as with higher doses and longer use.[10]

The use of NSAIDs is associated with a relative risk of 2 to 3 for a first-time hospital admission for congestive heart failure (CHF), and this risk increases to almost 10 times for patients with previous admissions for CHF.[11] This may be due to a change in renal function or changes in vascular resistance. A recent warning from the American Heart Association states that NSAIDs may also increase the risk of cardiovascular events such as stroke or myocardial infarction, but this issue is not completely resolved.[12]

## FACTORS CONTRIBUTING TO OVERUSE

Given the purpose for which these drugs are taken and the large number of patients taking them, the extent of morbidity due to failure to follow the manufacturer's instructions is not surprising. As noted above, there are numerous reports of patients developing liver failure following accidental overdose of acetaminophen. There are fewer reports of adverse events following accidental NSAID overdose, but these are probably underreported because of their similarity to the effects that occur with therapeutic doses.

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The exact rate of nonprescription analgesic overuse differs among patient populations. In a random telephone survey, almost half of respondents who used a nonprescription analgesic stated they had exceeded the nonprescription dose at some time.[13] Two other studies found that 8% of nonprescription analgesic users in a dental clinic[14] and 6% of nonprescription analgesic users in an emergency department[15] reported taking amounts in excess of nonprescription daily dosages. While there are no explicit estimates from national samples, it is likely that there are hundreds of thousands of people who unknowingly overdose on nonprescription analgesics.

Excessive dosing is not the only way patients misuse nonprescription analgesics. The maximum recommended duration of use is 10 days, but many patients will continue to use a nonprescription analgesic for weeks without seeking medical attention.[16] In addition, the product label for ibuprofen suggests that patients with any of eight medical conditions should "ask a doctor before use" and then lists another five conditions that warrant conversation "with a doctor or pharmacist before use." These conditions include ulcer disease, hypertension, renal disease, heart disease, and age greater than 60 years. The warning for acetaminophen directs patients with liver disease and those who drink three or more alcoholic beverages daily to consult their physician before use. Obviously, one or more of these concerns will apply to many users.

The reasons for overuse are not entirely clear, but we do know that users tend to underestimate the risks of nonprescription analgesics. Between 50% and 90% of NSAID users are unaware that these medications can cause ulcers or renal injury and more than half of acetaminophen users are unaware that overuse could cause liver injury.[17] Ignorance of these dangers may allow users to believe that they can take more than the recommended amount of medication safely.

The high prevalence of nonprescription analgesic use makes it imperative that health care providers discuss appropriate use with their patients. While this is common practice in primary care, it is less common in the emergency department. Patients often do not include nonprescription medications when providing histories, and even when they are noted, the clinician may not take the step of verifying correct dosage. Nonprescription analgesics are often recommended in preprinted discharge instruc-

tions given to all patients with a certain condition (for example, ibuprofen for a sprained ankle or acetaminophen for fever). These handouts, by seeming to imply the provider's approval of the recommended products, may lead high-risk patients to assume that they can safely use them.

When a patient is identified as misusing a nonprescription analgesic, the first step is to determine if the patient has any adverse effects. If the evaluation reveals no signs of toxicity, then the need for the medication should be reassessed and possible alternatives considered.

## EVALUATION AND MANAGEMENT OF NSAID MISUSE

Patients taking excessive doses of nonprescription NSAIDs, and any patient using NSAIDs despite contraindications, should be asked about any recent history of dyspepsia, hematemesis, or melena. Renal function tests may be warranted in high-risk patients, and patients taking anticoagulants should be questioned about signs of over-anticoagulation (such as bleeding or easy bruising).

In the absence of symptomatic complaints or contraindications in the history, the patient can be instructed to continue using the product, but not to exceed the maximum prescription dose, and should be counseled on the signs of common adverse events.

For asymptomatic patients who have contraindications such as age or who require prolonged NSAID use, prophylaxis with a proton pump inhibitor can be started. These medications cut the risk of duodenal and gastric ulcers by 60%.[18] However, if there is any history of GI bleeding, the patient should be switched to acetaminophen or an opioid. The same is true for any individual with renal insufficiency or congestive heart failure (see Case Study 1).

Patients at risk for cardiovascular events should be instructed to avoid long-term NSAIDs; if they must use NSAIDs, naproxen is the medication of choice. It is also reasonable to take cardioprotective doses of aspirin at least 30 hours prior to and 8 hours after taking any other NSAID.[12]

Complications of NSAID misuse may require hospitalization. Gastrointestinal bleeding is self-limited and medically manageable with close monitoring and proton pump inhibitors in most cases, but can require aggressive resuscitation, blood products, and endoscopy. Acute renal failure, while usually reversible, may require prolonged dialysis. Cardiovascular complications such as heart failure, myocardial infarction, or stroke following NSAID use are managed with standard therapies.

### Case Study 1

A 54-year-old man with a history of diabetes, hypertension, and congestive heart failure returned to the emergency department four days after evaluation for a mild ankle sprain. The patient reported experiencing weight gain, fatigue, shortness of breath, and lower extremity swelling over the past 48 hours. He had been compliant with his medications and had been taking ibuprofen according to the printed instructions he was given at discharge from his last visit. On examination, his vital signs were normal. Mild rales, an audible S4, and moderate bilateral lower extremity edema were noted.

The diagnosis was exacerbated congestive heart failure caused by the ibuprofen, which was discontinued. The patient was admitted for gentle diuresis. Over the next 72 hours his edema cleared and his symptoms resolved.

## EVALUATION AND MANAGEMENT OF ACETAMINOPHEN MISUSE

Serum acetaminophen concentration and serum alanine aminotransferase (ALT) should be measured in patients believed to be taking excessive doses of acetaminophen. The acetaminophen nomogram cannot be used to risk-stratify repeated ingestions.

For patients who have a normal ALT and a therapeutic (less than 21 µg/mL) acetaminophen concentration in the setting of repeated supratherapeutic ingestion, no treatment is necessary. However, they should not take any additional acetaminophen for at least 72 hours. If they require ongoing analgesia, they can take nonprescription doses of an NSAID (if not contraindicated) or a prescribed moderate-strength opioid (not an acetaminophen-opioid combination product). If the serum ALT is elevated, or the acetaminophen concentration is above 20 µg/mL, the patient should be treated as outlined below.

It is easy to underestimate the potential for severe toxicity from repeated acetaminophen ingestion. Often, the presenting abnormalities are merely the pro-

## Case Study 2

A 21-year-old woman presented with a one-week history of mouth pain, which she said was unrelieved by a nonprescription analgesic, and a report of three vomiting episodes with nausea earlier in the day. Her previous medical history was unremarkable. She had normal vital signs, no facial or intraoral swelling, and poor dentition.

During the examination, the physician noted that the patient had scleral icterus. On further questioning, she revealed that she had been taking three 500-mg acetaminophen tablets every 2 to 3 hours for the past five days. Her total acetaminophen dose was estimated to be 22 grams. Her serum ALT was 2570, her total bilirubin was 3.7 mg/dL, and her acetaminophen concentration was 25 µg/mL.

The patient was diagnosed with acetaminophen toxicity and, in view of her history of vomiting, she was started on the recommended protocol of intravenous acetylcysteine therapy (150 mg/kg over 60 minutes, 12.5 mg/h for 4 hours, and 6.25 mg/kg/h for 16 hours). Following treatment the patient's acetaminophen concentration was undetectable, but her ALT had risen to 4500 IU/L. The regional poison control center was contacted, and they recommended continuing the 6.25 mg/kg/h infusion until the ALT improved. After 36 hours, her ALT had fallen to 800 IU/L and she was feeling well, so the acetylcysteine was stopped and the patient was discharged home with dental follow-up and an opioid for pain control.

verbial tip of the iceberg; the initial ALT elevation demonstrates only the damage from liver cells that have already died. In most cases, hepatocyte death will continue and liver injury will progress. Patients presenting with minimal liver injury can progress to hepatotoxicity within 24 hours. Our center, therefore, recommends that all patients with either elevated ALT or a supratherapeutic serum acetaminophen concentration be started on acetylcysteine.[19]

Over the past 10 years, there have been some significant changes in the treatment of acetaminophen toxicity. Prior to 2005, acetylcysteine was only available for oral administration, and it took 72 hours to complete a course of treatment. In 2004, the approval of acetylcysteine for injection (Acetadote) introduced the alternative of giving three infusions over 21 hours (see Case Study 2). While this "one size fits all" approach is adequate for most cases, it does not account for variation in patient presentations and may result in over- or undertreatment.

Many toxicologists recommend a tailored approach based on treating the patient to a clinical end point.[20] In many ways, this is similar to the treatment of most medical conditions—therapy continues until the patient has recovered and is in no danger of deteriorating. When there is a history of accidental repeated ingestion of more than 4 g/day, a normal ALT and no indication for treatment other than a supratherapeutic acetaminophen level, the patient should be treated for a minimum of 12 hours. After 12 hours of treatment, the patient can be discharged if the ALT remains normal and serum acetaminophen is nondetectable.

Once liver injury (defined as ALT elevation) occurs, the patient should be treated until the ALT is clearly decreasing and the patient has no other evidence of toxicity (such as encephalopathy or renal injury). If injury has progressed to hepatic failure, the patient should be admitted to an intensive care unit and treated with intravenous acetylcysteine until encephalopathy resolves and serum transaminase activity is decreasing.[19] In complicated cases, a regional poison center (800-222-1222) can provide valuable assistance.

## SERIOUS THREAT

Nonprescription analgesics offer patients a way to treat minor symptoms without visiting a health care provider. While these products are safe when used as directed, they have the potential to cause serious adverse effects when misused or used by susceptible populations. Clinicians should question patients about their use of nonprescription analgesics, provide education about the appropriate use of such medications, and warn of the adverse effects they may provoke. □

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