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On July 9, 2015, the U.S. Food and Drug Administration (FDA) bolstered warnings about the use of non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) and the associated risk of heart attack or stroke. Prescription and over-the-counter (OTC) non-aspirin NSAID Drug Facts labels will soon contain updated information regarding heart attack and stroke, which can occur within a week of beginning NSAID use.¹

Prescription NSAIDs are frequently used to treat conditions like rheumatoid arthritis, osteoarthritis, or pain, while OTC NSAIDs may be used to treat fever, pain, tendonitis, strains, sprains, and menstrual cramps.² Commonly used OTC examples include ibuprofen and naproxen. In 2010, arthritis accounted for approximately $128 billion in U.S. expenditures, with 49.9 million adults ≥ 18 years having self-reported, doctor-diagnosed arthritis.³ Approximately 29 million adults in the United States were regular NSAID users in 2010.⁴

The FDA Arthritis Advisory and Drug Safety and Risk Management Committees met in February 2010 to discuss NSAID cardiovascular safety, and review literature published since 2005. Experts debated whether differentiation among the NSAID class could be made regarding cardiovascular risks.⁵ For at least 15 years, NSAIDs have been known to increase heart attack and stroke risk, in addition to potentially elevating blood pressure and leading to heart failure. These risks drew special attention with the release of rofecoxib (Vioxx®) to market, which caused roughly 140,000 heart attacks in five years before removal from the U.S. market in 2004. Further studies have shown that this risk exists with other NSAIDs.⁶

While previously published literature implied that all NSAIDs conferred a similar cardiovascular risk, recent information has led experts to conclude that there is insufficient evidence to apply specific risk levels to any particular agent. Current increased risk estimates range from 10% to 50% or greater, varying by drug and dosage studied.¹ A double-blind, randomized clinical trial is currently underway in which 24,000 users of ibuprofen, celecoxib, or naproxen are being assessed for cardiovascular adverse effects. Results are expected in 2016, and may aid in developing specific guidance regarding long-term effects of NSAID use.²

Based on current FDA safety information, patients with and without cardiovascular disease (CVD) maintain a higher relative increase in cardiovascular thrombotic events with NSAID use, but patients with known CVD or risk factors have shown a higher absolute number of events. After an initial heart attack, patients taking NSAIDs were more likely to die within the first year compared to patients not taking NSAIDs.¹ The FDA notes that the risk is higher when larger doses are taken; therefore, prescription NSAIDs maintain the highest risk, particularly due to their usual daily dosage.⁷

Acetaminophen has been recommended as an alternative pain reliever, but is not without its own risks and FDA updates. Previous FDA notifications have mandated prominent identification of acetaminophen as an active ingredient on product packaging, label warnings highlighting the possibility of liver toxicity, and limitations on acetaminophen quantities in combination products. McNeil Consumer Healthcare, the Extra-Strength Tylenol® manufacturer, has also updated labeling to include a maximum daily dose of 3000 milligrams.⁸ In response to pediatric overdoses attributed to confusion between acetaminophen concentrated drops and acetaminophen oral liquid, the FDA issued final guidance on OTC pediatric acetaminophen solutions on August 5, 2015, requiring all single-agent products to have a concentration
of 160 mg/5 mL with dosing directions provided only in mL. The FDA considers reducing the risk of acetaminophen-related liver injury an ongoing initiative, maintaining committees to continually review OTC and prescription acetaminophen-containing products. For many patients, however, acetaminophen remains a viable option to aid in the reduction of NSAID use in pain treatment.

With regard to OTC NSAIDs, practitioners may benefit from the following recommendations:

- Patients with CVD should avoid NSAID use, if possible
- If a patient must use an NSAID, therapy should be limited to a single agent at the smallest dosage possible for the shortest duration to relieve symptoms
- Alternatives, such as acetaminophen, may be considered, although patients who consume moderate amounts of alcohol, take warfarin, or have liver disease should consult their physician before use, and all patients should limit daily intake to a maximum of 3,000 mg
- Occasional weeklong “drug holidays,” in which acetaminophen may be used for pain relief, may also be considered
- Physicians and other healthcare team members should diligently assess for the development of cardiovascular adverse effects
- Patients are urged to seek medical attention if experiencing chest pain, shortness of breath, weakness, or difficulty speaking while taking an NSAID

OTC analgesics, although widely used by many Americans for pain relief, are not without inherent risks and should be used prudently. For more information regarding the FDA drug safety communication on NSAIDs, see: [http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm](http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm).

References

