Pain is among the most common of all symptoms for which patients seek medical attention. Recent clinical guidelines and advisories have emphasized the importance of thorough risk assessment and follow-up to ensure the safety of analgesic medications. Several reports have described an increased risk of QTc prolongation and cardiac arrhythmias in patients who were treated with methadone. Newly published usage guidelines from the American College of Physicians have recommended several steps to reduce the risk of cardiac events in patients using methadone, including the identification of high-risk patients, pretreatment and post-treatment electrocardiography, and careful attention to potential interactions with other drugs that may also prolong the QT interval. A recent review from the American College of Clinical Pharmacy provided an in-depth assessment of the role of nonsteroidal anti-inflammatory drugs (NSAIDs) for many types of nonmalignant pain, including arthritis, back pain, fibromyalgia, and peripheral neuropathy. A recent US Food and Drug Administration advisory has cautioned clinicians about the risk of hepatotoxicity in patients treated with diclofenac. NSAIDs disrupt gastric mucosal cytoprotection and increase the risk of gastric ulcers and bleeding. This risk may be even greater for patients who are using selective serotonin reuptake inhibitors, corticosteroids, or alcohol. Ulcer prophylaxis with misoprostol, proton pump inhibitors, or high-dose H2 antagonists is reasonable for high-risk patients. By inhibiting prostaglandin production, NSAIDs may disrupt glomerular filtration in older patients, in patients with increased renin production based on various coexisting disease states, or in patients with intravascular volume contraction. NSAIDs may also be prothrombotic by disrupting the balance of platelet-derived thromboxane and arterial wall-derived prostacyclin. Ibuprofen may counteract the antiplatelet effect of aspirin in patients who use aspirin to prevent cardiovascular events. Finally, the opioid analgesic propoxyphene has been associated with an elevated risk of accidental or intentional overdose, and its use requires particular care in patients with depression, those who are at risk of suicide, or those who are using other drugs that depress the central nervous system. Reviewing patient risk factors and potential medication interactions by health-system pharmacists is essential to ensure that patients with pain are treated effectively and safely.

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ry care physicians. Pain that is not adequately diagnosed or treated significantly diminishes quality of life, impairs workplace productivity, and creates a substantial financial burden for patients, their families, and society as a whole.

Although there are many ways to classify pain, one of the most common and clinically important is to distinguish between acute pain and chronic pain. Acute pain is generally caused by tissue injury (e.g., surgery, dental extraction, or a bone fracture), is usually intense but short-lived, may provoke significant anxiety, and often requires aggressive intervention. In contrast, chronic pain may not be directly related to a specific injury. For example, conditions such as metastatic cancer or painful diabetic neuropathy may cause chronic pain despite the absence of an identifiable lesion. Chronic pain is often very intense, may lack a clearly identifiable beginning or end, and is often associated with depression, disability, and social and economic impairment. The treatment of patients with chronic pain requires considerable patience and an effective ongoing relationship between the healthcare provider and the patient. Chronic pain is often defined as pain lasting more than 30 days. It should be noted that acute and chronic pain may overlap with one another and many patients experience acute pain episodes that are superimposed on chronic pain.

Pain management is a rapidly evolving specialty, and the standard of care is continuously evolving as new treatments and guidelines enter clinical practice. Important recent developments in the treatment of pain have included new guidelines from the American College of Physicians (ACP) on the risk of cardiac arrhythmias with methadone, an opinion paper from the American College of Clinical Pharmacy (ACCP) on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in nonmalignant pain, and the addition of a US Food and Drug Administration (FDA) black box warning to the analgesic propoxyphene. In addition, 2 new pain medications were recently approved by the FDA: tapentadol, a novel analgesic that acts as both a µ-opioid agonist and norepinephrine reuptake inhibitor; and a tamper-resistant combination product containing morphine sulfate and naltrexone.

Reducing Arrhythmia Risk in Patients Receiving Methadone

As previously stated, methadone has been associated with an increased risk of cardiac arrhythmias, which have resulted in fatalities in some cases. The ACP recently published clinical guidelines to reduce the risk of QTc prolongation in patients receiving methadone. These guidelines emphasize the importance of screening patients who are at risk for cardiac arrhythmia based on risk factors such as gender, the coadministration of other medications that prolong the QT interval, the dose of methadone prescribed, and the patient's QTc before treatment. Patients should be informed of the risk of cardiovascular effects when methadone is prescribed, and electrocardiograms should be obtained before treatment, within 30 days of beginning methadone, and then annually thereafter. Additional electrocardiographic testing is recommended for patients using methadone doses greater than 100 mg per day, who have unexplained syncope or seizure, and for those with QTc intervals greater than 450 milliseconds but less than 500 milliseconds. For patients with QTc intervals exceeding 500 milliseconds, consideration should be given to discontinuing or reducing the methadone dose, using an alternative therapy, or modifying other risk factors for arrhythmia (e.g., avoiding drugs that promote hypokalemia). The ACP recommendations also emphasize that clinicians should be aware of potential interactions between methadone and other drugs that may prolong the QT interval or slow the rate of methadone elimination. A comprehensive listing of drugs with the potential to prolong the QT interval is maintained by the Arizona Center for Education and Research on Therapeutics, and is available online at: http://www.azcert.org/.

Management of Chronic Nonmalignant Pain with NSAIDs

A recent joint position paper from the Ambulatory Care, Cardiology, and Pain and Palliative Care Practice and Research Networks of the ACCP reviewed the potential benefits and harms of NSAID use for the treatment of chronic nonmalignant pain. These guidelines identified several practice-related questions that must be considered in the use of NSAIDs, including the role of chronic NSAID treatment for osteoarthritis, rheumatoid arthritis, low back pain, fibromyalgia syndrome, and peripheral neuropathies. The authors also reviewed the risks of gastrointestinal, central nervous system (CNS), cardiovascular, renal, and hepatic adverse events with NSAIDs. The full review and clinical recommendations are available online at: http://www.accp.com/docs/positions/opinionPapers/Pharm2806_Herndon-NSAIDs.pdf.
In addition, the FDA recently released a new advisory statement about the potential for significant hepatotoxicity with diclofenac. Although the risk of hepatotoxicity with diclofenac has been recognized for many years, this new guidance from the FDA encompasses all products containing diclofenac, including diclofenac topical gels. The FDA statement notes that cases of drug-induced hepatotoxicity with diclofenac have been observed primarily during the first month of treatment, but that hepatotoxicity may occur at any time. Reported hepatic effects have included liver necrosis, jaundice, fulminant hepatitis with or without jaundice, and liver failure. In some cases, these events have resulted in death or the need for liver transplantation. These observations suggest that it may be reasonable to select an alternate medication when initiating empiric NSAID therapy for patients with chronic pain.

GASTROINTESTINAL, RENAL, AND CARDIOVASCULAR SAFETY IN PATIENTS RECEIVING NSAIDS

Nonsteroidal anti-inflammatory drugs increase the risk of gastric ulcers in hospitalized patients. Several relatively simple steps can help to reduce the risk of gastrointestinal adverse events with NSAID therapy in these patients, including evaluating patient risk factors for bleeding, using the lowest effective NSAID doses for the shortest possible period of time, avoiding the use of multiple NSAIDs or agents that are known to have a higher risk of bleeding complications, and educating patients about the presence of NSAIDs in over-the-counter products. The risk of NSAID-induced ulceration may be increased by several other medications. For example, selective serotonin reuptake inhibitors (SSRIs) may compromise gastric healing by interfering with normal platelet function, and recent studies have suggested that the combination of an NSAID and an SSRI markedly increases the risk of gastric bleeding. Other agents that also increase the risk of ulcers in patients receiving NSAIDs include co-administered corticosteroids and alcohol. It is reasonable to consider the use of prophylactic agents for high-risk patients, including misoprostol, proton pump inhibitors, or high-dose H2 antagonists.

Nonsteroidal anti-inflammatory drug-induced renal syndromes are also a potential cause for concern, especially in elderly patients. NSAIDs significantly affect the kidney’s response to declining renal perfusion pressure, which can occur as a consequence of volume contraction, blood loss, excessive diuresis, heart failure, or other causes. Under normal circumstances, decreased renal perfusion pressure triggers a compensatory response that includes the prostaglandin-dependent dilation of the renal afferent arterioles, increased angiotensin II, and constriction of the efferent arterioles. Together, these changes maintain the glomerular filtration rate despite decreased renal perfusion. NSAID administration results in decreased production of vasodilatory prostaglandins with resultant vasoconstriction of afferent arterioles. This may cause a sudden and abrupt drop in perfusion pressure and diminished glomerular filtration rate. This can significantly decrease urine output and increase circulating creatinine and potassium, increasing the risk of significant morbidity. A high degree of vigilance is required when NSAIDs are administered to patients who have volume-sensitive disease states such as congestive heart failure, those receiving diuretics, the elderly, or those with pre-existing renal dysfunction.

Finally, the FDA and European regulatory agencies have issued advisories warning of an increased risk of serious cardiovascular thrombotic events, myocardial infarction, stroke, and cardiovascular mortality for all NSAIDs, including both the newer cyclooxygenase-2 selective agents and older, nonspecific agents. The risk may be greater in patients who use NSAIDs for longer periods of time or those who have cardiovascular disease risk factors. It should also been noted that the use of ibuprofen for pain relief may interfere with the effects of aspirin on platelet function and decrease the potential benefits of low-dose aspirin for patients at risk of cardiovascular disease. The antiplatelet effects of aspirin are considered irreversible for the life of the platelet, and the occasional use of ibuprofen—especially if taken 2 hours after the daily aspirin dose—is therefore not likely to significantly decrease the cardioprotective effect of aspirin. However, it may be preferable to use naproxen, which has a better cardiovascular safety profile than other NSAIDs.

PROPOXYPHENE BOX WARNING

The opioid analgesic propoxyphene has been associated with a relatively high risk of accidental fatal overdose and suicide, which has led to recent speculation that it might be withdrawn from the market. However, rather than suspending the marketing of propoxyphene, the FDA recently issued a box warning about the risk of death or CNS depressant effects.
The labeling warns that excessive propoxyphene doses, alone or in combination with other CNS depressants (including alcohol), are a major cause of drug-related deaths. Patients who have a history of emotional disturbance, previous suicide attempts, or suicidal ideation may be at especially high risk. Nonnarcotic medications should be considered for patients with depression or who are at risk of suicide. The warning also notes that propoxyphene should be prescribed with caution for patients with medical conditions that require sedatives, tranquilizers, muscle relaxants, antidepressants, or other drugs that cause CNS depression. Caution is also expressed for altered kinetics and accumulation of propoxyphene if co-administered with strong CYP3A4 inhibitors.

CONCLUSIONS

Several common medical conditions pose an increased risk of adverse events for patients who require pain medications. Methadone has been associated with an increased risk of cardiac arrhythmias, and careful cardiac monitoring and assessment for drug interactions is required to ensure patient safety. Topical and systemically administered diclofenac have been associated with an increased risk of potentially severe hepatotoxicity. NSAIDs increase the risk of gastric ulceration, especially when used in combination with SSRIs, corticosteroids, or alcohol. NSAIDs are also associated with a potentially serious decrease in glomerular filtration rate and increased risk of thrombotic events. Propoxyphene has been associated with a relatively high risk of accidental and intentional overdose, and should be used with caution in patients who are potentially at risk of suicide or who are using other CNS depressants. Increased attention to patient risk factors and potential drug interactions is essential to ensure that patients receive the pain relievers they need in an effective and safe manner.

REFERENCES