ABSTRACT

Recent approaches to pain management have increasingly emphasized the use of individualized treatment strategies that are based on the patient's specific and patient-centered physiologic and psychologic analgesic needs, the underlying pathophysiology of pain, the use of new analgesic polymodal medications and combinations, the application of pharmacokinetic and pharmacodynamic drug profiles, and the prevention of drug-seeking or other aberrant behaviors. A thorough pain assessment is the foundation of an individualized treatment plan. Clinicians must know the right questions to ask when reviewing the patient's medical, surgical, and psychiatric history, but they must also be able to listen carefully to the patient's responses and to those who accompany the patient. Assessment of pain should go far beyond the typical 10-point rating scale to include an evaluation of the pain quality and intensity. Thorough periodic assessment of patients who are being treated for pain is required to confirm treatment efficacy and effectiveness and to identify adverse events. Confirmatory drug testing using ultra-high-pressure liquid chromatography and mass spectrometry is preferred to ensure that patients are utilizing and metabolizing pharmacotherapies as prescribed. Nonsteroidal anti-inflammatory drugs and acetaminophen are widely used for the treatment of pain and are available in many prescription and nonprescription products. However, these agents are associated with clinically significant adverse events, and careful patient selection is required to ensure that they are utilized safely. Two new opioid agents have recently entered clinical practice. Tapentadol is a µ-opioid agonist and a monoamine reuptake inhibitor (primarily norepinephrine); oxymorphone is a specific µ-opioid agonist. Both agents are metabolized primarily by phase II metabolism and do not produce toxic metabolites that various older opioids, most of which are metabolized by phase I metabolism, produce. It is important to understand the distinction between addiction (a pattern of impaired compulsive drug use control with a careless disregard for harm to self and others, usually with the goal of achieving drug-induced euphoria) and pseudoaddiction (a pattern of escalating analgesic demands in response to inadequate pain relief). Finally, effective pain management necessitates effective ongoing bilateral communication between the pharmacist and the prescriber(s) to ensure adequate pain control while reducing the risk of adverse effects and medication misuse, abuse, or diversion.

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physiology, the use of new analgesic polymodal drugs and combination regimens, the patient’s psychologic and physiologic analgesic needs, the prevention of drug-seeking or other aberrant behaviors, using pharmacokinetic and pharmacodynamic profiles to design and individualize the treatment regimen, and the use of time-specific dosing to provide maximum analgesic effectiveness when pain intensity is greatest. A thorough pain assessment and an understanding of the clinical science of pain treatment are essential for personalized, individual therapy, relieving pain, avoiding adverse effects, and recognizing individuals who are at risk of misusing, abusing, or diverting prescription medications.

**Pain Assessment: The Foundation of Individualized Therapy**

Effective communication with the patient is the basis of a thorough and accurate pain assessment. The clinician must be able to ask the right questions, but must also listen carefully to the patient’s responses. The evaluation of a patient with pain should include a complete medical, surgical, psychiatric, social, laboratory, and pharmacologic history; classification of the underlying causes of pain; and the identification of medical, psychiatric, or surgical conditions or pharmacotherapies that may influence the analgesic response or the metabolism of analgesic therapies.

The assessment of pain must go beyond the typical 10-point pain rating scale, and should explore the patient’s pain quality (e.g., burning, stabbing, aching, or throbbing), intensity, and time of peak pain events. Patients should be carefully questioned about their complete medical, surgical, social, and psychiatric histories, and any laboratory and radiographic findings (e.g., magnetic resonance imaging, computed tomography scans, or electromyogram) should be carefully reviewed. A thorough medication history should include not only all past and current prescription medications, but also over-the-counter (OTC) and herbal products (phytopharmaceuticals), street drugs, and nutritional supplements, as well as the patient’s previous treatment successes and failures. An alcohol history should evaluate the specific pattern of alcohol use, including the size of the glass, the contents of the glass, and how many glasses the patient drinks per day.

Patients who are being treated for pain should be questioned about the adequacy of analgesia, their ability to carry out their normal activities, functionality, activities of daily living, and about adverse effects or allergies. The pharmacist should also consider whether there is any evidence suggesting treatment noncompliance, aberrant behaviors, or medication diversion or misuse. Confirmatory clinical urine drug testing using ultra-high pressure liquid chromatography and mass spectroscopy (UPLC/MS/MS) is a quantitative drug testing method that is superior to presumptive radioimmunoassay testing for ensuring that the patient is using controlled substances as prescribed. Presumptive urine drug testing assessed with immunoassay is a qualitative method that is more susceptible to false-positive or false-negative results. Many states have patient prescription monitoring programs that provide invaluable information about all controlled substance prescribed for that patient within the state. Establishing good relationships with medication prescribers is also essential to ensure in good faith that patients are being treated adequately by the prescriber while minimizing the risk of medication misuse or diversion, and that the prescription was obtained under good faith circumstances with a thorough evaluation for the pain and resultant controlled substance prescription.

Knowledge of the underlying pain pathophysiology is essential in selecting a treatment strategy. Pain is often divided into multiple broad categories; in this article, the focus is nociceptive pain and neuropathic pain. Nociceptive pain occurs when potentially tissue-damaging stimuli are detected by specialized nerve endings (nociceptors) embedded in tissues throughout the body. Nociceptors are activated and sensitized by many different stimuli, including changes in temperature, mechanical deformation, or a variety of chemical mediators (e.g., bradykinin, prostaglandins, and interleukin-1). Nociceptive pain may be subcategorized as somatic, visceral, or cutaneous. Somatic pain is generally dull and poorly localized, and involves nociceptors that are located in deep tissues such as bone, ligaments, tendons, soft tissue, blood vessels, and muscle. Visceral pain is caused by injury to the internal organs, and often produces deeper pain that is dull, aching, and difficult to locate precisely. Cutaneous pain is caused by stimulation of nociceptors that are embedded in the skin or in soft tissues that are adjacent to the body surface, and generally produces a sensation of sharp pain. In contrast, neuropathic pain is initiated or caused by a primary lesion or dysfunction within the nervous system. Neuropathic pain occurs in many different pathologic conditions, including dia-
Symptoms of neuropathic pain may include a constant dull, viselike ache that is superimposed with pain that is burning, shooting, stabbing, paroxysmal, or similar to an electric shock.

Finally, it is important to identify medical conditions or concomitant medications that may influence drug metabolism. For example, patients with liver disease or those who use other drugs that alter hepatic CYP450 enzyme activity (induce, inhibit, competitively inhibit) may be at risk for clinically significant changes in plasma drug levels, efficacy, and adverse events. Most opioids use phase I metabolism (oxidation, reduction, and hydrolysis), which may yield metabolites that are either active or inactive as opioids or nonopioids. Active phase I metabolites may contribute to the analgesic effect of the opiate, but they also may have potential nonopioid analgesic events or cause toxic effects. For example, the metabolism of meperidine yields normeperidine, which is potentially neurotoxic, whereas the metabolism of propoxyphene yields norpropoxyphene, which may cause cardiotoxicity and pulmonary toxicity. In contrast, opioids that are metabolized by phase II metabolism (conjugation, sulfation, acetylation, and methylation) are utilized to produce biologically significant metabolites as with morphine-6-glucuronide and morphine 3-glucuronide. The newer opioids such as oxymorphone or tapentadol are metabolized primarily by phase II metabolism and yield minimal nonopioid active analgesic metabolites.

### Prescribing Considerations with Nonopioid Analgesics

Many different nonsteroidal anti-inflammatory drugs (NSAIDs) are available for the treatment of pain (Table). NSAIDs are found in a wide variety of prescription and nonprescription products, and a careful review of all of the patient’s medications—including all OTC products—is essential to avoid inappropriately combining NSAIDs from different sources. Despite their widespread availability, NSAIDs are not appropriate for some patients, including individuals with sodium depletion, hypovolemia, nephrotic syndrome, liver failure, and risk factors for stroke and myocardial infarction (eg, alcohol use, smoking, high cholesterol, hypertension, and diabetes). Patients with kidney disease (eg, creatinine clearance <50 mL/min) should not use NSAIDs due to an increased risk of renal failure. NSAIDs are also associated with a risk of additional end-organ damage, such as gastrointestinal ulceration, bleeding, hepatic failure, and cardiovascular effects.

Acetaminophen is currently recommended at a maximum daily dose of 4000 mg. Higher acetaminophen doses have been associated with a significant risk of hepatotoxicity due to the formation of a toxic metabolite (N-acetyl-p-benzoquinone imine) that depletes glutathione, binds covalently to proteins, and induces oxidative damage and mitochondrial injury. The safety margin between the maximum recommended adult acetaminophen dose and the dose at which significant toxicity is observed is relatively narrow, and acetaminophen-induced hepatotoxicity has
been described by the US Food and Drug Administration (FDA) as a significant public health concern.15 Individuals with low glutathione levels (eg, patients with HIV infection or alcohol abuse) are at increased risk of hepatotoxicity. The maximum recommended daily adult dose of acetaminophen may soon be reduced, possibly to as low as 2600 mg/day.15

Several other nonopioid options are available for the treatment of pain. Antiepileptic drugs (AEDs) are often very effective for the management of neuropathic pain, as well as for fibromyalgia, diabetic peripheral neuropathic pain, and migraine headache.16 FDA-approved AEDs for neuropathic pain include carbamazepine, gabapentin, and pregabalin. Oxcarbazepine, lamotrigine, topiramate, and valproate are also used off-label for pain management. AEDs may act as sodium or calcium channel blockers, N-methyl-D-aspartic acid receptor antagonists, γ-aminobutyric acid agonists, glutamic acid inhibitors, or carbonic anhydrase inhibitors.17 Topical anesthetics such as lidocaine patches or capsaicin may also be effective for neuropathic pain.18 Antidepressants that are used for pain management include tricyclic antidepressants (eg, amitriptyline, nortriptyline, and desipramine) and serotonin/norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, venlafaxine, milnacipran, and desvenlafaxine.19-21 Activation of descending noradrenergic pain pathways appears to be an especially important mechanism of pain relief with these agents because selective serotonin reuptake inhibitors (SSRIs), which lack noradrenergic activity, are generally less effective for the treatment of pain.22,23 Skeletal muscle relaxants are effective for some patients with pain, including dantrolene, baclofen, cyclobenzaprine, metaxalone, orphenadrine, and tizanidine.24 Of these agents, only dantrolene acts at the myoneural junction.25 These agents may relieve pain primarily by reducing anxiety.

**Tapentadol and Oxymorphone: New Opioid Analgesics**

Tapentadol was recently approved for the relief of moderate to severe acute pain in patients aged at least 18 years.26 Tapentadol acts by a novel binary mechanism of action: it is both a µ-opioid receptor agonist and a norepinephrine reuptake inhibitor.27 Only a small amount of tapentadol is metabolized by phase I metabolism (approximately 13% by CYP2C9 and 2% by CYP2D6).28 As a consequence of its extensive phase II metabolism, tapentadol is unlikely to produce biologically active metabolites or cause significant CYP450 interactions with other drugs. The half-life of tapentadol is approximately 4 hours, with a time to maximum plasma concentration of 1.25 to 1.5 hours. Elimination is rapid and complete, with 95% elimination within 24 hours and 99.5% eliminated within 5 days.26 Tapentadol has been examined in patients aged up to 80 years, and for durations of up to 90 days.28,30 Whereas most clinical trials of new analgesics are performed in comparison with placebo, tapentadol was compared with oxycodone in 3 recent randomized, double-blind clinical trials.28-30 Tapentadol at doses of 50 to 75 mg were approximately equal in analgesic efficacy to 10 mg oxycodone (Figure 1).28 For older patients, a single 50-mg tablet may be split in half, providing an analgesic effect similar to 5 mg of oxycodone. In contrast with other opioids, tapentadol is unlikely to cause euphoria,31 and many patients say that, aside from pain relief, they experience no discernable effect of tapentadol.
administration. In clinical trials, tapentadol was also less likely than oxycodone to produce nausea, dizziness, vomiting, or constipation.26-30 The labeling of tapentadol includes a class warning regarding serotonin syndrome.26 However, no cases of serotonin syndrome were observed in clinical trials of tapentadol, even when coadministered with SSRIs or SNRIs. Tapentadol is revealed in confirmatory clinical urine drug testing (UPLC/MS/MS).

A second new opioid analgesic, oxymorphone, was recently approved for the treatment of acute pain following orthopedic or abdominal surgery.32 Oxymorphone is a pure opioid agonist that is similar in mechanism of action to other phenanthrenes (eg, codeine, hydrocodone, hydromorphone, morphine, and oxycodone). Oxymorphone produces dose-related analgesia with no analgesic ceiling effect, and the maximum dose is imposed by the appearance of intolerable adverse events.19 The efficacy of oxymorphone for the treatment of postsurgical pain is shown in Figure 2.34 Similar to tapentadol, oxymorphone is metabolized by phase II metabolism. The oral bioavailability is approximately 10%. The half-life of oxymorphone immediate release is approximately 7.25 hours for the 5-mg dose, 7.8 hours for the 10-mg dose, and 9.4 hours for the 20-mg dose. The extended-release half-life is 9 to 11 hours.32,35

As with all opioids, patients who are treated with oxymorphone should be on a bowel management plan. Less than 1% is excreted unchanged in urine, and oxymorphone is detectable in a clinical urine drug test. With confirmatory urine testing using UPLC/MS/MS, the results may indicate a very small amount of oxycodone. However, this trace amount of oxycodone is a result of the manufacturing process and does not reflect oxycodone use by the patient.

**CLINICAL ISSUES IN ANALGESIC TREATMENT**

The selection of an analgesia strategy for an individual patient with pain is a multifactorial process that requires careful consideration of the pharmacokinetic, pharmacodynamic, pharmacologic, and drug interaction effects of the analgesic treatment plan and all of the patient’s pharmacotherapies. The treatment plan should also consider the patient’s specific pain relief needs, age, gender, pregnancy or breastfeeding, and the patient’s vocation and avocation. It is also essential to consider the expectations of the patient, the patient’s family, and the patient’s treatment team, and to try to ensure that patients have realistic expectations about the level of pain relief achievable with analgesics. Disability is a central concern for many individuals with pain, and individuals who remain on disability for 1 year or longer are unlikely to fully return to work. Identifying the times of day when the patient most needs pain relief also can help to individualize the analgesic treatment regimen. For patients with persistent pain, it is important to accept the pain as genuine until proven otherwise. Treatment must take into consideration all underlying disorders, as well as psychosocial issues such as anger and frustration. Analgesics may be combined with several invasive interventions, adjuvant agents, and nonpharmacologic methods to manage the pain.

When evaluating possible aberrant behaviors by patients who are using opioids, it is important to recognize the distinction between addiction and...
pseudoaddiction. Addiction is a pattern of impaired compulsive drug use control and careless disregard for the self and others, usually with the goal of drug-induced euphoria.\textsuperscript{38} In contrast, pseudoaddiction is a pattern of escalating analgesic demands and drug dosage that occurs when the patient is experiencing inadequate analgesia.\textsuperscript{39} Although some behaviors that are characteristic of pseudoaddiction may superficially resemble addiction, the goal of the patient with pseudoaddiction is to achieve more complete analgesia, as opposed to achieving euphoria. Treating patients with a history of addiction can be challenging. Options for pain management that are less likely to produce euphoria include buprenorphine as an injectable agent for inpatients\textsuperscript{37} and oxymorphone or tapentadol as oral agents. In our practice, patients in recovery and those not in recovery have not experienced euphoria. Also, more often than not the patient describes "not feeling" the oxymorphone or tapentadol, an event on the dopamine pathway.

Finally, the effective and appropriate use of opioid medications requires ongoing bilateral communication between the pharmacist and the patient's prescriber(s). It is reasonable to alert the patient's physician to questionable or high-risk behaviors, and to request and review the patient's urine drug testing results. Under the Controlled Substances Act of 1970, pharmacists and physicians share the responsibility for prescribing and dispensing controlled substances. Pharmacists also have joint accountability for opioid prescribing under state laws and under the federal Omnibus Budget Reconciliation Act (OBRA). Patients may not understand that their signature on some pharmacy documents during the dispensing activity waives the right to consultation. Providers may wish to include a note on all prescriptions directing the pharmacist to consult with the patient. This increases the likelihood that the patient will receive the education needed to correctly use the analgesic and other medications.

CONCLUSIONS

The management and treatment of pain have evolved considerably in recent years as new analgesic medications have become available and treatment has become more individualized. The selection of a pain management strategy must begin with a thorough assessment of the patient's medical and social history, the type and intensity of pain, and fluctuation in pain intensity over time, as well as a review of all prescrip-

REFERENCES