Navigating the Management of Chronic Pain: A Pharmacist's Guide

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Provide the pharmacist with practical information to support the assessment and management of patients with chronic pain.

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Introduction

The general public considers pharmacists the most easily accessible health care professionals. In most cases, no appointment, prior relationship, or payment is required before an individual is permitted to approach the pharmacist with a health care concern. Because of this convenience and accessibility, pharmacists contend with questions ranging from basic first aid to more complex situations concerning the management of multiple comorbidities. Regardless of the setting, pharmacists are the primary drug information resource for laypersons and health care professionals alike. A common ailment pharmacists hear of (often on a daily basis) is the management of chronic pain.

The International Association for the Study of Pain (IASP) has defined pain as, "an unpleasant sensory or emotional experience." Chronic pain does not serve a biological purpose; this is in comparison to acute pain, which provides protection by warning of impending physical damage. Chronic pain has also been defined as pain that persists after the underlying injury or insult has healed.[1] It may be described as pain that lasts for more than 4 or 5 weeks, more than 3 months, or more than 6 months. A clinically useful definition may read as follows: pain that negatively affects patients' daily functioning, pain that is associated with a chronic condition, or pain that lasts longer than would be anticipated after the healing process. Chronic pain is also associated with longstanding conditions that are known to produce persistent pain; a common classic example would be osteoarthritis.

Incidence

Estimates regarding the prevalence of chronic pain vary widely, depending on the methods used to capture these data; but, according to most reports, approximately 30% of the population lives with chronic pain.[2, 3] One recent study found a 41% overall prevalence, with rates that ranged from 23% in those aged 18 to 24 years to 50% among those aged 55 to 64 years.[4] Women report chronic pain more frequently than men and, not surprisingly, the incidence of chronic pain increases with age. Interestingly, pain patients account for 20% of total primary care visits[5] and 50% to 80% of physician visits, overall.[6] These estimates include patients that span the entire age continuum, including children and younger adults, who are not exempt from experiencing chronic pain. The overwhelming prevalence of chronic pain is only a brief introduction to its effect on the population as a whole. In addition to causing physical distress, chronic pain is a major source of disability. The Joint Commission (formerly JCAHO) estimates that 50 million Americans are

disabled because of pain.[7] Absenteeism is high among those that remain in the workforce; 25% of patients with chronic pain reported lost work time because of pain[6] and more than 50 million lost workdays each year can be directly attributed to pain.[5]

Costs

Estimates state that the total direct and indirect costs of chronic pain in the United States (U.S.) exceeds $100 billion per year,[8] but this may be a conservative figure; low-back pain, alone, is estimated to cost nearly $86 billion annually. In 2005, Americans spent more than $20.4 billion on over-the-counter (OTC) and prescription analgesics,[9] (it is important to note that this figure does include financial ramifications from adverse events such as a gastrointestinal [GI] bleed or renal failure); these are attainment costs only.

Sources of Chronic Pain

Determining both the etiology and the best treatment approach for chronic pain begins with a detailed patient evaluation, including a thorough patient history, a physical exam, and a review of diagnostic studies, as well as a psychological exam, if appropriate. A complete medication history must also be obtained, including the patient's own assessment of prior medications, as a means to develop a rational approach to treatment (Table 1). A careful review may reveal an unexpected source of pain. In essence, chronic pain has numerous etiologies; chronic conditions, such as osteoarthritis, fibromyalgia, and low-back pain, are a few of these.[10]

Table 1: Components of Patient History

General Information	Medication-Specific Information
• Patient demographics (age, ethnicity, weight, height) • Acute and chronic medical problems • Pertinent medical history • Vital signs and other monitoring information • Pain Diagnosis • Current symptoms (including impact on mood and sleep) • Pain Intensity, location, etc. • Effect of symptoms on activities of daily life • Diet • Exercise/recreation • Social substance use (e.g., tobacco/alcohol/caffeine) • Illegal substance use or misuse • Pertinent laboratory • Health beliefs • Name and location of pharmacies • Financial/insurance/health plan	• Medication allergies • Medication intolerances • ALL current prescription medications (include strength, dose, route, frequency, actual use, effect on pain/symptoms, adverse effects, length of use, prescriber) • ALL current nonprescription medications (include strength, dose, route, frequency, actual use, effect on pain/symptoms, adverse effects, length of use) • Past medications used for pain (include strength, dose, route, frequency, actual use, effect on pain/symptoms, adverse effects, length of use, prescriber) • Home remedies and other types of health products used, including herbal and complementary agents • Concerns or questions about pain therapy • Assessment of understanding of therapy

Osteoarthritis (OA) is a progressive, disabling joint condition that affects 20 million Americans, 10% of whom become totally disabled.[11] While OA can present at any age and involves a progressive deterioration of the joint, 70% of those affected are between 55 and

78 years.[12] Disability resides primarily in the weight-bearing joints of the hip and knee. It has been proposed that the rates of OA will increase as the rates of obesity continue to rise.[13] It was previously believed inflammation was not associated with this condition, but recent research shows that inflammation, synovitis, and joint effusions are all associated with the joint erosion found in OA.[12, 14] Prior injury, heredity, and faulty healing mechanisms also play roles in disease progression by hastening cartilage degradation.[14]

Fibromyalgia translates, literally, as fiber-muscle-pain. It manifests as widespread pain that occurs on both sides of the body, above and below the waist. Patients report a deep aching and tiredness. Accompanying the ache are tender spots, or spots that elicit pain when pressure is applied. The diagnosis is based on the American College of Rheumatology (ACR) criteria that includes widespread muscle pain for 3 months or more and pain in at least 11 of 18 potential tender spots.[15] While other diagnostic criteria have been suggested, none is as widely accepted as the ACR guidelines. Fibromyalgia affects 2% of the population, with higher rates observed for women and the elderly. The prevalence of fibromyalgia is higher in those with iron deficiency anemia,[16] irritable bowel syndrome, depression, and restless legs syndrome, among others.[17]

Back pain is a common occurrence, ranging from discitis, sciatica, and spinal degradation to compression fractures and stenosis. More than 10% of the population is estimated to be living with chronic, incapacitating low-back pain,[18] and the elderly are disproportionately affected; 40% of women aged 80 years and older are estimated to have vertebral compression fractures.[19]

Neuropathic pain comprises another group of diverse pain presentations. Some common etiologies of neuropathic pain include postherpetic neuralgia (PHN), which results from the reactivation of the varicella zoster virus (shingles), painful diabetic peripheral neuropathy (pDPN), which is caused by hyperglycemia from poorly controlled diabetes, complex regional pain syndrome type I (CRPS I), and phantom limb pain. Another condition is painful HIV-associated distal sensory polyneuropathy (HIV-DSP). HIV-DSP causes numbness and tingling pain in the hands and feet; up to one-third of patients with HIV/AIDS have neuropathic pain attributable to HIV-DSP.[20]

Individualized Therapy

When you consider the many different ways chronic pain presents itself, the need for individualized care becomes an evident, but often overlooked, necessity. The primary focus of treatment for chronic pain is the relief from symptoms, which may result in the return to normal functionality or an improved quality of life. To facilitate treatment success, the clinician must be aware of all aspects of the pain experience. This includes acknowledging both the anxiety and the depression that often accompany chronic pain. Some older patients will not report the full extent of their pain and the clinician must actively inquire about symptoms. Treatment of pain in the older population can be complex because this segment of the population is more likely to experience an adverse

drug reaction or a drug-drug interaction. Cognizance regarding the impact of pain symptoms on daily functioning, family life, and work productivity is the first step to making rational choices about therapy.

Setting and communicating specific, focused goals is critical to achieving effective pain management. It is also important to remember that baseline pain intensity can, and usually does, wax and wane over time. This information is useful clinically, since issues such as daily activity, exertion, rest, stress, and diurnal variation can all impact the type and intensity of pain.

Pathological Differentiation

For purposes of directing therapy, it is useful to classify pain in terms of signaling differences. In simplistic terms, pain signals travel via either nociceptive or neuropathic pathways, and patients with chronic pain often experience components of both of these types of pain (**Figure 1**).

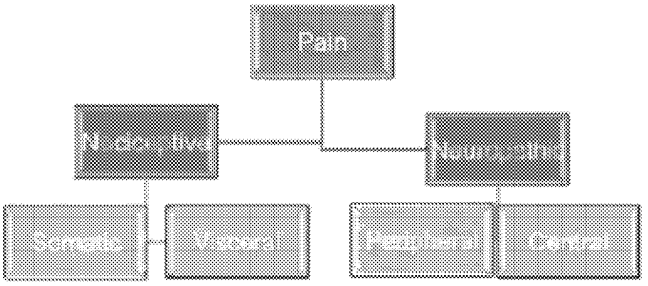

Figure 1: Pathophysiology of Pain

Nociceptive pain emanates from the activation of peripheral receptors called nociceptors. Following activation, the pain signal is transmitted along normal, undamaged neuronal tissue to the somatosensory cortex. Nociceptive pain is described in terms of potential or actual tissue damage and can be further divided into somatic (well localized) or visceral (poorly localized; organ or abdominal) pain. Somatic pain is generally described in terms of musculoskeletal pain and involves the skin, soft tissues, muscle, and bone structures. Somatic pain results from the stimulation of normal peripheral nociceptors within the somatic nervous system. Patients often describe this type of pain as sharp, aching, and/or throbbing. Because the muscle, bone, and soft tissues are highly enervated, somatic pain is easy to localize and the patient can point to the pain when prompted by the physician (i.e., easily identify the specific location of the pain). Visceral pain is referred to as an internal pain and involves organ systems within the thorax, abdomen, and pelvis. Visceral pain is generated by the stimulation of nociceptors located in and around the organs; symptoms may be described as dull, aching, throbbing, or cramping and this type of pain is often precipitated by inflammation, stretching, or oxygen deprivation. Some of the visceral organs (e.g., stomach, bladder, uterus) are highly enervated with sensory neurons and exquisitely sensitive to pain, but not all organs contain nociceptors (e.g., lung, liver, kidneys), so pain felt in these areas is usually caused by abnormal functioning systems. Another distinctive feature of visceral pain is its propensity to radiate. This is because many of the nociceptors in the visceral system do not have dedicated sensory pathways, so

it is not easily described in relation to a specific anatomical location.

Neuropathic pain indicates damage to either the central or peripheral nervous system versus nociceptive pain, which results from ongoing negative stimuli. Very simply, neuropathic pain originates in damaged neuronal tissue and this damage may occur in either peripheral or central nervous system tissue, or in both areas simultaneously. Neuropathic pain is often described as a burning, tingling, numbness, shooting, stabbing, or electrical pain. Common peripheral neuropathies include pDPN, PHN, and malignant plexopathies. Examples of central neuropathies include phantom limb pain, poststroke, and thalamic pain. Patients may experience a mixture of peripheral and central pain syndromes; it is important to remember that some types of neuropathic pain have dual etiologies. CRPS I and II (previously causalgia or reflex sympathetic dystrophies) are examples of mixed etiology neuropathies.

A factor that adds complexity to treating chronic pain is the issue of breakthrough pain. Breakthrough pain can be defined as pain that is either not anticipated or pain that occurs unexpectedly or at a greater intensity than is considered normal for a particular condition. Breakthrough pain may occur spontaneously or it may be related to specific triggers, such as activity, eating, or a change in position. In terms of pharmacologic treatment for neuropathic pain, it is important to have different analgesic formulations available (e.g., long-acting and short-acting medications) as a means to lesson or alleviate both baseline and breakthrough pain; focusing treatment without flexibility will foster negative outcomes. It is extremely important that the patient becomes educated about pain medications and understands their treatment algorithm. Appropriate use of extended-release preparations and immediate-release products in combination can significantly enhance analgesia and quality of life.

Overview of Analgesic Medications for Use in Chronic Pain

Chronic pain embodies a wide variety of diverse conditions and causes, so it is not surprising that medications used to treat chronic pain comprise a diverse group of substances. These range from common OTC analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) to opioids, anticonvulsants, antidepressants, and prescription NSAIDs. Some of the commonly used prescription agents do not have U.S. Food and Drug Administration (FDA) labeling for pain.

Acetaminophen

Acetaminophen is one of the most widely used analgesics in the world. It is available OTC both as a single-agent product and as a combination product, in OTC cough and cold preparations. It is also available in prescription formulations when mixed with opioids. Acetaminophen products are available in oral and rectal dosage forms; total daily acetaminophen use should not exceed 4 grams because dosing past this level may be hepatotoxic, even in healthy patients. Patients with excessive alcohol intake, hepatic or renal insufficiency, or poor nutritional status may benefit from lower daily dosing. Acetaminophen has an analgesic ceiling as well, doses in excess of 4 grams in a 24-hour time period do not provide additional analgesia.

The mechanism of action for acetaminophen remains elusive and is often described as unknown in the medical literature. It has been suggested that some of the activity may be related to cyclooxygenase-3 (COX-3) inhibition, and even some COX-2 inhibition, in the central nervous system (CNS).[21, 22 23] Other potential mechanisms include central inhibition of nitric oxide (NO) and inhibition of substance P.[24] Although acetaminophen is an effective antipyretic agent, and is commonly recommended to treat fever, it does not appear to have any clinically significant anti-inflammatory properties.

NSAIDs

In addition to being the patient's first choice for self-treating pain, NSAIDs are often front-line prescription therapy as well. As the name implies, NSAIDs have substantial anti-inflammatory properties. They inhibit the COX-2 enzyme system and the resulting prostaglandin suppression is primarily responsible for their analgesic, anti-inflammatory, and antipyretic activity; there is also a central mechanism responsible for analgesia in some types of pain.[25] NSAIDs are available as OTC medications (e.g., aspirin, ibuprofen, naproxen) as well as in prescription formulations (e.g., celecoxib, indomethacin, ketorolac). Similar to acetaminophen, NSAIDs are often used in combination with opioids for synergy and can reduce opioid requirements.[26] With the vast number of NSAIDs available (currently more than 20), a common consideration is which product to choose. The interpatient variability in terms of response to different agents has been well described in the literature,[27.28] but guidance with the choice of available options remains scarce. At this time, there is no reliable way to predict how a patient will respond to a given agent. One rational approach is to base the decision on the expected adverse events profile. As with acetaminophen, all NSAIDs have an analgesic ceiling, which should not be exceeded. Unlike acetaminophen, the range of available dosage forms is expanded with NSAIDs. Several NSAIDs are available in topical formulations; ketorolac is even available parenterally.

All NSAIDs have a significant adverse events profile that affects most often the gastrointestinal (GI) tract and kidneys. Because of concerns over toxicity, the ACR now recommends that osteoarthritis patients use proton-pump inhibitors (PPIs) when taking NSAIDs long-term.[29] Much of the toxicity is related to the nonselective inhibition of the COX-1 enzyme. COX-2 selective agents were developed with the hope of eliminating, or at least greatly diminishing, these problems. While the more selective COX-2 inhibitors have fewer GI complications, the FDA removed several drugs in this class (i.e., rofecoxib, valdecoxib) from the market after they were shown to be associated with a significant increase in cardiovascular events.[30, 31] In addition to concerns surrounding COX-2 selective agents, an increase in cardiovascular risk has also been demonstrated in relation to the overall use of NSAIDs.[12] The FDA has added wording to NSAID labels that warns of the risk for cardiovascular events.[13] NSAIDs administered topically will have reduced toxicity as compared with traditional systemic dosing; patients must be made aware that, with improper or excessive use, even topical preparations have substantial systemic

absorption that can lead to toxicity.[14]

Opioids

Full agonist opioid analgesics are the most potent and effective analgesics available, and a central component of the analgesic ladder for moderate-to-severe cancer pain, established by the World Health Organization (WHO) .[32] Full agonist opioids exert their analgesic effects by acting as agonists at the mu receptor; they have a potentially unlimited dose response and, thus, a theoretically unlimited dosing ceiling. In practice, however, patients often experience significant adverse effects as opioid doses increase. (Table 2) These adverse effects result in a functional dose ceiling that can limit the utility of these agents, as dose requirements increase. Opioid- induced side effects are common and should be anticipated by clinicians. Fortunately, most opioid adverse effects can be managed with careful planning and patient education. Older patients are usually more sensitive to both the analgesic and the adverse effects of opioids than other patients. In a departure from previous guidelines, The American Geriatrics Society (AGS) now recommends a trial of opioids be considered for older patients with moderate-to-severe pain.[33]

Table 2: Adverse Effects of Opioid Medication

Constipation	Nausea & Vomiting	Sedation & Mental Clouding	Agitation, Confusion, Hallucinations, Nightmares & Myoclonus
• Almost universal • Tolerance rare • Manage with stimulant laxatives (e.g., senna, bisacodyl) • Stool softeners (e.g., docusate sodium) are not usually effective by themselves, but may be useful if patients have hard, dry stools	• Tolerance develops within first few days • Effective treatments include prochlorperazine, haloperidol, & metoclopramide • If treatment is not effective patient may require a change in opioid	• Tolerance develops within first 7 – 10 days following initiation or dose escalation • May result from poor sleep • May require change in opioid • If change is not an option, may benefit from use of a psychostimulant (e.g., methyl-phenidate)	• Less common • Generally indicates too much opioid is being administered • May imply poor renal elimination and toxic metabolite accumulation • Patient may benefit from change in opioid

In contrast to full agonist opioids, partial agonist and mixed agonist-antagonist opioids are known to have an analgesic ceiling. While both of these opioid classes interface with the mu receptor, their activity results in either partial activation of the receptor or blocked activity at the mu receptor, respectively. As doses for these agents near or exceed their analgesic ceiling, substantial adverse effects (e.g., psychomimetic effects) can occur. There is little to no value from these agents for the vast majority of patients with chronic pain.

Another issue that impedes opioid use, is the fact that many clinicians harbor concerns about addictive behaviors, as well as the mistaken belief that these medications are not effective for the relief of certain types of pain (primarily neuropathic pain). Patients and clinicians, alike, have various fears and prejudices associated with the use of opioid analgesics, which seems to unnecessarily limit the use of this class of medications. The term opiophobia has been coined to refer to these fears, which may be a result, at least in

part, of misunderstandings regarding the concepts of addiction, physical dependence, and tolerance (Table 3). By virtue of achieving adequate pain control, many of the adverse behavioral aspects of opioid therapy may be avoided. A good understanding of terms such as pseudoaddiction and pseudotolerance will assist clinicians with educating colleagues and patients about the proper use of these analgesics.

Table 3: Terms Associated With Opioid Use

Addiction	Opioid use that causes the user harm, yet the user continues to use the opioid.
Pseudoaddiction	Patients using opioids have inappropriate drug seeking behavior for the purpose of pain relief, and not for abuse or substance misuse. This occurs when patients request more opioid for analgesic purposes, but exhibit behaviors attributed most often to addiction (e.g., anger, hostility).
Tolerance	Pharmacological phenomenon where a patient's routine exposure to an opioid causes an adaptation in the central nervous system, which results in a decrease in the response to the opioid over time. Analgesic tolerance with opioid analgesics is variable and is more pronounced with acute and subacute administration.
Pseudotolerance	Behavior where opioid dose escalation appears consistent with tolerance. After careful assessment, this behavior is better attributed to other issues: These may include progressive disease, new pathology, changes in physical activity, nonadherence, drug interactions, or medication diversion.

In general, opioids are considered effective for most types of nociceptive and neuropathic pain, even though they are typically not considered a first-line treatment for neuropathic pain. When opioids have been designated as the appropriate choice for analgesia, scheduling a long-acting agent for around-the-clock (RTC) analgesia and an immediate-release formulation for breakthrough pain is usually the best approach (Table 4). A variety of long-acting oral opioids are available, including a new subgroup of long-acting oral agents that contain an abuse deterrent component. Similar to the partial and mixed agonist-antagonist opioids, several of the available full agonist opioids do not have a place in chronic pain therapy. These agents are codeine, propoxyphene, and meperidine. Codeine provides poor pain relief and, because a large proportion of the population does not convert it to morphine (the active component), predicting response is difficult. Propoxyphene is often prescribed to older patients with the misguided belief that it minimizes adverse effects because it is a weak opioid. In actuality, it is so weak that its analgesic effects are comparable to acetaminophen alone, but it does share other opioids' adverse effects of nausea, drowsiness, and constipation. Meperidine is never appropriate for long-term use because of the risk of seizures caused by the metabolic product normeperidine. Normeperidine is neurotoxic and can accumulate in patients with renal impairment. In addition, it is a short-acting drug and the risk of CNS adverse effects outweighs its efficacy as an analgesic.

Table 4: Long-Acting Oral Opioids

Pharmacologically Long-Acting	Pharmaceutically Long-Acting
• Levorphanol (Levo-Dromoran)	• Morphine Sulfate (Kadian®,

• Methadone (DOLOPHINE®)	Morphine ER, MS Contin®, ORAMORPH SR™) • Oxycodone (OxyContin®) • Oxymorphone (OPANA® ER)
	Pharmaceutically Long-Acting with Abuse Deterrence
	• Morphine sulfate with naltrexone hydrochloride (Embeda™)

When opioids are dosed properly, with an RTC long-acting medication and an adequate adjunct medication for breakthrough pain, most chronic pain is manageable for those that respond well to opioid treatment. This method can maintain consistent opioid serum concentrations and decrease the incidence of episodic breakthrough pain.[34] For the ease of evaluation and to decrease the potential for addictive adverse effects, the short-acting agent should be the same medication as the long-acting opioid, whenever possible. Breakthrough doses should be determined according to the total long-acting daily dose. Generally, each breakthrough dose should be in the range of 5% to 15% of the total daily long-acting dose and administered according to the duration of action (i.e., every 3 to 4 hours, as needed). For those that routinely require more than 2 or 3 daily rescue doses, consider increasing the long-acting dose; add the amount of breakthrough medication that has been required to the current dose (e.g., RTC dose + BT doses = new RTC dose).[34] Another approach is to increase the long-acting dose by 50% after steady-state serum concentrations are achieved.[34a]

Adjuvant Therapy

As previously noted, chronic pain requires a diverse group of agents to provide adequate pain relief. Historically, the nontraditional agents have been lumped into a category known as adjuvant analgesics, which include anticonvulsants and antidepressants; these agents are commonly recommended for treatment of neuropathic pain.

Using antidepressants to manage chronic pain can be beneficial from 2 completely different perspectives: these medications will treat concomitant depression while they help to manage pain symptoms. This is an important distinction because an estimated 70% of patients with chronic pain may also have a mood disorder.[35] From an analgesic standpoint, the 2 primary classes of antidepressants are the tricyclic antidepressants (TCAs) and the serotonin-norepinephrine reuptake inhibitors (SNRIs). Their analgesic activity appears to be related to the regulation of both serotonin and norepinephrine, independent of antidepressant action[36]; this becomes evident when you consider that the dose of a TCA prescribed for pain is usually substantially lower than the dose prescribed for depression. The starting dosage of TCAs prescribed for pain is 10 to 25 mg/day administered orally, and the dosage for pain will not typically exceed 100 mg/day[33]; for many patients, TCA doses may be 2 to 3 times higher when prescribed for depression.[36a]

Currently, there is no evidence that any one TCA is more effective than another for pain control, so classifying these medications according to their side-effect profile is a convenient dosing aid. For example, tertiary amines have significantly more anticholinergic effects than secondary amines, therefore nortriptyline or desipramine may be the preferred agents. Please note, TCAs have a significant number of sexual side effects, and drug interactions, as well as being considered cardiotoxic because they prolong the QTc interval.

Duloxetine and milnacipran are SNRIs that have been FDA-approved and indicated for pain. Duloxetine is approved to treat both diabetic peripheral neuropathy and fibromyalgia; milnacipran is indicated for the treatment of fibromyalgia. Both agents are generally well tolerated and may be useful for patients with chronic pain conditions. Both agents carry black- box warnings to indicate the increased risk of suicidal ideation and behavior.

Anticonvulsants have long been used to manage neuropathic pain. The primary agents in use are gabapentin and pregabalin. Gabapentin is approved for postherpetic neuralgia; and pregabalin is approved for peripheral diabetic neuropathy, postherpetic neuralgia, and fibromyalgia.[37] The effects of other anticonvulsants on chronic pain have been studied but the evidence demonstrating their efficacy is limited.

Common side effects of both gabapentin and pregabalin are somnolence and generalized fatigue; these are usually transient, and can often be managed with appropriate dose initiation and titration. Gabapentin should be initiated at 300 mg/day (usually in 2 to 3 divided doses) and slowly increased by 300 mg every 3 to 5 days to the normal effective dose range of 900 to 1800 mg daily. For older patients and those with renal impairment, the initial dose of gabapentin is typically 100 mg, with subsequent dose increases of 100 mg every 3 to 5 days. Pregabalin is usually initiated at 150 mg/day, 2 to 3 divided doses, and increased to 300 mg/day after the first week. Future dose increases can be considered, in a similar fashion, to a maximum of 600 mg/day. Patients with compromised renal function (creatinine clearance (CrCl) < 60 mL/min) should be limited to a daily maximum dose of 300 mg. Like antidepressants, anticonvulsants, as a class, have been linked with suicidal ideation and behavior; a recent publication specifically linked gabapentin to this risk.[38]

Topical Therapies

Patients with well-localized pain may benefit from the use of topical analgesics. These products can be divided into several main categories: rubefacients, topical NSAIDs, capsaicin, and lidocaine. While rubefacients act through vasodilation to create a warming sensation, capsaicin (although it does create a feeling of heat) acts by depleting substance P.

Capsaicin initially causes excitation of the nociceptors (creating the burning sensation), followed by an insensitive refractory period after repeated applications (product must be applied 3 to 4 times each day). Patients must be warned of the irritant properties associated with capsaicin products and instructed to wash their hands immediately after application.

Randomized, controlled trials with capsaicin have demonstrated its efficacy, when compared with placebo, for both neuropathic and musculoskeletal pain.[39]

Topical salicylate is structurally similar to both aspirin and NSAIDs, but it acts as a rubefacient when applied topically. In the few randomized trials that evaluated topical salicylates for use treating chronic pain, a 50% pain reduction was achieved in 7 to14 days. This is an important counseling point for your patients who may expect a faster effect from these products.[40]

While topical NSAIDs (e.g., ketoprofen, diclofenac, piroxicam) are often used to reduce systemic exposure to a medication, it is important to note that efficacy depends on medication reaching the site of action at concentrations high enough to reduce inflammation, implying at least some systemic absorption. This holds true experimentally: while there is systemic absorption of topically applied NSAIDs, the plasma concentrations are typically less than 5% that of orally administered products. Interestingly, cartilage concentrations are higher with topical use versus that of oral administration.[41] Randomized trials comparing topical with oral NSAIDs for the treatment of chronic pain had similar outcomes at 2 weeks: 37% of subjects achieved a 50% reduction in pain and topical NSAIDs were clearly more effective than placebo for pain relief.[42] There is no evidence that topical NSAIDs share the GI toxicity of oral NSAIDs.

The lidocaine patch offers a useful approach for patients with a variety of chronic well-localized pain conditions. It is the only FDA-approved topical product for treating postherpetic neuralgia. It has also proven effective in a number of pain syndromes besides postherpetic neuralgia. The lidocaine patch has been studied in diabetic neuropathies, low-back pain, and myofascial pain and demonstrated little systemic absorption and few adverse events.

Management

The World Health Organization (WHO) has developed a simple 3-step approach to the management of cancer pain; the WHO pain relief ladder.[32] While the WHO pain treatment process was initially designed to manage patients with cancer pain, this simple and well-validated approach is now commonly employed across all pain populations. This approach provides for the use of simple analgesics, such as acetaminophen or NSAIDs for mild pain and transitions to opioid-based pharmacotherapy for moderate-to-severe pain when appropriate. For pain that does not respond well to traditional pain therapies, the WHO advocates the use of adjuvant analgesics, regardless of pain intensity. While use of the analgesic ladder may be too simplistic for all types of chronic pain, it does provide a useful introduction for the many clinicians who do not specialize in pain management.

Use of acetaminophen to treat chronic pain remains a viable option for many patients with mild pain. The ACR guidelines for the treatment of osteoarthritis lists this as first-line therapy for patients with mild pain.[29] While acetaminophen can be useful, it is not without complications. This is an important consideration, especially since many patients perceive that because it is available OTC, it must be benign. Patients should be counseled each time

they receive a product containing acetaminophen about the risks of unintentional overdose. Since so many OTC and prescription products contain this ingredient, it is easy for a patient to inadvertently exceed the maximum dose. In fact, concern surrounding acetaminophen has been so widespread that the FDA convened a hearing that voted overwhelmingly to include a black-box warning on all prescription products that contain acetaminophen.

The suitability of NSAIDs for chronic pain remains a difficult subject because of the potential for end-organ toxicity. Considering that many patients have significant comorbidities, long-term NSAID use may not be appropriate for many patients, especially older patients who are more prone to experience the adverse effects of NSAIDs.

Opioids have considerable potential to treat persistent, moderate-to-severe pain. They are the mainstay of the WHO pain relief ladder and are also recognized as an option in other treatment guidelines, such as the ACR osteoarthritis guidelines. One of the appealing aspects of this class of medications is that, unlike the other analgesic classes, opioids do not have any end-organ toxicity. Unfortunately, they can cause significant adverse reactions, not the least of which is the potential for substance abuse. Misuse and abuse has become a focus in recent years; the FDA now requires that all new drug applications for long-acting opioids have a risk evaluation and mitigation strategy (REMS).

Ongoing clinical evaluation and management can promote proper opioid use. The Federation of State Medical Boards (FSMB) has published a model policy for the management of chronic pain, which includes opioids and other controlled substances.[43] The central theme of these guidelines is patient assessment, reassessment, and appropriate written documentation of care, including the medication history process. Written treatment plans, along with a record of current and past substance abuse and informed consent (e.g., opioid agreements) are touted as necessary processes for patients using opioids long-term. A key component of success is limiting patients to only receiving opioid prescriptions from one physician and filling prescriptions at one pharmacy. This enhances the patient/practitioner relationship, while decreasing the risk of doc shopping—defined as the situation where a patient gets multiple prescriptions from multiple providers, usually without the others' knowledge. Where prescription-monitoring programs exist on a patient level, clinicians should consider taking advantage of this information.

Summary

Chronic pain is a national health concern that affects each of us. Appropriate pharmacotherapy can help to diminish much of the negative impact chronic pain has on society as a whole. Understanding the multiple factors associated with prescribing any one of the various agents used to treat chronic pain is an essential step in promoting appropriate analgesic use. Regardless of the setting, pharmacists can assist in multiple ways, by providing detailed medication histories, as well as dosing recommendations and drug information. It is essential that pharmacists and other clinicians understand the range of issues associated with these agents and how an interdisciplinary approach to managing drug therapy can improve patient outcomes.

Case

- Mrs. Turner is a female, 63 years of age, who has been patronizing your pharmacy for years. You notice that during the past several months she has been filling prescriptions for propoxyphene/acetaminophen #180 each month. She complains that she has been quite constipated and is still waking up in the middle of the night with pain.
- After talking with Mrs. Turner, you find that she has been having severe low-back pain that interferes with her daily activities. She complains that she is not able to participate in her church choir anymore and that even making it to weekly bingo is becoming difficult. What issues other than chronic pain may be affecting Mrs. Turner?
- Speaking with her primary care physician, you find that Mrs. Turner has been less than forthcoming about her pain to her practitioner — she simply mentioned to Dr. Kaiser that her back "hurts a bit." What patient-specific issues are complicating her therapy?
- Mrs. Turner now returns to your pharmacy with a prescription for both extended-release morphine, 30 mg every 12 hours, and immediate-release morphine,10 mg to be used as needed every 3 to 4 hours. She is concerned about becoming addicted. What is your response?
- Mrs. Turner has had a good response to the morphine but, even though she is using a stimulant laxative, she continues to have constipation. Her friend Irma uses a topical rub for her knee pain, so Mrs. Turner would like to know if there are any topical products that might work for her back pain and allow her to decrease the dose of morphine.

REFERENCES

1. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med.* 2003;349 (20):1943-1953.
2. Berry PH, Covington EC, Dahl JL, et al; for the Editorial advisory board. Pain: current understanding of assessment, management, and treatments. Presented as: Continuing Education sponsored by the American Pain Society and supported by an unrestricted educational grant from the National Pharmaceutical Council. June 2006.
3. Verhaak PF, Kerssens JJ, Dekker J, et al. Prevalence of chronic benign pain disorder among adults: a review of the literature. *Pain.* 1998;77(3):231-239.
4. Parsons S, Breen A, Foster NE, et al. Prevalence and comparative troublesomeness by age of musculoskeletal pain in different body locations. *Family Pract.* 2007;24(4):308-316.
5. Marcus DA. Practical approach to the management of chronic pain. *Compr Ther.* 2005;31(1):40-49.
6. Schmitt P. Rehabilitation of chronic pain: a multidisciplinary approach. *J Rehabil.* 1985;51:72-75.
7. Joint Commission on the Accreditation of Healthcare Organizations (JCAHO). *Pain Assessment and Management: An organizational approach.* Oakbrook Terrace, IL: JCAHO; 2000.
8. National Institutes of Health (NIH). *New Directions in Pain Research.* NIH Web site. http://grants.nih.gov/grants/guide/pa-files/PA-98-102.html. Release date September 4, 1998. Accessed May 6, 2010.

9. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesth Analg.* 2007;105:205-221.
10. Rainov NG, Heidecke V. Experimental therapies for chronic pain. *Acta Neurochir Suppl.* 2007;97(PT 1):473-477.
11. Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. *Clin Orthop Relat Res.* 2004;427(suppl):S6-S15.
12. Brooks P. Inflammation as an important feature of osteoarthritis. *Bull World Health Organ.* 2003;81(9):689-690.
13. Bitton R. The economic burden of osteoarthritis. *Am J Manag Care.* 2009;15(suppl 8):S230-S235.
14. Ehrlich GE. The rise of osteoarthritis. *Bull World Health Organ.* 2003;81(9):630.
15. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33(2):160-172.
16. Pamuk GE, Pamuk ON, Set T, et al. An increased prevalence of fibromyalgia in iron deficiency anemia and thalassemia minor and associated factors. *Clin Rheumatol.* 2008;27(9):1103-1108.
17. Hudson JI, Goldenberg DL, Pope HG Jr, et al. Comorbidity of fibromyalgia with medical and psychiatric disorders. *Am J Med.* 1992;92(4):363-367.
18. Freburger JK, Holmes GM, Agans RP, et al. The rising prevalence of chronic low back pain. *Arch Intern Med.* 2009;169(3):251-258.
19. Melton LJ 3rd, Kan SH, Frye MA, et al. Epidemiology of vertebral fractures in women. *Am J Epidemiol.* 1989;129(5):1000-1011.
20. Dorsey SG, Morton PG. HIV peripheral neuropathy: pathophysiology and clinical implications. *AACN Clin Issues.* 2006;17(1):30-36.
21. Botting RM. Mechanism of action of acetaminophen: is there a cyclooxygenase 3? *Clin Infect Dis.* 2000;31(suppl 5):S202-S210.
22. Kis B, Snipes JA, Busija DW. Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties. *J Pharmacol Exp Ther.* 2005;315(1):1-7.
23. Kis B, Snipes JA, Simandle SA, Busija DW. Acetaminophen-sensitive prostaglandin production in rat cerebral endothelial cells. *Am J Physiol Regul Integr Comp Physiol.* 2005;288(4):R897-R902.
24. Björkman R. Central antinociceptive effects of non-steroidal anti-inflammatory drugs and paracetamol. Experimental studies in the rat. *Acta Anaesthesiol Scand Suppl.*1995;103:1- 44.
25. McCormack K. Non-steroidal anti-inflammatory drugs and spinal nociceptive processing. *Pain.* 1994;59(1):9-43.
26. Miranda HF, Silva E, Pinardi G. Synergy between the antinociceptive effects of morphine and NSAIDs. *Can J Physiol Pharmacol.* 2004;82:(5)331-338.
27. Furst DE. Are there differences among nonsteroidal antiinflammatory drugs? Comparing acetylated salicylates, nonacetylated salicylates, and nonacetylated nonsteroidal antiinflammatory drugs. *Arthritis Rheum.* 1994;37(1):1-9.
28. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs — differences and similarities. *N Engl J Med.* 1991;324(24):1716-1725.

29. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum.* 2000;43(9):1905-1915.
30. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA. 2001;286(8):954-959.
31. Chen YF, Jobanputra P, Barton P, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess.* 2008;12(11):1-278.
32. World Health Organization (WHO). Cancer pain relief: With a guide to opioid availability. 2nd ed. Geneva: World Health Organization; 1996.
33. American Geriatrics Society. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc.* 2009;57(8):1331-1346.
34. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain.*1990;41(3):273-281.
34a. Jackson KC. Pain Management. In: *Boh's Pharmacy Practice Manual: A Guide to the Clinical Experience.* 3rd ed. Susan Stein SM, ed. United States: Lippincott, Williams & Wilkins; 2009.
35. Arnow BA, Hunkeler EM, Blasey CM, et al. Comorbid depression, chronic pain, and disability in primary care. *Psychosom Med.* 2006;68(2):262-268.
36. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med.* 1992;326(19):1250-1256.
36a. Jackson KC 2nd, St. Onge EL. Antidepressant pharmacotherapy: considerations for the pain clinician. *Pain Pract.* 2003;3(2):135–143.
37. Stacey BR. Management of peripheral neuropathic pain. *Am J Phys Med Rehabil.* 2005;84(suppl 3):S4-S16.
38. Patorno E, Bohn RL, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA 2010;303:1401-1409.
39. Mason L, Moore RA, Derry S, et al. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ.* 2004;328(7446):991.
40. Mason L, Moore RA, Edwards JE, et al. Systematic review of efficacy of topical rubefacients containing salicylates for the treatment of acute and chronic pain. *BMJ.* 2004;328(7446):995.
41. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases. a comparison. *Drugs.* 2000;60(3):555-574.
42. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ.* 2004;329(7461):324.
43. The Federation of State Medical Boards of the United States (FSMB). FSMB Web site. *Model Policy for the Use of Controlled Substances for the Treatment of Pain.* http://www.fsmb.org/pdf/2004_grpol_Controlled_Substances.pdf. Issued May 2004. Accessed May 9, 2010.

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