Opioids for Chronic Pain: New Evidence, New Strategies, Safe Prescribing

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ABSTRACT

In the United States, the prevalence and burden of chronic pain is large and still growing. Older adults (aged ≥65 years) make up a large portion of the population with chronic pain, and their presentation, diagnosis, and treatment tends to be more complicated because of age-related physiological changes and comorbidities. Guidelines on treating patients with severe back pain recommend opioids as an option for those who do not find adequate pain relief from acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). For older adult patients at higher risk for NSAID-related adverse effects, such as those who have gastrointestinal or cardiovascular disease, diabetes mellitus, or who are taking low-dose aspirin, opioids are recommended instead. Opioids may also be an appropriate option for patients with neuropathic pain who have not achieved adequate analgesia from maximum doses of first- and second-line antineuropathic agents. Still, opioids are not appropriate for all patients; rather, a differential diagnosis, consideration of other comorbidities, and the potential for opioid-related adverse effects and substance abuse are required to confirm the value of opioid treatment for each individual. For nonresponders to opioid therapy, opioid rotation should be considered before discontinuation is pursued.
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KEYWORDS: Adverse effects; Differential diagnosis; NSAIDs; Older adults; Opioids; Opioid rotation

Chronic pain is a significant problem in the United States. The Institute of Medicine estimated that there were 100 million individuals with pain in the United States in 2011.[1] It is noteworthy, however, that this number does not include patients with acute pain or children with pain. Thus, about one-third of the American adult population experiences chronic pain,[1] based on the current population of approximately 309 million; other sources suggest that a much higher number of Americans, 130 million, have persistent pain.[2] Furthermore, undertreatment of pain is common. The American Academy of Pain Medicine estimates that >4 of 10 patients with moderate-to-severe pain do not get adequate relief from their analgesics, while nearly 1 of 4 patients change health care professionals ≥3 times because of perceptions of suboptimal pain care.[3]

Another concern facing the pain community in the United States is the increase in a segment of the population with a high incidence of pain: the aged. As the "baby boomer" generation reaches age 65 years and older (as of 2011), the demographic distribution of the American population will change significantly (**Figure 1**[4]). By 2020, the portion of the population aged 65 to 74 years is projected to grow 74%, while the portion of the population aged <65 years is projected to grow only 24%.[4] Older adults (aged ≥65 years) have a higher prevalence of chronic pain conditions, lower tolerance for pain, and increased interference from pain in their daily lives.[5,6] Older adults with pain conditions also have very diverse presentations, and pain assessment can be complicated in this population because of reluctance to report pain, cognitive impairment, and communication deficits.[7]

Because of the immensity of the burden of chronic pain, there is a critical need for family physicians and general practitioners to manage patients with chronic pain. Otherwise, in order to manage all Americans with persistent pain, each and every practicing pain specialist in the United
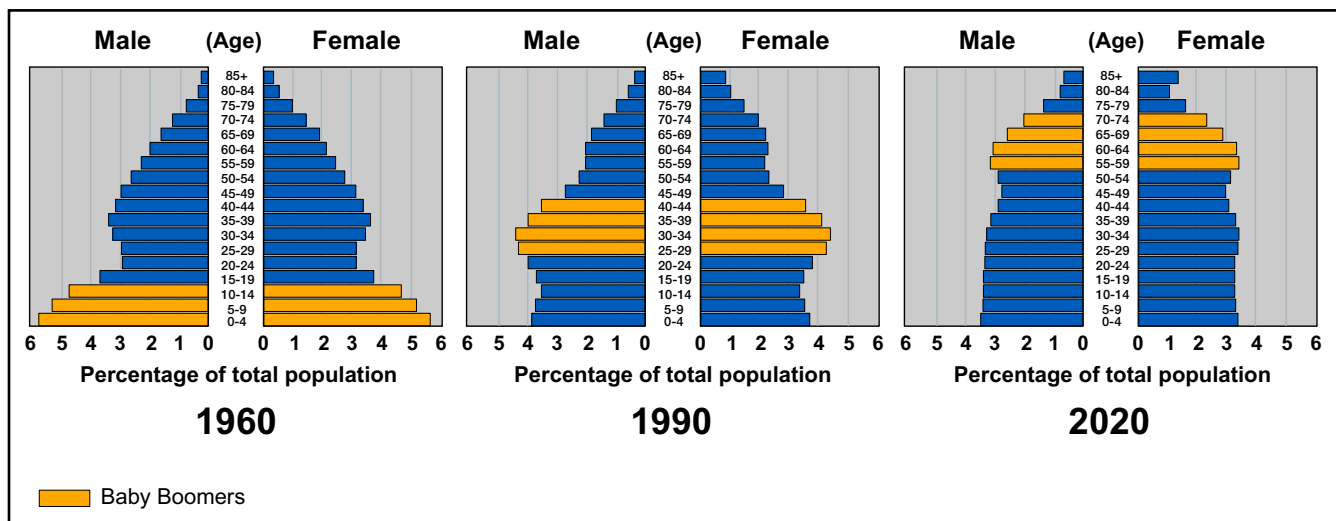
Figure 1   The number of persons (in millions) in the United States aged ≥65 years: 1900–2030.[4]

States would have to treat approximately 21,000 patients. This projected statistic underscores the need for multidisciplinary cooperation in the treatment of chronic pain, with joint efforts by primary care physicians as well as other health care professionals. Toward this end, there have been initiatives by pain societies to educate clinicians regarding the management of chronic pain. For a portion of patients with chronic pain, treatment may need to involve strong analgesics, such as opioids; yet managing the prescription of these controlled substances requires skills not commonly included in routine training curricula. Most recent estimates suggest that only one-fifth of physicians have received medical school training on recognizing drug diversion, and only 20% have received training on identifying signs of addiction or drug abuse.[8] The dearth of family physicians willing to prescribe opioids for noncancer pain will likely become more poignant now that the United States is implementing the Risk Evaluation and Mitigation Strategies (REMS) program for individual long-acting and extended-release opioids. This is because specialty certification for prescribers may be required along with monitoring/registry of patients, in an effort to determine a drug's benefit-to-harm ratio and to minimize risks associated with prescribing controlled substances.[2]

There are several populations with chronic noncancer pain for whom opioid therapy may be appropriate. The bulk of American patients who need relief from persistent, moderate-to-severe pain have back pain conditions (~38 million) or osteoarthritis (~17 million).[9] Coincidentally, the majority of candidates for opioid therapy are the following: (1) patients with chronic low back pain of somatic/mechanical origin who are not responding to nonopioid agents, or patients with chronic low back pain who require a third-line adjuvant when neuropathic pain is present; (2) patients with osteoarthritis who are not responding to acetaminophen and who have a contraindication

for administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 inhibitors; and (3) patients with neuropathic pain who have not achieved adequate analgesia despite treatment with maximum doses of first- and second-line antineuropathic therapies.

TREATMENT RECOMMENDATIONS AND CAVEATS

For patients with severe back pain, the American College of Physicians and the American Pain Society 2007 clinical guidelines recommend opioids, including tramadol, as an option for those who do not gain adequate pain relief from the use of acetaminophen or NSAIDs.[10] Indeed, older adults have further constraints due to changed organ physiology associated with aging. Particularly for older adult patients with gastrointestinal or cardiovascular disease, the use of NSAIDs or COX-2 inhibitors can lead to serious adverse effects.[11] The American Geriatrics Society recommends opioids as an option for these patients at higher risk for NSAID-related adverse effects.[11] A case report in 1985 of 38 patients documented the beginnings of opioid clinical use for nonmalignant persistent pain,[12] and since then, randomized controlled trials have established the efficacy of opioids for managing persistent pain from low back pain, osteoarthritis, and neuropathic pain conditions. Thus, opioids can be a beneficial alternative for older adults with some types of low back pain unresolved by treatment with acetaminophen. A differential diagnosis is required to ascertain the type of back pain a patient has and whether it will likely respond to opioid treatment. In fact, a mechanistic analysis, including a thorough medical history, physical examination, and diagnostic testing, can identify whether the source of low back pain is mechanical, neuropathic, or mixed in origin.

A DIFFERENTIAL DIAGNOSIS OF LOW BACK PAIN

In general, axial mechanical pain is associated with osteoporotic fractures, metastatic bone lesions with or without fractures, internal disc disruption, and ligament tears. Classically, patients with internal disc disruption are young and may or may not have undergone back surgery, but have not found resolution of their pain. These patients with failed back surgery syndrome then often rely on opioids for pain relief. Lateral mechanical pain can result from facet arthropathy, sacroiliac joint dysfunction, fascial strain or injury (myofascial pain), or ligament strain. These patients may present with different patterns of radiating pain, but typically the pain does not spread to below the knee. Both lateral and axial mechanical pains are typically responsive to opioid-based medications, with the exception of myofascial pain. Evidence indicates that opioids do not ameliorate this muscle-related pain, which frequently involves the longissimus thoracis and iliocostalis lumborum, and sometimes the quadratus lumborum. In older adults, strains can also lead to pain due to kyphosis, scoliosis, malpositioning, and/or joint disease. Another frequently misdiagnosed condition involves both low back pain and leg pain due to stress on the piriformis muscle resulting from an inability to sit appropriately in a chair, or in patients with one leg that is shorter than the other. Evaluation of the buttocks region is needed to establish a diagnosis of piriformis syndrome.

Neuropathic-based back pain conditions, such as disc herniation with radiculopathy in which leg pain is involved, generally are not amenable to opioid treatment as a first-line agent, but, as noted before, opioids may be indicated in the short term if the doses of antineuropathic medications have been optimized. Mixed low back pain, such as spinal stenosis associated with osteoarthritis in which there is leg pain below the knee combined with back pain, can be partially responsive to opioids; however, in more severe cases of hypertrophic osteoarthritis, which produces lateral foraminal stenosis due to nerve compression, patients typically will not respond to opioid treatment alone; adjuvant antineuropathic agents will be needed.

Because of the different responses of different types of low back pain to opioids, it is critical to identify the etiology of the pain whenever possible. Furthermore, for all patients presenting with persistent pain, a diagnosis with an appropriate differential is the first step to a "universal precautions" approach to pain management. Universal precautions is a theory borrowed from the infectious disease discipline, wherein realizing the impossibility of reliably assessing the risk of developing drug abusive behaviors or addiction, an appropriate minimum level of caution is applied to all patients being prescribed a controlled substance.[13] An algorithm for establishing the type of low back pain with which a patient is presenting is depicted in **Figure 2**. Regardless, it is important to point out that even if an appropriate evaluation suggests that a patient is a candidate for opioid therapy, an exit strategy is an integral part of every plan. If after 3 to 6 months of opioid titration there is no evidence of clinical efficacy, the opioid should be discontinued. There is
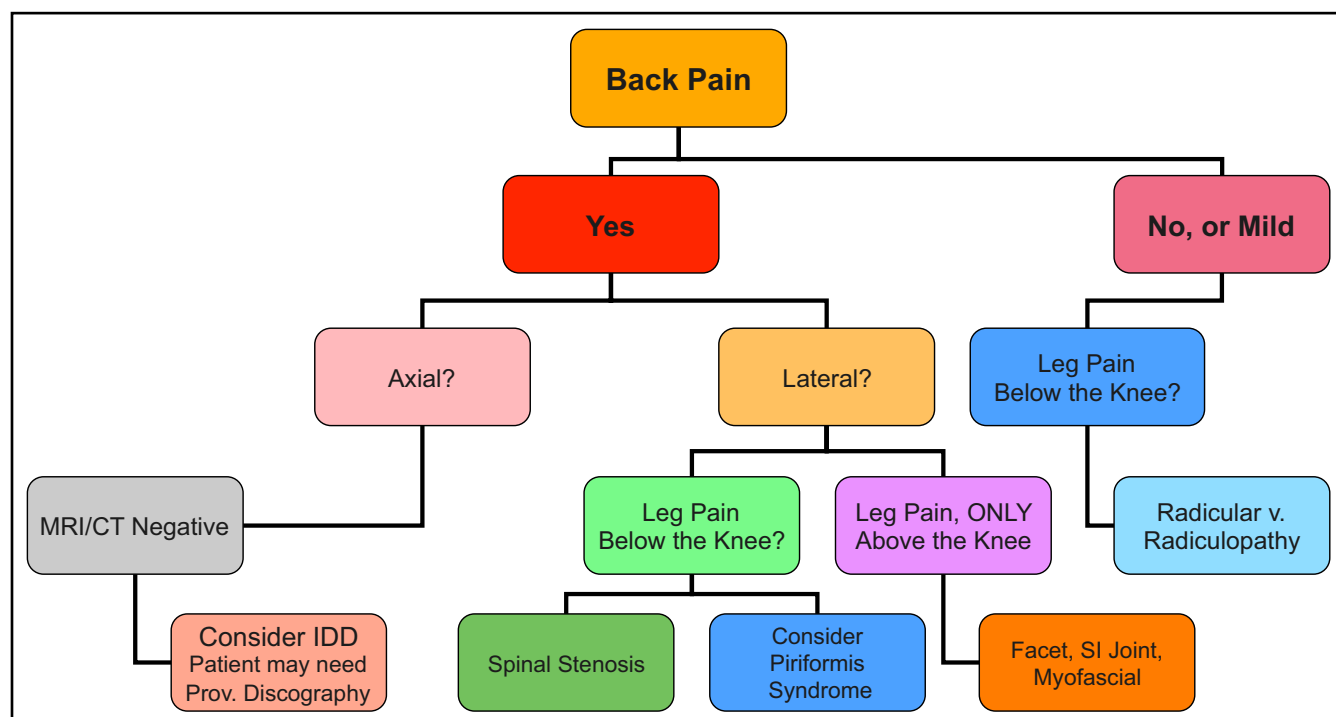

Figure 2   A clinical approach to diagnosing low back pain. CT = computed tomography; IDD = internal disc disruption; MRI = magnetic resonance imaging.

an increased level of awareness among prescribers that opioids may be associated with long-term side effects, as discussed by Dr Brennan in this supplement.[14]

Osteoarthritis is another prevalent condition that leads to moderate-to-severe pain with the potential to be responsive to opioids. Opioids can be an appropriate option for patients with osteoarthritis who have not responded to acetaminophen therapy and who have a contraindication for use of NSAIDs or COX-2 inhibitors. Once again, because of the adverse effects associated with NSAIDs and COX-2 inhibitors, the American Geriatrics Society cautions against using these medications in older persons at risk for cardiovascular and gastrointestinal complications.[11] This group of individuals includes adults with significant renal disease, a history of heart disease, and left ventricular dysfunction. Whereas the risk of developing gastrointestinal bleeding with NSAID use in patients aged ≥65 years is well known and accepted, the increased risk of congestive heart failure with use of NSAIDs in older adults with a history of cardiovascular disease has also been known for 10 years, yet is not always recognized by clinicians.[15,16] A matched case-control study found that the incidence of congestive heart failure in 1023 hospital inpatients studied was higher with increasing age, preexisting heart disease, and the use of piroxicam, naproxen, or tenoxicam, in particular.[15] Compared with participants without heart disease who did not use NSAIDS, the use of NSAIDs by patients with a history of heart disease increased the odds ratio for developing congestive heart failure to 26.3 (95% confidence interval [CI], 5.8-119.1).[15] Also, a large Canadian study of individuals aged ≥66 years showed an increase in the risk of hospital admission for congestive heart failure in participants taking rofecoxib (n = 14,583; adjusted rate ratio, 1.8; 95% CI, 1.5-2.2) or nonselective NSAIDs (n = 5,391; adjusted rate ratio, 1.4; 95% CI, 1.0-1.9) compared with non–NSAID-using controls (n = 100,000; adjusted rate ratio, 1.0).[17] This longitudinal study also included 18,908 participants who took celecoxib; it established that celecoxib use is not associated with a heightened risk of congestive heart failure in older adults (adjusted rate ratio, 1.0; 95% CI, .8-1.3).[17]

Even in patients without significant renal disease or left ventricular dysfunction, however, COX-2 inhibitors can be problematic because of the high risk of thromboembolic phenomena, or when combined with low-dose aspirin. As older adults frequently take minidose aspirin for cardioprotective purposes, this situation poses 2 significant problems. First, the cardioprotective effect of aspirin is mediated through the irreversible acetylation of serine 529 in the enzyme cyclooxygenase, halting the production of thromboxane A_2 in platelets and thereby reducing platelet aggregation.[18] Competitive binding of cyclooxygenase favoring ibuprofen over concomitantly taken aspirin hinders the cardioprotective effect.[18] It is not clear whether this phenomenon also occurs with other NSAIDs, but caution should be exercised until studies with other NSAIDs are available. Furthermore, low-dose aspirin enhances the risk of gastro-

intestinal complications associated with COX-2 inhibitors. The landmark randomized controlled trial by Silverstein and colleagues, which enabled the US Food and Drug Administration (FDA) approval of celecoxib, showed that among nonusers of aspirin, celecoxib users had a statistically significant lower incidence of ulcer complications ($P = .09$) and symptomatic ulcers ($P = .02$) after 6 months than did users of nonspecific NSAIDs.[19] However, among those taking low-dose aspirin, there was no statistically significant difference in gastrointestinal complications and ulcers between COX-2-specific and COX-2-nonspecific NSAIDs, indicating a loss of the gastroprotective effect.[19] Thus, patients who have failed to garner adequate pain relief from acetaminophen and who use low-dose aspirin are another population in whom opioids could be an appropriate option for pain control. Alternatively, a COX-2 inhibitor could be used for pain control with an alternative antiplatelet therapy, but these latter treatments tend to be expensive.

Additionally, patients with a history of diabetes mellitus and evidence of proteinuria, suggesting the presence of glomerular disease, are another population for whom NSAIDs can be detrimental. In this population, NSAID or COX-2 inhibitor use can decrease the blood flow to the kidneys and thus increase the risk of renal failure.[20] Also, in patients receiving treatment with angiotensin-converting enzyme inhibitors to treat arterial hypertension or for afterload-reducing purposes, the use of NSAIDs or COX-2 inhibitors can potentially lead to adverse effects such as hyperkalemia and acute renal failure from critically reduced renal blood flow.[21] Therefore, NSAIDs or COX-2 inhibitors should not be prescribed long term to manage pain in these patients.

Another concern in prescribing drugs for persistent pain is the necessity of managing the potential for drug-drug interactions. Many of the medications used by patients with low back pain and osteoarthritis are metabolized through the cytochrome P450 (CYP) enzyme system—the enzymes responsible for metabolizing 40% to 50% of all medications.[22] Small changes in enzyme activity can cause significant changes in the drug plasma concentrations by prolonging or reducing the half-life of the drug. Specifically, medications that induce or inhibit the CYP3A4 and/or the CYP2D6 enzymes may prolong or reduce the effects of the opioid analgesics—oxycodone, hydrocodone, fentanyl, and methadone[23]—as well as of many antidepressants and neuroleptics.[24,25] For example, CYP3A4 activity is induced by many anticonvulsants (including carbamazepine, oxcarbazepine, phenytoin, and valproic acid) and by caffeine, while grapefruit juice, star fruit, and simvastatin inhibit the enzyme's activity.[26] Inhibitors of CYP2D6 include the serotonin and norepinephrine reuptake inhibitor duloxetine, as well as celecoxib and ritonavir, while dexamethasone is an inducer of the enzyme.[27] Meanwhile, patients who take medications that use or affect the CYP2C9 enzyme pathway may be susceptible to drug-drug interactions with NSAIDs.[28,29] Consequently, in patients receiving medications that induce or inhibit cytochrome P450 enzymes and who also require therapy for moderate-

to-severe persistent pain, use of an opioid not affected by this metabolic pathway may be indicated.[30,31] Opioids in this class include morphine, oxymorphone, hydromorphone, and tapentadol.

Opioids also may be an appropriate option for patients with neuropathic pain who have not achieved adequate analgesia despite treatment optimization with maximum doses of first- and second-line antineuropathic agents, such as anticonvulsants and tricyclic antidepressants/dual re-uptake inhibitors. A systematic review by Eisenberg and colleagues found that intermediate-length (8 days to 8 weeks; median 28 days) randomized controlled trials have demonstrated significant efficacy of opioids over placebo for treating persistent nonmalignant neuropathic pain, likely indicating clinical relevance.[32] The American Academy of Neurology has included opioids as a first-line medication for a specific type of neuropathic pain: postherpetic neuralgia (PHN).[33] The full list of recommended first-line therapies for PHN is as follows: gabapentin, lidocaine patch 5%, oxycodone and morphine sulfate controlled-release, pregabalin, and tricyclic antidepressants.[33] These recommendations are in agreement with an algorithm for treating neuropathic pain constructed by experts and published in the journal *Pain*.[34] Therein, tricyclic antidepressants, opioids, gabapentin, and pregabalin are recommended for relieving peripheral neuropathic pain, and the lidocaine patch is recommended for treating PHN based on numbers-needed-to-treat data. Furthermore, a Neuropathic Pain Special Interest Group under the auspices of the International Association for the Study of Pain (IASP) published evidence-based guidelines echoing the other 2 sets of recommendations, wherein the previous therapies were suggested along with dual reuptake inhibitors of serotonin and norepinephrine.[35]

Positron emission tomography of patients being given experimentally induced painful stimuli has also provided important evidence that opioids do indeed target regions of the brain involved in processing pain.[36] Previous studies identified the brain structures activated by pain; these same cerebral structures had normalization of blood flow and decreased activation with increasing opioid doses in the face of a painful stimulus.[36]

Still, recent studies have questioned the efficacy of long-term opioid therapy for treatment of pain. Current data suggest that opioids have a "limited effect"; for treating back pain, as much as 50% of opioid-naive patients placed on potent opioids report no change or worsening of their chronic pain.[37] In fact, approximately 10% to 30% of patients randomized to opioids in primarily short-term clinical trials (most studies were <4 weeks in length, although some were as long as 24 months including an open-label extension period) withdrew because of lack of efficacy or the development of severe side effects.[38,39] Subsequent to those literature reviews, Martell and colleagues published an analysis suggesting that opioids are used commonly for chronic low back pain, but long-term data support its efficacy for only 16 weeks of use.[40] Indeed, this review assessed 4 studies on the efficacy of opioids compared with placebo or

a nonopioid control and found no evidence of reduced pain with opioids, as judged by the Visual Analog Scale for pain; measures of psychosocial functioning or quality of life, however, were not considered—a notable shortcoming of the literature analysis. Meta-analysis of the 5 studies directly comparing the efficacy of various opioids demonstrated a nonsignificant reduction in pain from baseline.[40] In this review, significant issues with substance abuse and aberrant drug-taking behaviors also limited the benefit of opioid therapy in the low back pain population studied. Therein, the prevalence of lifetime substance use disorders ranged from 36% to 56% and current substance use disorders were estimated to be as high as 43%.[40] Aberrant medication-taking behaviors ranged from 5% to 24%. Such information highlights the fact that opioids are not appropriate for all patients; rather, a differential diagnosis and consideration of other comorbidities are required to confirm the value of opioid treatment for each individual patient with moderate-to-severe persistent pain.

CLINICAL IMPLEMENTATION OF OPIOID THERAPY

In 1998 the Federation of State Medical Boards (FSMB) of the United States published a set of guidelines for prescribing controlled substances for persistent pain; the guidelines were revised in 2005.[41] As of the end of 2010, 24 state medical boards have adopted all or part of the FSMB *Model Policy* for their own.[42] In the FSMB *Model Policy,* opioids are recognized as an essential tool in the armamentarium for relieving pain; equally important is the imperative to minimize the misuse and abuse of these controlled substances, so as not to pose a threat to society.[41] In line with a universal precautions approach, the guidelines recommend a thorough evaluation of each new patient with a complaint of pain, involving documentation of pain characteristics, disease characteristics, comorbidities, functional deficits, and substance abuse or lack thereof by consideration of medical history, physical examination, diagnostic and laboratory results, and other evaluations. From this information, a treatment plan is developed, recorded, and discussed with the patient before informed consent is gathered. It is notably important to construct a pain management program for patients that addresses pain as well as other pain-related issues, and includes services such as psychological support, physical therapy, and rehabilitative therapy. Then, an agreement for treatment is agreed upon and signed by the patient and the physician; all these documents are archived, along with the details of the initial evaluation, subsequent treatment, and ongoing care and monitoring.

There is no pathognomonic sign of a substance abuse disorder; rather, most often, addiction diagnoses must be made by careful observation over time. Furthermore, because pain and addiction can coexist, there are risks associated with prescribing opioids, as addressed in the recommendations of the FSMB's *Model Policy*. A universal precautions approach to pain medicine involves a thorough

inquiry about drug and alcohol history for every patient considered for opioid therapy. Tools such as the Opioid Risk Tool (ORT) and the Screener and Opioid Assessment for Patients with Pain Revised (SOAPP-R) can be useful in helping to gauge a patient's risk of drug misuse or abuse.[43,44]

A savvy universal precautions management approach involves establishing reasonable limits before the outset of therapy, because boundary-setting can assist in identifying and controlling problematic opioid use.[13] Most commonly, problematic use involves a patient unilaterally increasing his or her dose. Notably, it is easier to loosen limits than to make them more restrictive; still, the limits should be reasonable so that a patient is able to adhere to them over the long term. Although treatment agreements are not contracts, they can be a very effective means of recording patient and physician expectations regarding treatment, thereby establishing boundaries. Toward this end, treatment agreements should be readable, reasonable, and flexible. Also, a scheme for managing repeated or serious aberrant drug-taking behaviors should be established before treatment initiation so that patients in these circumstances can receive needed referrals or consultations, such as to an addiction medicine specialist. Although a 2010 synthesis of the literature on treatment agreements found that little evidence supports their use in clinical practice for managing drug misuse in patients with chronic pain,[45] treatment agreements are included in virtually all clinical guidelines on opioid treatment and are quickly becoming the standard of care in pain management.

The current clinical approach for implementing opioid therapy once a trial of opioid therapy has been decided on begins by cautiously titrating the dose to an adequate effect.[46] Once a therapeutic drug dose is established, then ongoing screening and monitoring play important roles in minimizing misuse and diversion in patients with persistent pain who are taking opioids. Appropriate monitoring can involve random urine drug testing, pill counts, implementation of interval dispensing—wherein the prescribing interval is tightened (eg, a prescription is written for a month but dispensed in weekly allotments), and contingency dispensing—wherein, for example, a patient is required to attend a referral appointment or leave a urine drug specimen in order to receive the opioid prescription. Urine drug testing is anything but uniform in the compounds tested for, sensitivity of the assay, or interpretation of the results[45]; this, however, can be ameliorated by establishing a good working relationship with a reliable laboratory. Importantly, urine drug screens are one way to identify and document drug abuse or diversion even among patients not exhibiting aberrant drug behaviors, and these tests have been recommended in some clinical guidelines on opioid prescribing.[41,47,48]

Good practice in pain management should also involve adhering to federal and state government-based regulatory policies, prescribing and dispensing opioids according to guidelines of established pharmacy and medical organizations, and participating in prescription drug monitoring programs (PDMPs). A 2004 study concluded that PDMPs reduce diversion, but PDMPs are highly variable from state to state in the information gathered and the access physicians have to the information.[49] Regularly, each case should be reviewed to assess treatment efficacy and tolerability as per state requirements (which vary in periodicity). A universal precautions approach to reevaluation of the patient suggests regular assessment of pain levels, as well as the amount of pain relief (analgesia), activities of daily living (psychosocial functioning), adverse effects, aberrant behaviors, and psychological functioning (affect/presence of addictive disorders)—collectively called "The Five A's."[13,50] Periodic reassessments keep the treating physician current with a patient's potentially evolving pain disease or comorbidity, and enable him or her to take advantage of new developments in diagnostic testing. Then, if needed, the treatment plan is adjusted to optimize analgesia and functioning, or to address new or evolving pain comorbidities, such as drug misuse, depression, and sleep disturbance.

In the face of a nonresponse to treatment, the opioid can be substituted with a different opioid, otherwise known as opioid rotation. Theoretically, opioid rotation takes advantage of individual differences in the presence and expression pattern of opioid receptor subtypes, for which each opioid has a different preference.[51] Empirically, opioid rotation has been shown to improve pain control and/or lessen the side-effect burden.[52,53] Opioid rotation involves a calculation of the dose of a new opioid based on equianalgesic equivalencies, followed by further dose adjustments as necessary to account for potency differences between opioids, as well as interindividual differences between patients and pain/disease characteristics.[54]

If adequate pain relief with tolerable side effects, if any, is not attained after several increases in the opioid dose over a period of 3 to 6 months, opioid therapy is discontinued.[46] Several guidelines supporting the use of opioid therapy developed by the American Society of Interventional Pain Physicians,[49] The British Pain Society,[55] the European Federation of Chapters of the International Association for the Study of Pain,[56] The Canadian Pain Society,[57] and The Australian Pain Society[58] detail reasons for the discontinuation of opioid therapy, such as failure to achieve adequate analgesia or functional improvements, immitigable and intolerable adverse effects, failure to adhere to the patient-physician treatment agreement or continuing nonadherence, and serious or repeated aberrant drug-related behaviors or diversion. These guidelines, however, do not outline exit strategies for ending opioid therapy. When a patient is released from care because of aberrant drug-related issues, a contingency plan for management must be implemented, because the patient still presents a problem to the community and to himself or herself. The 2009 guidelines developed collaboratively by the American Pain Society and the American Academy of Pain Medicine mention approaches for discontinuing opioids, including tapering the dose by 10% per week, or more rapidly by reducing the dose either 25% or 50% every few days, but, owing to "insufficient evidence," refrain from recommending a specific strategy.[47] In the 2010 update of the original 2003 US Department of

Table 1   Specific Recommendations on Opioid Discontinuation From the US Department of Veterans Affairs (VA) and the Department of Defense (DoD) Guidelines

Protocol for Tapering

- Taper by 20%–50% per week [of original dose], for patients who are not addicted. The goal is to minimize adverse/withdrawal effects.
- The rapid detoxification literature indicates that a patient needs 20% of the previous day's dose to prevent withdrawal symptoms.
- Decisions regarding tapering schedule should be made on an individual basis. Sometimes faster or slower tapering may be warranted.
- Some experts suggest that the longer the person has been on opioids, the slower the taper should be.
- Remain engaged with the patient throughout the tapering process, and provide psychosocial support as needed.
- Consider using adjuvant agents such as antidepressants to manage irritability and sleep disturbance, or antiepileptics for neuropathic pain.
- Do not treat withdrawal symptoms with opioids or benzodiazepines after discontinuing opioids.

Recommendations

1. Decisions regarding tapering schedule should be made on an individual basis. Sometimes faster or slower tapering may be warranted.
2. For those patients who are at high risk of aberrant behaviors (parasuicidal acts, dealing/selling medications, or those with severe impulse control disorders), tapering opioid in a primary care setting is not appropriate, and they should be referred to an addiction or pain specialist with expertise dealing with difficult cases.
3. Patients with complicated withdrawal symptoms should be referred to a pain specialist or a center specializing in withdrawal treatment.
4. Patients being tapered owing to development of addiction should be referred for substance use disorder treatment. Opioid detoxification in a primary care setting followed by ongoing substance use treatment may be appropriate.
5. Complete evaluation of treatment, comorbidity, psychological condition, and other relevant factors should be completed prior to the initiation of the taper.
6. Clear written and verbal instructions should be given to patients/family to educate them about the slow taper protocol that will minimize abstinence (withdrawal) syndromes.
7. Patients who are unable to tolerate the taper as described should be considered for referral to, or consultation with, a pain specialist, substance use specialist, or other expert.

Adapted from *VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain.*[47]

Veterans Health Administration and Department of Defense guidelines on prescribing opioids for chronic pain, however, methods for discontinuing opioid therapy have been detailed along with case examples (**Table 1**).[47] It is noteworthy that in the process of withdrawing opioids from a patient's drug regimen, the initial decrease is generally achieved without much problem. But once low doses are reached, a protracted course is to be expected, particularly in patients who have received long-term treatment with opioids.

SUMMARY

Opioids are a viable treatment alternative in patients with pain unrelated to cancer, particularly for those with contraindications for taking COX-2 inhibitors or NSAIDs. Recent data suggest that opioids may be useful in the treatment of neuropathic pain as a second-line agent and even as a first-line agent in select clinical circumstances.[35] One must be aware, however, of the pitfalls in the use of opioids, including adverse effects and other complications. To improve outcomes and manage risks associated with prescribing opioids, universal precautions should be implemented for each individual patient, and boundaries should be established regarding medication use. The development of aberrant behaviors should be noted and acted upon in a patient-

centered fashion, such as by contingency dosing. Before pursuing discontinuation in nonresponders to opioid therapy, prescribers should consider opioid rotation. An exit strategy should always be an element of any treatment plan involving controlled substances.

AUTHOR DISCLOSURES

The author of this article has no industry relationships to disclose.

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References

1. Committee on Advancing Pain Research, Care, and Education, Board on Health Sciences Policy, Institute of Medicine of the National Academies. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* Washington, DC: The National Academies Press; 2011. http://www.nap.edu/catalog.php?record_id=13172. Accessed May 25, 2012.
2. Fishbain D, Johnson S, Webster L, Greene L, Faysal J. Review of regulatory programs and new opioid technologies in chronic pain

management: balancing the risk of medication abuse with medical need. *J Manag Care Pharm*. 2010;16:276-287.

3. American Academy of Pain Medicine, American Pain Society, Janssen Pharmaceutica. "Chronic Pain in America: Roadblocks to Relief," a study conducted by Roper Starch Worldwide for American Academy of Pain Medicine, American Pain Society, and Janssen Pharmaceutica. Hanson, NY: Roper Starch Worldwide, 1999.

4. National Institute on Aging, US Department of Commerce, Economics and Statistics Administration, United States Census Bureau. *Aging in the United States—Past, Present, and Future*. Washington, DC: US Department of Commerce. http://www.census.gov/population/international/files/97agewc.pdf. Accessed July 31, 2012.

5. Thomas E, Peat G, Harris L, Wilkie R, Croft PR. The prevalence of pain and pain interference in a general population of older adults: cross-sectional findings from the North Staffordshire Osteoarthritis Project (NorStOP). *Pain*. 2004;110:361-368.

6. Cole LJ, Farrell MJ, Gibson SJ, Egan, GF. Age-related differences in pain sensitivity and regional brain activity evoked by noxious pressure. *Neurobiol Aging*. 2010;31:494-503.

7. Fine PG. Chronic pain management in older adults: special considerations. *J Pain Symptom Manage*. 2009;38(suppl):S4-S14.

8. The National Center on Addiction and Substance Abuse at Columbia University. *Under the Counter: The Diversion and Abuse of Controlled Prescription Drugs in the U.S*. New York, NY: The National Center on Addiction and Substance Abuse at Columbia University; July 2005.

9. Seget S. *Pain Management: World Prescription Drug Markets*. New York, NY: PJB Publications USA Inc; 2003.

10. Chou R, Qaseem A, Snow V, et al, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians, American College of Physicians, and the American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007;147:478-491.

11. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57:1331-1346.

12. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain*. 1986;25:171-186.

13. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med*. 2005;6:107-112.

14. Brennan MJ. The effect of opioid therapy on endocrine function. *Am J Med*. 2013;126:S12-S18.

15. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. *Arch Intern Med*. 2000;160:777-784.

16. Merlo J, Broms K, Lindblad U, et al. Association of outpatient utilisation of non-steroidal anti-inflammatory drugs and hospitalised heart failure in the entire Swedish population. *Eur J Clin Pharmacol*. 2001;57:71-75.

17. Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet*, 2004;363(9423):1751-1756.

18. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345:1809-1817.

19. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. [Celecoxib Long-term Arthritis Safety Study.] *JAMA*. 2000;284:1247-1255.

20. Henao J, Hisamuddin I, Nzerue CM, Vasandani G, Hewan-Lowe K. Celecoxib-induced acute interstitial nephritis. *Am J Kidney Dis*. 2002; 39:1313-1317.

21. Rogulj D, Hauptfeld M, Iskra MS, Zorko VK, Strasek M. Extreme hyperkalaemia caused by concomitant use of a NSAID and an ACE inhibitor in an elderly patient. *Arh Hig Rada Toksikol*. 2010;61:241-245.

22. Rogers JF, Nafziger AN, Bertino JS Jr. Pharmacogenetics affects dosing, efficacy, and toxicity of cytochrome P450-metabolized drugs. *Am J Med*. 2002;113:746-750.

23. Smith HS. Opioid metabolism. *Mayo Clin Proc*. 2009;84:613-624.

24. Bijl MJ, Visser LE, Hofman A, et al. Influence of the CYP2D6*4 polymorphism on dose, switching and discontinuation of antidepressants. *Br J Clin Pharmacol*. 2008;65:558-564.

25. Bertilsson L. Metabolism of antidepressant and neuroleptic drugs by cytochrome P450s: clinical and interethnic aspects. *Clin Pharmacol Ther*. 2007;82:606-609.

26. Zhou SF, Xue CC, Yu XQ, Li C, Wang G. Clinically important drug interactions potentially involving mechanism-based inhibition of cytochrome P450 3A4 and the role of therapeutic drug monitoring. *Ther Drug Monit*. 2007;29:687-710.

27. Flockhart DA. P450 Drug Interaction Table. Updated January 25, 2012. Indianapolis, IN: Indiana University School of Medicine, Division of Clinical Pharmacology. http://medicine.iupui.edu/clinpharm/ddis/table.aspx. Accessed June 10, 2012.

28. Pilotto A, Seripa D, Franceschi M, et al. Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: role of cytochrome P450 2C9 polymorphisms. *Gastroenterology*. 2007;133:465-471.

29. Zi J, Liu D, Ma P, et al. Effects of CYP2C9*3 and CYP2C9*13 on diclofenac metabolism and inhibition-based drug-drug interactions. *Drug Metab Pharmacokinet*. 2010;25:343-350.

30. Prommer E. Oxymorphone: a review. *Support Care Cancer*. 2006;14: 109-115.

31. Kadiev E, Patel V, Rad P, et al. Role of pharmacogenetics in variable response to drugs: focus on opioids. *Expert Opin Drug Metab Toxicol*. 2008;4:77-91.

32. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. *JAMA*. 2005;293:3043-3052.

33. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H, for the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of postherpetic neuralgia. An evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004;63:959-965.

34. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain*. 2005;118:289-305.

35. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132:237-251.

36. Wagner KJ, Sprenger T, Kochs EF, Tolle TR, Valet M, Willoch F. Imaging human cerebral pain modulation by dose-dependent opioid analgesia: a positron emission tomography activation study using remifentanil. *Anesthesiology*. 2007;106:548-556.

37. Allan L, Richarz U, Simpson K, Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. *Spine (Phila Pa 1976)*. 2005;30:2484-2490.

38. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004; 112:372-380.

39. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther*. 2005;7:R1046-R1051.

40. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007;146:116-127.

41. Federation of State Medical Boards of the United States, Inc. Model policy for the use of controlled substances for the treatment of pain. *J Pain Palliat Care Pharmacother*. 2005;19:73-78.

42. Federation of State Medical Boards. (2010). Advocacy, Government Affairs & Policy. Pain Policy Resource Center. http://www.fsmb.org/grpol_links.html. Accessed January 21, 2011.

43. Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009;10:131-146.

44. Butler SF, Budman SH, Fernandez KC, Fanciullo GJ, Jamison RN. Cross-Validation of a Screener to Predict Opioid Misuse in Chronic Pain Patients (SOAPP-R). *J Addict Med*. 2009;3:66-73.

45. Starrels JL, Becker WC, Alford DP, Kapoor A, Williams AR, Turner BJ. Systematic review: treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. *Ann Intern Med*. 2010;152:712-720.

46. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003;349:1943-1953.

47. The Management of Opioid Therapy for Chronic Pain Working Group. *VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain*. [VA/DoD Evidence Based Practice Guideline.] Washington, DC: US Department of Veterans Affairs, Department of Defense; May 2010.

48. Chou R, Fanciullo GJ, Fine PG, et al, for the American Pain Society– American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain. *J Pain*. 2009;10:113-130.

49. Trescot AM, Boswell MV, Atluri SL, et al. Opioid guidelines in the management of chronic non-cancer pain. *Pain Physician*. 2006;9:1-39.

50. Passik SD, Kirsh KL. Assessing aberrant drug-taking behaviors in the patient with chronic pain. *Curr Pain Headache Rep*. 2004;8:289-294.

51. Fine PG, Portenoy RK. Strategies for opioid rotation: decision support in chronic pain management. MedScape Education. Release Date: March 30, 2010. http://cme.medscape.com/viewarticle/717832. Accessed March 30, 2010.

52. Thomse AB, Becker N, Eriksen J. Opioid rotation in chronic non-malignant pain patients: a retrospective study. *Acta Anaesthesiol Scand*. 1999;43:918-923.

53. Quang-Cantagrel ND, Wallace MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review. *Anesth Analg*. 2000;90:933-937.

54. Fine PG, Portenoy RK, for the Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation. Establishing "best practices" for opioid rotation: conclusions of an expert panel. *J Pain Symptom Manage*. 2009;38:418-425.

55. The British Pain Society. *The British Pain Society's Opioids for Persistent Pain: Good Practice: A Consensus Statement Prepared on Behalf of the British Pain Society, the Faculty of Pain Medicine of the Royal College of Anaesthetists, the Royal College of General Practitioners and the Faculty of Addictions of the Royal College of Psychiatrists*. London, England: The British Pain Society; January 2010. http://www.britishpainsociety.org/pub_professional.htm#opioids. Accessed June 10, 2012.

56. Kalso E, Allan L, Dellemijn PL, et al. Recommendations for using opioids in chronic non-cancer pain. *Eur J Pain*. 2003;7:381-386.

57. Jovey RD, Ennis J, Gardner-Nix J, et al, for the Canadian Pain Society. Use of opioid analgesics for the treatment of chronic noncancer pain—a consensus statement and guidelines from the Canadian Pain Society, 2002. *Pain Res Manag*. 2003;8(suppl A):3A-28A.

58. Graziotti PJ, Goucke CR. The use of oral opioids in patients with chronic non-cancer pain: management strategies. *Med J Aust*. 1997; 167:30-34.