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Rational use of opioid analgesics in chronic musculoskeletal pain

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Dr Schneider, a specialist in pain management and addiction medicine in Tucson, is the author of Living With Chronic Pain (2009, 2nd ed). For this article, she has updated her discussion of treatment with opioids that first appeared in 2006 in The Journal of Musculoskeletal Medicine.

ABSTRACT: *Opioid analgesics are used routinely in managing acute musculoskeletal pain. However, physicians often hesitate to use them for chronic pain, such as that seen in rheumatoid arthritis, osteoarthritis, osteoporosis, and low back pain. Starting the patient at a low dose and progressively titrating upward for pain relief minimizes the adverse effects. The fear that prescribing opioid analgesics for chronic pain will engender addiction is not supported by experience. Opioid analgesics are not first-line therapy for chronic pain; they should be used with other medications, such as nonopioid analgesics, anti-inflammatory drugs, muscle relaxants, antidepressants, anticonvulsants, topical preparations, and sleeping pills. A comprehensive patient assessment and an addiction history are essential. Consultation with a specialist in pain management often is helpful. (J Musculoskel Med. 2010;27:142-148)*

Throughout history, various forms of morphine have been the most effective medications in relieving pain. Opioid analgesics—the natural, semisynthetic, and synthetic derivatives of morphine—are used routinely in the management of acute musculoskeletal pain. However, myths and misunderstandings about these drugs often prevent primary care physicians from prescribing them for chronic pain, such as that seen in common musculoskeletal conditions (eg, rheumatoid arthritis, osteoarthritis [OA], osteoporosis, and low back pain [LBP]). Although pain is one of the most common symptoms that bring patients to the physician's office, those with chronic musculoskeletal or other noncancer pain all too often are undertreated.

In many cases, the use of opioid analgesics for patients with chronic musculoskeletal pain is a legitimate treatment approach, and it is gaining acceptance in the medical community. Although some reports question the efficacy of long-term use of opioid analgesics in improving function,¹ several randomized controlled trials of these agents showed at least a 30% reduction in pain.² Although these medications are effective, physicians tend to underuse them because they lack knowledge about them and about addiction. They also fear regulatory scrutiny.

In this article, I review the properties and adverse effects of opioid analgesics and describe the differences between physical dependency and addiction. I discuss how to assess patients who have chronic pain, determine the safety and appropriateness of treating them with these agents, and monitor them on a regular basis.

EFFECTS AND EFFECTS AND ADVERSE EFFECTS

Opioid analgesics exert their effects by binding to μ , κ , and δ receptors in the CNS (brain and spinal cord), the GI tract and, to a lesser extent, the peripheral tissues. They counteract pain signals ascending to the brain. Pain relief is their desired effect, but they also have adverse effects (eg, nausea, sedation, and constipation).

Starting the patient at a low dose and progressively titrating upward for pain relief minimizes the adverse effects while permitting development of tolerance (the need for an increased dose to achieve the same adverse effect or a diminished effect with the same dose) to the nauseating and sedating effects. Tolerance to nausea and sedation (and its extreme, respiratory depression) is desirable, but there is no tolerance to the constipating effect of opioid analgesics. Therefore, it is important for the patient to maintain a bowel regimen (stool softener, bowel stimulant, fluids, and activity) for as long as an opioid analgesic is being taken.

Tolerance to the pain-relieving effects of opioid analgesics is uncommon. Once titrated to an effective pain-relieving dose, most patients continue taking the same or a similar dose for long periods.³⁻⁵ Pain specialist Russell Portenoy, MD,⁶ wrote, “Contrary to conventional thinking, the development of analgesic tolerance appears to be a rare cause of failure of long-term opioid therapy.”

Although there is some evidence to indicate that long-term exposure to high doses of opioid analgesics results in hyperalgesia (increased pain sensitivity),⁷ this is rarely of clinical significance. Most often, a request for an increased dose reflects increased physical activity, a worsening physical problem, or deterioration in the patient’s psychological status (eg, depression).

An often unappreciated adverse effect of long-term opioid analgesic use is lowered sex hormone levels in men. In those who are taking significant doses of opioid analgesics long-term, subnormal testosterone levels are the rule rather than the exception.⁸

Plan on checking total and free testosterone levels in all men who are taking moderate to high doses of opioid analgesics. Many will need testosterone replacement, preferably with patches or transdermal preparations. It is wise to also monitor their prostate-specific antigen levels.

I recommend checking testosterone levels even in asymptomatic patients. Untreated hypotestosteronism can lead to osteoporosis in men, as well as decreased muscle strength.

Some patients taking morphine experience itching. Morphine is more likely than other opioid analgesics to cause histamine release and pruritus. If antihistamines do not provide enough relief, switching to another opioid analgesic may be the answer.

There is no accepted upper limit of safety for opioid analgesics. Because of genetic differences and varying pathology, there are enormous differences in patients in the amount of opioid analgesics they need for adequate pain relief. Historically, some patients with cancer have required grams of morphine. For many patients, however, 5 mg of hydrocodone (in Vicodin or Lorcet) provides adequate pain relief.

As long as the dose is started low and increased gradually, large doses may be taken and are limited only by adverse effects. Unlike acetaminophen, aspirin, and many other drugs, opioid analgesics do not have any specific organ toxicity. Thus, the right dose is the one that provides adequate pain relief without unacceptable adverse effects.

Typically, it takes 3 to 7 days for the body to overcome sedation produced by opioid analgesics. Thus, it is wise for patients to avoid driving when they begin to take these drugs and when they increase the dose. Once patients are taking a stable dose and feel alert, generally it is safe to drive because they have adequate psychomotor functioning.⁹⁻¹¹ Of course, it is wise to avoid using alcohol and benzodiazepines before driving, because they are likely to increase any sedative effects of opioid analgesics.

Opioid analgesics are significantly safer than NSAIDs; they are not associated with upper GI bleeding or renal toxicity. This may be particularly important in older patients who are at risk for the GI and renal toxicity of NSAIDs.

PHYSICAL DEPENDENCY VERSUS ADDICTION

Many physicians and laypersons believe that anyone who is taking opioid analgesics long-term becomes addicted. This misunderstanding results from confusion with the concepts of physical dependency and addiction.

Physical dependency

This is a form of physiological adaptation to the continuous presence of certain drugs in the body. Abrupt discontinuation of the drug after the body has become accustomed to it results in a predictable withdrawal syndrome. For opioid analgesics, this may include anxiety, irritability, goose bumps, salivation, lacrimation, rhinorrhea, diaphoresis, nausea and vomiting, abdominal cramps, and insomnia.

Withdrawal from morphine begins at 6 to 12 hours after last use and peaks at 1 to 3 days. The symptoms associated with longer-acting opioids, such as methadone, have a slower onset and are less severe than those with shorter-acting drugs, such as morphine and hydromorphone. Withdrawal symptoms may be avoided by tapering the drug over days.

Patients who take opioid analgesics for more than a few days should be considered physically dependent. The patient should be cautioned to avoid stopping the opioid suddenly because withdrawal symptoms may appear. Even if pain stops totally, the medication should be tapered. Opioid withdrawal is not dangerous, but it can be very uncomfortable.

A patient's physical dependence on an opioid analgesic is a physiological state in which abrupt cessation of it or administration of an opioid antagonist results in a withdrawal syndrome, according to the American Society of Addiction Medicine.¹² It is expected in all persons in the presence of continuous use of opioids for therapeutic or nontherapeutic purposes and does not, in and of itself, imply addiction.

Corticosteroids are another class of drugs that produce physical dependency. The corollary, known by all physicians, is that when corticosteroids are stopped after ongoing use, they should be tapered rather than stopped abruptly. The same is true of opioid analgesics.

Addiction

This is a psychological and behavioral disorder characterized by the presence of all 3 of the following:

- Loss of control (compulsive use).
- Continuation despite experiencing adverse consequences.
- Obsession or preoccupation with obtaining and using the drug or other substance.¹³

As an addiction advances, the person's life becomes progressively more constricted. The addiction becomes the addict's top priority, and relationships with family and friends suffer. The addict's mental interior becomes filled with preoccupation about the drug. Other activities are given up. Life revolves around obtaining and using the drug. This constriction distinguishes use of a drug by an addict from its appropriate use by a patient who has chronic pain.

In the medical setting, a patient who is addicted to drugs will show some of the following signs:

- Unreliable drug-taking behavior.* The patient does not take the medication as prescribed and makes changes without consulting the physician. He or she takes the drug on a different schedule; may combine it with other, nonprescribed drugs; and, despite admonitions to discuss any changes with the physician in advance, repeatedly reports changes after the fact. The patient "borrows" prescribed opioid medications from friends and family or gives their medications to others.
- Loss of control over drug use.* The patient repeatedly uses up the drug before the time for the next refill. If asked to bring in partly used medication containers for a pill count, instead the patient makes excuses.
- Drug-seeking behavior.* In the context of chronic pain, this does not refer to simply wanting the drug. Rather, the patient frequently requests early refills by offering a host of creative reasons (eg, the medication was stolen, was left on the bus, fell down the sink, or was eaten by the dog). The patient obtains prescriptions from various doctors and has them filled at multiple pharmacies. He may visit several emergency departments to obtain opioid drugs rather than consult his physician.
- Abuse of drugs other than the prescription drugs.* The patient may be using marijuana, cocaine, and other illegal drugs or may be using alcohol or sedative/hypnotic drugs excessively.
- Contact with the street drug culture.* The patient sells his prescription drug or buys and uses street drugs.

Clinicians who are uncomfortable prescribing opioid analgesics probably have patients who keep requesting more medication and seem preoccupied with the quantity being prescribed. These patients often are stigmatized with the label of "drug seeker." The real problem may be that the pain management is inadequate. Once a sufficient dose of opioid analgesic is prescribed, this phenomenon—termed "pseudoaddiction"—vanishes.

Does prescribing opioid analgesics for pain lead to addiction? The fear that prescribing them for chronic pain will engender iatrogenic addiction is not supported by experience. Addiction to opioid analgesics in patients who do not have a history of addiction rarely results from long-term opioid treatment for pain.^{3,14}

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Several screening tests now available to help determine a patient's risk of abusing opioids include the Opioid Risk Tool (ORT)¹⁵ and the Screener and Opioid Assessment for Pain Patients (SOAPP),¹⁶ which has 14- and 24-item versions. These tools should be used to gain a sense of which patients may need additional structure as part of their treatment plan rather than to exclude specific patients from consideration for chronic opioid treatment.

Even patients who have a previous history of addiction need not automatically be excluded from opioid analgesic treatment for chronic pain. Experience has demonstrated that known addicts may benefit from

the carefully supervised, judicious use of opioid analgesics for pain resulting from cancer, surgery, or recurrent painful illnesses.¹⁷ When contemplating prescribing opioid analgesics for a patient with an addiction history, however, primary care physicians are advised to consult with a pain or addiction medicine specialist.

For such patients, careful supervision is the key. This includes a contract outlining the physician's expectations of the patient, provisions made for random urine screens, and increased attendance at 12-step self-help meetings.^{18,19}

Recovering alcoholics are less likely to relapse than are patients who once were addicted to opioid analgesics.²⁰ Prescribing them for the latter group should be considered only as a last resort—when every other approach has failed and with the participation of an addiction medicine specialist. Patients who are current drug addicts cannot be trusted to manage their opioid pain medications reliably. Therefore, these patients are not candidates for opioid therapy unless they are in a supervised setting with someone else dispensing the medication.

A COMPREHENSIVE TREATMENT PLAN

Opioid analgesics are not first-line therapy for chronic pain and are not recommended as the only treatment. They should be used as part of a comprehensive treatment plan that involves other medications and other modalities. Other medications to consider may include the following:

- Nonopioid analgesics (for example, acetaminophen).
- Aspirin and other anti-inflammatory drugs.
- Muscle relaxants.
- Antidepressants (because patients with chronic pain often are depressed). (Low-dose tricyclic agents may have some utility in managing some chronic pain conditions, such as fibromyalgia syndrome [FMS] and neuropathic pain.) The dual selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) duloxetine (Cymbalta) and milnacipran (Savella) also alleviate neuropathic pain; both are now FDA-approved for FMS.
- Anticonvulsants for neuropathic pain, including gabapentin (Neurontin), pregabalin (Lyrica), and divalproex sodium (Depakote).
- Topical preparations (eg, a lidocaine patch).
- Drugs that are used to counteract residual opioid sedation, including modafinil (Provigil) and methylphenidate (Ritalin).
- Sleeping pills (because patients who have chronic pain often have insomnia).

Optimal management of chronic pain involves a team effort. In addition to the primary care physician, possible team members include a rheumatologist, orthopedic surgeon, physiatrist, physical therapist, anesthesiologist, pain specialist (who can perform invasive procedures, such as epidural corticosteroid injections or nerve ablation, or insert a spinal cord stimulator or intrathecal pump), biofeedback specialist, hypnotist, acupuncturist, neurologist, neurosurgeon, addictionist, and psychologist. Psychotherapy, especially that involving cognitive-behavioral and spiritual therapies, may help some patients by teaching them how to be more accepting of their condition.

ASSESSING PATIENTS FOR OPIOID USE

Before a patient starts taking opioid analgesics for chronic pain, a comprehensive assessment is indicated. The first step is to assess the goal of treatment—is it to make a diagnosis of pain and eliminate it by removing the source or to allow the patient to live more comfortably with the pain? Next, has the patient had a workup to determine the cause of the pain and the treatment options? For

example, a patient with severe hip pain resulting from OA might be best served by undergoing a hip replacement, which might result in no pain and improved function. Of course, this requires obtaining an adequate history of the pain problem, its onset and cause, and what treatments and medications have been used. If the pain problem is not new, obtaining old records from other treating physicians (including imaging studies, procedures, and consultations) is important.

A detailed description of the pain may help direct treatment. For example, neuropathic pain—pain related to direct nerve damage or injury—may benefit from treatment with anticonvulsants or the SSNRI antidepressants duloxetine and milnacipran that alleviate both depression and some types of neuropathic pain. Examples of this type of pain are peripheral neuropathy, postherpetic neuralgia, and reflex sympathetic dystrophy (now called chronic regional pain syndrome).

Note that musculoskeletal pain, such as LBP, often has a neuropathic component (eg, sciatica). Therefore, a trial of an anticonvulsant or an SSNRI (eg, venlafaxine [Effexor] or duloxetine) may be worthwhile.

Taking an addiction history is essential to determine the appropriateness of considering opioid therapy. This history should include questions about the patient's present and past use of alcohol, cigarettes, or illegal drugs, as well as any family history of addiction problems. Administration of the ORT or SOAPP also is helpful. Old medical records should be examined for indications of previous problems with prescribed opioid analgesics. A physical examination in which particular attention is paid to the painful areas is needed to obtain additional information about the pain problem.

If the patient has not seen a physiatrist or an anesthesiologist who specializes in pain management, such a consultation may be extremely helpful. Both specialists can evaluate the role of local injections, physical therapy, transcutaneous electric nerve stimulation units, and other physical modalities in relieving pain. The physiatrist may recommend assistive devices, such as wheelchairs and braces. The anesthesiologist might consider placement of a spinal cord stimulator for some types of pain. If the patient has an addiction history or there are emotional or psychological issues, consultation with an addictionist or psychiatrist can be very informative.

PRESCRIBING OPIOIDS

If the decision to prescribe an opioid analgesic is made, an understanding of the role of sustained-release versus short-acting opioids is helpful. Long-acting medications generally are recommended for round-the-clock pain; short-acting preparations are best for intermittent pain or breakthrough pain (a combination of underlying pain with exacerbations that are related to increased activity, the weather, or mood changes or that have no apparent explanation).

Most long-acting formulations now available actually are opioid analgesics with a short half-life that have been formulated into a sustained-release preparation. These include the following:

- Sustained-release morphine: generic MSER (lasts 8 to 12 hours), MS-Contin (lasts 8 to 12 hours), Avinza (a true 24-hour formulation), and Kadian (lasts 12 to 24 hours).
- Sustained-release oxycodone: generic oxycodone ER, OxyContin (OxyContin lasts 8 to 12 hours [about 25% of patients require every-8-hour dosing]; the generic version often lasts a shorter time).
- Sustained-release fentanyl patch: generic patch, Duragesic. The 12- μ g patch is available only as Duragesic; higher doses are also available as generic. Duragesic patches last 3 days in most persons, although about 25% of patients require every-2-day dosing.
- An extended-release oxymorphone (Opana) is now available.

The most commonly used truly long-acting opioid analgesic is methadone, which has a variable serum half-life averaging 24 hours (range, 8 to 59 hours). Once-a-day dosing prevents withdrawal symptoms, but for pain relief, 3 or 4 doses per day are usually necessary. Any provider who has a DEA license can prescribe methadone for pain, just like any other opioid.

The cost of methadone is much lower than that of other opioid analgesics. However, because it has a long serum half-life, methadone needs to be titrated upward more slowly than other opioid analgesics, with increases only every few days. In November 2006, after multiple methadone overdose cases were reported in patients who had recently started methadone therapy and whose dose was increased too quickly, the FDA issued a warning about the need for caution when increasing methadone doses (<http://www.flisipp.org/BolenNotice.pdf>).

Methadone also must be tapered more slowly. If it is stopped suddenly, withdrawal symptoms can be prolonged.

An additional problem is that conversion between methadone and other opioids is not linear; that is, the higher the dose of morphine (or other opioid) the patient receives, the relatively greater is the equianalgesic ratio of morphine to methadone. For example, a patient who has been receiving 10 mg/d of morphine can be switched to 10 mg/d of methadone, but the equianalgesic daily dose of methadone for a patient who previously received 100 mg/d of morphine may be only 20 mg.

In addition, methadone metabolism is affected significantly by commonly used drugs. For example, some anticonvulsants (eg, carbamazepine [Tegretol]) increase its metabolism so that patients who receive these drugs at the same time may require very large doses of methadone. When you are starting to prescribe methadone, consultation with a knowledgeable physician is advised.

The short-acting opioid analgesics on the market usually are combinations with acetaminophen (eg, Tylenol with Codeine, Lorcet, Percocet, Vicodin, and Norco) or with aspirin (Lortab and Percodan). They have a faster onset of action than the long-acting opioid analgesics, but they also have a shorter duration of action. Morphine, oxycodone, hydromorphone (Dilaudid), oxymorphone, codeine, and others are available in immediate-release formulations without added acetaminophen or aspirin. They may be preferable if the risk of high doses of aspirin or acetaminophen is a concern. In addition, for pain that is intense at onset, ultrarapid-release formulations of fentanyl (Actiq and Fentora) are available.

For ongoing pain, the sustained-release or long-acting opioid analgesics are preferable to the short-acting combinations for 2 reasons: a long-acting formulation requires less frequent dosing and provides a smoother blood level, resulting in more consistent pain relief and less euphoric effect, and although there is no upper limit to the quantity of opioid analgesic that can be prescribed safely, taking more than 4 g/d of acetaminophen (equivalent to 12 regular Tylenol tablets) increases the risk of liver toxicity. Similarly, excessive aspirin use may have adverse effects on the GI tract. It is best to separate the opioid analgesic from the aspirin or acetaminophen and then titrate each individually.

Managing breakthrough pain

Many patients with chronic pain have breakthrough pain. Therefore, many pain specialists provide these patients with a combination of a long-acting or sustained-release opioid analgesic for round-the-clock dosing and some quantity of a short-acting opioid analgesic for breakthrough pain. If a patient consistently requires multiple doses of the short-acting drug, increasing his long-acting daily dose is preferable so that you can decrease the quantity of breakthrough medication.

For example, a physician may have prescribed MS-Contin, 60 mg twice a day, for chronic pain plus MSIR (immediate-release morphine), 15 mg up to 4 times a day, for breakthrough pain. If the patient ends up consistently taking 4 of the breakthrough doses daily, it would make sense to

increase his MS Contin to three 60-mg doses per day so that his MSIR can be decreased to one or two 15-mg doses per day for breakthrough pain. Typically, the average daily breakthrough dose prescribed is recommended to constitute no more than 15% to 25% of the sustained-release daily dose.

FOLLOW-UP VISITS

When first prescribing an opioid analgesic for chronic pain, scheduling the patient for another visit after a week or two is a good idea. Once the patient's pain stabilizes, monthly or bimonthly visits often suffice. An easy way of remembering the key elements of assessment at each follow-up visit, described by Passik and Weinreb²¹ as the "4 A's," is the following:

- Analgesia: Ask the patient, "On a scale of 1 to 10, how much pain are you having?"
- Adverse effects: Impaired thinking, somnolence, constipation, nausea, etc.
- Activities of daily living: Can the patient do more when taking the drug than when not? Document specific activities that the patient can perform (eg, walking, shopping for food, traveling to visit family, working in the garden, attending movies, and resuming employment).
- "Aberrant drug-related behaviors": Whenever there is such behavior, its cause should be assessed and a decision should be made whether to discontinue the medication. If the patient appears to have an addiction problem, referral to an addiction medicine specialist for further evaluation is appropriate.

Many clinicians have now added a fifth "A" for Affect, that is, the patient's mood. The answer to each question should be documented in the chart.

The increased activity that opioid analgesic use permits the patient often results initially in a need for a larger dose. Therefore, when the patient requests an increased dose, the physician should carefully assess the reason why rather than jump to the conclusion that this is drug-seeking behavior or tolerance.

At each visit, every prescription should be documented on a data sheet and every deviation from the expected date or amount should be explained fully in the chart. For example, if a prescription is dated 2 days early because of a holiday, I document this on the data sheet.

SUPERVENING ACUTE PAIN PROBLEMS

Patients taking opioid analgesics long-term who experience trauma or have surgery still need pain medication for their acute pain problem, usually larger amounts. They should be maintained on their usual dose of opioid analgesic plus medication for acute pain. Because general surgeons and other physicians may be uncomfortable prescribing the relatively high doses of opioid analgesics that are required, you may need to talk with these specialists before the surgery.

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