REVIEW

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Safe use of opioids in chronic noncancer pain

ABSTRACT

Many physicians avoid prescribing opioid analgesics for chronic pain because of misconceptions or fears about efficacy, adverse effects, abuse, and addiction potential. We discuss these issues and offer suggestions for the rational use of opioid analgesics in patients with chronic noncancer pain.

KEY POINTS

When considering opioid therapy for patients with chronic pain unrelated to cancer, careful screening helps identify those more likely to become addicted.

Assessment should include the type of pain, its intensity, and its functional impact.

Patients should be reassessed frequently during treatment to improve analgesia and effectively manage adverse effects.

If pain cannot be controlled, it is appropriate to refer the patient to a specialist; spinal infusion is effective in selected patients.

Opioid use for chronic pain not due to cancer is justified in patients who have severe pain with a clear pain diagnosis and supportive, objective findings, and who do not respond to other pain treatments.

OPIOID ANALGESICS can be used safely and effectively to treat chronic pain in patients who do not have cancer or a terminal illness, but concerns about efficacy and side effects and the potential for abuse and addiction discourage many physicians from prescribing them.

While some concern about the potential drawbacks of opioid therapy is justified, physicians should be aware of the potential benefits in patients with chronic pain and should know how to use opioids to maximize their benefits while minimizing adverse effects and the risk of addiction.

In this article, we discuss the issues that discourage the use of these potentially beneficial drugs, and we offer suggestions for their rational use in patients with chronic pain.

OPIOIDS THROUGHOUT HISTORY

The word "narcotic" comes from the Greek word for stupor and is typically used for strong opioids. Historically, any drug that induces sleep was labeled a narcotic. Opium is made from the dried juice of the opium poppy (*Papaver somniferum*). Morphine is the principal alkaloid of opium. Opioids are drugs with morphine-like activity, including synthetic drugs.

Narcotics have been widely used throughout history. Morphine was the mainstay of medical therapy in the United States in the 19th century, being used to treat pain, anxiety, and respiratory problems, as well as "consumption" and "female ailments."[1] Opium poppy was a legal crop in some states, and products made with opium were sold over the counter. Cocaine was also freely available through

*The author has indicated that he is on the speakers' bureau of Pfizer, Merck, and Medtronic corporations.

This paper discusses therapies that are not approved by the US Food and Drug Administration for the use under discussion.

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TABLE 1

Signs and symptoms of opioid withdrawal

Signs

- Hypertension
- Tachycardia
- Hyperthermia
- Diarrhea
- Mydriasis
- Rhinorrhea
- Chills
- Lacrimation
- Myoclonus
- Tremors

Symptoms

- Anxiety
- Irritability
- Pain
- Dysphoria
- Insomnia
- Abdominal cramps
- Drug craving

pharmacies and also over the counter in wine mixtures and in products such as Coca-Cola.

Physicians tend to see the risks of opioids more than the benefits

In 1914 Congress passed the Harrison Act in an attempt to control and limit the commercial preparation and distribution of opium and coca leaves, via taxation. The Harrison Act was eventually used, however, to penalize producers and distributors of products containing opium and cocaine.

Physicians were allowed to prescribe these substances, but not to addicts, because addiction was not thought to be a medical illness. Facing the possibility of arrest or censure, physicians became more hesitant in prescribing opioids even for chronic pain.[1]

Government attempts to curb drug abuse

Drug abuse has long been a concern in the United States, with new drugs going in and out of fashion, including LSD, barbiturates, amphetamines, and marijuana. In 1970, Congress tried to curb abuse of certain substances through the Controlled Substance Act, which categorizes ("schedules") substances according to their addictive potential. There are six schedules: schedule I includes heroin and marijuana; II includes cocaine, opium, and morphine; III includes codeine; IV includes diazepam and alprazolam; V includes drugs with small amounts of codeine; and VI includes penicillin and ibuprofen. Criminal penalties for illegal possession were set according to the drug's schedule. The Drug Enforcement Agency was formed in 1973 to enforce the Controlled Substance Act.

In general, there is no impediment to prescribing schedule II, III, or IV drugs for appropriate indications, including chronic pain unrelated to cancer, but federal law requires that physicians have a special license to prescribe opioids to patients with addictive disorders (ie, in methadone or buprenorphine maintenance therapy).

PERCEIVED BARRIERS TO OPIOID USE

Many patients do not receive adequate analgesia, whether for acute problems in the hospital, for chronic pain, or for cancer pain. This failure can be due to clinician issues and patient issues.[2]

Clinicians may not prescribe opioids in adequate doses because they do not know how to give them effectively, do not systematically assess pain or the effect of therapy, fear sanctions from medical boards, and overestimate the risks of the medications, including addiction and adverse effects.[2]

On the other hand, patients may not communicate their pain symptoms to their doctors or may not take their medications as directed because they may fear becoming addicted to "narcotics." In addition, they may not understand the dosing regimen, and they may worry about high costs of medications.

Evidence of underuse of opioids

Although the use of opioids for cancer pain is generally accepted in theory, there is evidence that even in cancer patients—for whom symptom control and pain management should be a priority—the medical community still has a long way to go to provide adequate treatment.[3,4]

Portenoy[5] reviewed the use of opioid analgesics in patients with chronic pain (some due to cancer, some not) and found that, when appropriately managed, opioids provided analgesia and improved quality of life, and the adverse effects were controllable.

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How opioids work

OPIOID analgesics interact with three types of opioid receptors: mu, delta, and kappa.

Mu receptors have two subtypes. Mu-1 receptors mediate the analgesic effects of opioid drugs, whereas mu-2 receptors are associated with adverse effects such as respiratory depression, euphoria, and sedation.[2,16] Mu receptors are found in the periphery (following inflammation), at presynaptic and postsynaptic sites in the dorsal horns of the spinal cord (laminae I-II), and in the brain stem, thalamus, and cortex, in what constitutes the ascending pain transmission system. In addition, mu opioid receptors are found in the midbrain periaqueductal gray matter, the nucleus raphe magnus, and the rostral ventral medulla, where they constitute a descending inhibitory system that modulates transmission of pain in the spinal cord.[16]

Delta opioid receptors have been found in the cerebral and cerebellar cortex, hippocampus, thalamus, hypothalamus, brainstem, medulla, and the dorsal horns of the spinal cord (particularly in laminae I-II).[15] These receptors are associated with spinal and supraspinal analgesia, as well as with dysphoria and hallucinations.

Kappa opioid receptor agonism produces effective spinal analgesia, but is associated with miosis and significantly more sedation than is mu receptor agonism.

Most opioids currently used in medicine are mu receptor agonists. Pentazocine, butorphanol, and nalbuphine are mixed mu and kappa receptor agonists. Buprenorphine and dezocine bind to mu receptors but only partially activate them (TABLE 2).

For cancer pain, considerable experience and research suggest that, in appropriately selected patients, long-term opioid use causes little morbidity and poses a low potential for addiction. Long-term opioid therapy and appropriate symptom management relieve pain, reduce suffering, enhance function, and improve quality of life without significant risk of addictive behaviors in patients with chronic pain.[6]

For chronic or chronic recurrent pain not related to cancer or its treatment (eg, for sickle cell crises), use of opioid analgesics has been more controversial. Nevertheless, Jamison et al[7] surveyed opioid use in chronic pain patients and found a low incidence of iatrogenic addiction in patients who did not have a history of substance abuse.

DEPENDENCE, TOLERANCE, ADDICTION, ABUSE

It is important to understand what addiction is and what it is not, and to distinguish between physical dependence, tolerance, addiction, and substance abuse.[8]

Physical dependence

Physical dependence is a state of neurophysiologic adaptation, manifested as rebound symptoms or withdrawal signs and symptoms if the opioid is abruptly stopped, if the dose is precipitously reduced, or if a pharmacologic antagonist is given.

Rebound symptoms are an exacerbation of the symptoms for which the drug was initially given (eg, pain). Withdrawal signs and symptoms are drug-specific and may overlap with rebound symptoms but may include new ones, such as lacrimation, hypertension, and abdominal cramps (TABLE 1).

A history of drug abuse raises the risk of addictive behavior during opioid therapy

Tolerance

The effect of an opioid analgesic may diminish over time, so that higher and higher doses are needed to produce the initial level of pain relief, an effect called tolerance. Rather than increase the dose, one can switch to another drug.

Tolerance may be due to pharmacokinetic adaptations (ie, increased metabolism or clearance of the drug) or, more importantly, pharmacodynamic adaptations (ie, diminished responsiveness of the receptors to the drug). Pain-facilitating systems such as the *N*-methyl-D-aspartate (NMDA) receptors, nitric oxide, and cyclo-oxygenase (COX) may play important roles in opioid tolerance. For example, Hsu and Wong[9] found that COX inhibitors could attenuate opioid tolerance

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without enhancing morphine's antinociceptive effects. Tolerance develops more readily when large doses are given at short intervals, particularly parenterally.

Tolerance to the sedative, euphoric, and respiratory depressant effects of opioids usually develops more quickly than tolerance to the emetic and urinary effects. Patients may never develop tolerance to the miotic, convulsant, or constipating effects of opiates.

Addiction

Addiction is a constellation of maladaptive behaviors, including loss of control over the use of the opioid drug, preoccupation with opioid use despite adequate pain relief, and continued use of opioids despite apparent adverse consequences. It should not be confused with pseudoaddiction—drug-seeking behavior related to underdosing. Addiction is a medical and psychological illness that requires treatment.

Drugs of abuse are typically taken because they produce euphoria or indifference to stimuli or because they relieve distress. These drugs mimic the actions of the neurotransmitters that activate the brain reward system that normally motivates behavior associated with positive stimuli or the memory of circumstances under which rewards occurred.[7,10] In vulnerable persons, ie, those with a personal or family history of substance abuse, giving these drugs often enough, long enough, and in sufficient doses produces long-lived molecular adaptations that can result in compulsive, out-of-control drug use. Some of these changes may reverse with detoxification. Others may create a lifelong vulnerability to relapse.[11,12]

Assess the psychosocial impact of the pain on the patient and the family

Substance abuse

Substance abuse is the use of a medication in a way that may cause harm to oneself or to others, or its use for an indication other than the one intended by the prescribing physician.

When considering the use of opioid analgesics for chronic pain, it is essential to determine if the patient has a history of substance use or abuse.[13]

Red flags of substance abuse once a patient is taking opioids include:

- Dose escalation
- Lost or stolen prescriptions
- Use of street drugs
- Forging or tampering with prescriptions
- Selling the prescribed opioid drugs
- Injecting oral medications
- Crushing sustained-release preparations.

PRINCIPLES OF PAIN MANAGEMENT

For mild pain, nonopioid analgesics such as nonsteroidal anti-inflammatory drugs are effective.

For moderate pain, combination preparations consisting of a low-potency opioid such as codeine or oxycodone plus aspirin or acetaminophen are most commonly used. For acetaminophen preparations, dosing is limited by the total acetaminophen dose, owing to this drug's hepatic and renal toxicities.

For severe nociceptive pain, high-potency opioids are the mainstay of treatment. High-potency opioids are also used for moderate pain that does not respond to low-potency drugs, or if the patient requires a higher dose of drug for analgesia.

When to use opioids for chronic noncancer pain

Opioid use for chronic pain not due to malignancy is justified in a select group of patients who have severe pain with a clear pain diagnosis, supportive objective findings, and responsiveness to opioids, and who do not respond to a variety of other pain treatments.

There is strong consensus that opioids should be used aggressively when needed to relieve severe acute pain, pain associated with terminal cancer, and other painful potentially terminal illnesses (eg, acquired immune deficiency syndrome), as well as chronic intractable noncancer pain.[14]

Pain assessment

Before starting opioid therapy, an assessment is essential.

Pain is subjective. No objective test can measure or validate a patient's report of pain, and in most cases, the patient's own report should be trusted. Use of simple pain intensity scales such as a 0-to-10 rating scale or a 10-cm visual analog scale can help to document the

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patient's pain complaint and response to therapy. Frequent reassessment over the course of treatment helps to optimize the pain management.

A key part of the pretreatment pain assessment is to determine the psychological and social impact of the pain on the patient and his or her family, as well as coping strategies the patient uses.

Assessing the patient's risk of substance abuse

Assessment of current or previous substance abuse in the patient and family should be a routine part of any medical assessment. Patients with a personal history of substance abuse or alcoholism are at higher risk of becoming addicted; however, experience with opioid use for cancer pain shows that these drugs can still be given to patients with a history of addictive disorders as long as the treatment is managed appropriately.

A family history of substance abuse is important because family members who are chemically dependent might divert the patient's medications.

Written agreement and other documentation are essential

Savage[15] gives a number of sound, practical recommendations about prescribing opioid analgesics:

- Thorough documentation is essential; at our institution this includes an opioid maintenance agreement form, signed by the patient, and an opioid maintenance record, which is kept throughout the period of therapy.
- The patient should sign an informed consent form and must understand the goals of the therapy, the potential risks and benefits, and the need to come in for periodic reevaluations.
- Only one physician should prescribe opioid medications for an individual patient (unless it is an emergency), and one pharmacy should fill the prescriptions.
- Establish in advance how to manage lost or stolen prescriptions.
- Determine that the patient is psychologically stable. Some physicians sometimes obtain a second opinion to confirm that opioid therapy is appropriate.

MORE TIPS FOR RATIONAL OPIOID THERAPY

- Individualize the dosage and reassess frequently, taking into account the patient's previous opioid exposure and comorbid medical conditions.
- If the patient will be taking pain medications around the clock, then consider a long-acting opioid preparation with doses of a shorter-acting medication available as needed for breakthrough pain; this regimen may be preferable to frequent doses of a short-acting agent.
- If the pain is uncontrolled or increasing, the diagnosis should be reassessed, confirmed, and appropriately treated. A trial of increasing the pain medications is appropriate. A rule of thumb is to increase the opioid dose by the total of the rescue doses, or 30% to 50% of the current daily dose. Adverse effects should be recognized and treated appropriately.
- Use combination therapy as appropriate. Use of nonopioid analgesics and analgesic adjuncts also becomes important to improve analgesia and function and to decrease the development of tolerance to opioids.
- Understand and attempt to differentiate between tolerance, physical dependence, and addiction.
- Switch medications if analgesia remains poor, if tolerance develops, or if adverse effects are significant. When adding or changing opioid analgesics, keep in mind the approximate doses of different agents that are considered equivalent in analgesic effect (**TABLE 2**). These doses are only estimates, however, and it is possible to significantly overmedicate or undermedicate a patient using the calculated conversion.

When changing medications, it is appropriate to reduce the calculated dose by 20% to 50% and to assure that a dose of short-acting pain medication is available for breakthrough pain. Then reassess and recalculate the overall dose on the basis of the patient's use of the breakthrough medication.

Nonopioids, mixed agonist-antagonists, and partial opioid agonists (**TABLE 2**) have a "ceiling" effect for analgesia—ie, a maximum dose beyond which they do not provide any further effect. Mu receptor agonists (see further discus-

Essential documentation includes an opioid maintenance agreement form, signed by the patient

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TABLE 2

Opioid doses that are equivalent in analgesic effect

Mu receptor agonists*

Low-potency opioids

- Propoxyphene 65–100 mg by mouth
- Codeine (with acetaminophen) 200 mg by mouth:
  Opioids combined with acetaminophen should be dosed at < 2 g/24 hours
- Oxycodone 15–20 mg by mouth
- Hydrocodone 20–30 mg by mouth
- Meperidine 300 mg by mouth or 75–100 mg parenterally†

High-potency opioids

- Hydromorphone 4–7.5 mg by mouth or 1.3–2 mg parenterally
- Morphine 30 mg by mouth (60 mg for patients who have never taken morphine) or 10 mg parenterally (morphine is the gold standard)
- Levorphanol 4 mg by mouth
- Methadone 20 mg by mouth
- Fentanyl 0.1 mg parenterally
- Fentanyl patch 25 μg/hour every 72 hours

Mixed agonist-antagonists‡§

- Pentazocine 150–180 mg by mouth
- Butorphanol 1.5–2.5 mg parenterally
- Nalbuphine 10 mg parenterally

Partial agonists‡

- Buprenorphine 0.3-0.4 mg parenterally
- Dezocine 10 mg parenterally

*The maximum dose of a mu receptor agonist is related to side effects
†Meperidine is *N*-demethylated to normeperidine, which may cause seizures, particularly in the presence of renal insufficiency or if high doses are used.
‡Antagonists at the mu receptor and agonists at the kappa receptor
§Mixed agonist-antagonists and partial agonists are not recommended for chronic pain

FURTHER INFORMATION ON PAIN MANAGEMENT PROCEDURES IS AVAILABLE AT WWW.NCBI.NLM.NIH.GOV/BOOKS/BV.FCGI?RID=HSTAT6.TABLE.32358

Sedation and constipation are common, limiting effects of opioid therapy

sion in the sidebar, "How opioids work")[2,16,17] such as morphine, fentanyl, and oxycodone do not have a ceiling effect, but dosing may be limited by the ability to manage adverse effects.

MANAGING THE SIDE EFFECTS OF OPIOID ANALGESICS

The side effects of opioid analgesics are directly related to their binding with endogenous opiate receptors. Side effects may be neuropsychologic (sedation, fatigue, depression, seizures, myoclonus), respiratory (respiratory depression), gastrointestinal (constipation, nausea, vomiting), and urologic (urinary retention), and may also include miosis and sexual dysfunction. Seizures can occur with the accumulation of normeperidine, a meperidine metabolite. Myoclonus is associated with high intravenous doses of morphine.[18]

However, by far the most common side effects are constipation, sedation, nausea, vomiting, and pruritus.

Experience with pain treatment in cancer patients shows that in most cases these side effects can be managed to allow the continued use of opioid analgesics.

Respiratory depression, although a less common side effect, is one of the most worrisome. However, except for patients with increased intracranial pressure, cor pulmonale, or severe chronic obstructive pulmonary disease, most patients tolerate careful administration of opioids. With chronic therapy, some

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patients develop a tolerance to the respiratory effect of mu receptor agonists. Respiratory depression rarely occurs in patients who tolerate opioid analgesics, but keep in mind that other central nervous system depressants may have additive or synergistic effects.

Sedation may be a very limiting side effect and is probably one of the most common reasons that patients discontinue or change medications.

Constipation is very common and must be treated proactively, sometimes aggressively. The routine use of stool softeners and bulk laxatives is appropriate.

In a literature review, Mercadante[19] noted that if an opioid drug causes intolerable side effects, reasonable options are to give the same drug via another route or to give another opioid via the same route.[19] Other side effects should be evaluated and treated symptomatically as they occur.

INTRATHECAL OPIOID THERAPY

Intrathecal (spinal) infusion is an option when oral doses fail to control the patient's symptoms or cause unacceptable side effects. Currently, morphine is the only opioid approved by the US Food and Drug Administration for intrathecal administration in the treatment of chronic pain.

Intrathecal infusion bypasses the blood-brain barrier and results in much higher cerebrospinal fluid concentrations with less medication. It is particularly advantageous when the target receptors are in the spinal cord.[20] Compared with the epidural route, intrathecal infusion is associated with higher rates of satisfactory pain relief and lower rates of treatment failure and technical complications.

Intrathecal opioid infusion can provide significant, long-lasting analgesia with fewer adverse effects than oral or parenteral opioids. This is primarily related to the lower dose needed to achieve analgesia. This approach can therefore be beneficial in high-risk patients and patients with compromised pulmonary function.

Intrathecal morphine is 10 times as potent as epidural morphine. The analgesic doses for intrathecal morphine are only about 1% to 2% of those for parenteral morphine and about 0.3% of the oral dose.

Intrathecal infusion requires consideration of pharmacologic factors: the chemical properties of the drug (lipid solubility, density, baricity), the mode of delivery (bolus vs continuous), segmental location of target receptors in the spinal cord, and the level of the intrathecal catheter tip all play important roles in determining the efficacy of the treatment.[21] Referral to a pain management specialist is required when intrathecal opioids are considered for chronic pain management.

Depending on lipid solubility, opioids given intrathecally in the lumbar space can migrate rostrally in the cerebrospinal fluid.[21] Peak concentrations of morphine (which is hydrophilic) appear in the cisternal cerebrospinal fluid of sheep 3 hours after intrathecal lumbar administration, but methadone (which is lipophilic) does not reach the cisternal fluid due to clearance.[22]

Intrathecal infusion is considered 10 times more potent than epidural

Adverse effects of intrathecal infusion

The main adverse effects of intrathecal morphine are nausea, vomiting, constipation, hypotension, sedation, and respiratory depression. These are dose-related and appear to be due to vascular uptake. Constipation, nausea, vomiting, pruritus, and urinary retention are seen early in the course of the treatment but can be managed symptomatically.[23] The risk for delayed respiratory depression is highest with morphine and lower with more lipophilic drugs such as fentanyl and sufentanil, which are localized and absorbed into fat, so that less is available to migrate cephalad to the respiratory centers.[24] Neither of those drugs has been approved for this indication.

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