Opioid Essentials

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KEYWORDS

• Opioids • Pain management • Hospital medicine

HOSPITAL MEDICINE CLINICS CHECKLIST

1. When used according to best practices, opioids are safe and efficacious for pain.
2. Opioids are a generally accepted treatment option for acute pain, chronic cancer pain, and pain at the end of life.
3. Use of opioids for chronic noncancer pain is controversial and should be managed by a specialist paying detailed attention to pain, function, and side effects in addition to signs of abuse and addiction.
4. A skilled and thoughtful approach to dose titration and opioid rotation can lead to improved pain control while minimizing side effects.
5. Opioids can cause constipation, nausea, vomiting, sedation, respiratory depression, pruritus, and myoclonus. Of these analgesia and constipation are the most persistent, and other effects tend to diminish over days to weeks of exposure.
6. Opioids are a reliable treatment option for pain because dose is limited only by side effects. The many routes of administration, including oral, intravenous, sublingual, transdermal, and subcutaneous, make opioids useful across a wide range of clinical scenarios.
7. Special consideration should be taken when using opioids in the elderly and in patients with liver disease or kidney disease, owing to the impact of opioids on metabolism and the risk for accumulation of toxic metabolites with resultant toxicity.
8. Addiction is relatively uncommon with opioid use for acute pain, cancer pain, and end-of-life pain. Use of opioids for chronic pain may carry a greater risk

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for addiction. Clinicians should be aware of the phenomenon of pseudoaddiction, which mirrors addiction behaviorally. However, in pseudoaddiction, troublesome behavior will disappear once opioids are adjusted for adequate analgesia.

INTRODUCTION

A 2011 analysis of Centers for Disease Control and Prevention (CDC) data reported that prescription drug overdose led by overdose of pain medication has surpassed motor vehicle fatalities as the leading cause of death from unintentional injuries in the United States.[1] The risk for harm associated with opioids has been demonstrated in hospitalized patients. A recent retrospective cohort study suggests that as many as half of all patients admitted to an acute care hospital in the United States receive opioids, and that "hospitals with higher opioid prescribing rates had higher adjusted relative risk of a severe opioid-related adverse event per patient exposed."[2] The recent American College of Physicians (ACP) policy position paper on prescription drug abuse highlights concern over increasing use of opioids, including addiction, hyperalgesia, and lack of efficacy in the chronic pain population.[3]

Despite these findings, it is difficult to imagine treating severe pain without opioids. Because of their efficacy for nociceptive and neuropathic pain through oral, intravenous, and transdermal routes of administration, opioids offer novel therapeutic benefit with enough flexibility to be used in almost any clinical scenario. A well-defined profile of therapeutic effects and side effects allows clinicians to titrate dosage for efficacy, guard against or treat side effects as they arise, and even rotate opioids in the setting of treatment failure or intolerable or intractable side effects. In skilled hands, opioids represent an indispensable therapeutic tool that is efficacious, flexible, and safe.

A pendulum that recently advocated a more liberal approach to treating pain with opioids now rings alarm bells in the medical literature and mass media. Rather than a purely reactive avoidance of opioids, these findings should be taken as a call for hospitalists to strengthen their knowledge and practice in opioid therapy. The need to mitigate suffering with opioids in the face of severe acute pain and chronic cancer–related pain remains. Both are scenarios seen frequently in the practice of hospital medicine for which opioid therapy is not controversial. Hospitalists should develop expertise in the appropriate use of opioids.

INDICATIONS FOR OPIOIDS

Is there good evidence for efficacy of opioids in acute pain?

Opioids have long been part of the standard of care for the treatment of acute pain. Their efficacy and utility is so well established through clinical experience that a placebo-controlled trial would be considered unethical. The World Health Organization (WHO) recommends a "ladder" approach for acute pain in patients with cancer (http://www.who.int/cancer/palliative/painladder/en/).[4] Treatment should be initiated as quickly as possible and should progress from nonopioids, such as acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID), followed by a weak opioid (see later discussion), then a strong opioid as required to achieve control over the patient's pain. This logical approach demonstrates the centrality of opioids in the treatment of pain. In

the case of severe pain for which there is no reasonable expectation of adequate pain control with nonopioids, it is appropriate to initiate treatment with opioid before a trial of nonopioid pain medications.

A common scenario in which hospitalized patients suffer from acute pain is during recovery from surgery. Patient-controlled analgesia (PCA) as the preferred method of delivery has been supported by multiple trials and meta-analyses. Compared with intermittent dosing, PCA dosing improves analgesia, decreases risk for pulmonary complications, and is supported by patient preference.[5] PCA is also appropriate for acute pain in settings such as injury and pain crisis in the setting of sickle cell vaso-occlusive crisis.

Prescribing long-acting or controlled-release opioids to patients with acute pain and clearly identified reversible etiology who are leaving the hospital should be avoided if possible.[6] The amount of opioids prescribed or dispensed should be geared toward a goal of maintaining function during recovery. Dosing should be guided by clinical factors including the required dose before discharge and the expected duration of recovery.

Are opioids effective for cancer-related pain?

Estimates of the prevalence of pain among patients with cancer vary broadly, with clinically significant pain at some time during the course in at least half of patients. Pain occurs more commonly in those with solid tumors, older patients, and those in advanced stages of cancer.[7,8] Pain is the most common reason for referral for advanced symptom management in the hospice.[8] In broad terms, pain occurs as a result of direct tumor involvement, therapeutic and diagnostic procedures, and treatment-related toxicities.[9] Opioids have been shown to be effective for patients experiencing pain caused by cancer.[4] A 2007 Cochrane meta-analysis including more than 2000 patients reinforced the efficacy of oral morphine for cancer-related pain.[10] Studies have been conducted to compare the efficacy of other opioids, without clear evidence to recommend one agent over another at the population level.[11] Opioid availability in diverse formulations, their efficacy against pain from multiple sources, and their long history of efficacy in the treatment of cancer pain continue to justify a central role in the management of cancer pain.[12]

Are opioids a good treatment option for chronic noncancer pain?

The use of opioids for chronic nonmalignant pain conditions was long considered not to be recommended. Attitudes have gone through multiple changes over time. Since the late 1990s, many studies have been conducted using opioids in diverse chronic pain conditions, yielding mildly positive results on the whole. A review by Ballantyne and Shin[13] outlines these studies. Efficacy has been demonstrated with marginal improvements in pain control, function, and quality of life, with studies lasting from 4 to 32 weeks for diverse indications including both nociceptive and neuropathic pain. Unfortunately, data on the use of opioids after 32 weeks in chronic pain do not exist. Initiation of opioids leads to improvement in outcomes for chronic pain conditions in the short term, but longer-term effects are less certain because of the limitations of the controlled trials conducted. The social implication of expanded prescription of opioids is not considered in Ballantyne's analysis.[13]

In light of the massive and growing problem of prescription drug overdose attributable to opioids, the CDC has made recommendations to use opioids for chronic pain only after exhausting alternatives, to conduct urine testing periodically, to enlist the consultation of a pain specialist for anyone receiving more than 120 mg oral morphine

or equivalent per day, and to monitor with state agencies for prescriptions from other providers. The ACP has recently arrived at similar recommendations, adding the recommendation for the establishment of a national Prescription Drug Monitoring Program, including a mechanism to identify those patients at greatest risk for abuse, and the requirement of rigorous monitoring and testing for such patients.[3] In light of the public health implications and limited efficacy, opioids should be avoided, when possible, for chronic pain.

Are opioids effective for the treatment of neuropathic pain?

Despite neuropathic pain being challenging to diagnose and treat, opioids can be a safe and effective treatment option for painful neuropathic conditions, although the same reservations described for chronic pain conditions need to be considered. Owing to the chronic nature of many neuropathic conditions and difficulties inherent with chronic opioids, they are relegated to second-line status. O'Connor and Dworkin[14] outlined a reasonable approach, summarized in **Table 1**. The efficacy of opioids has been established for painful diabetic peripheral neuropathy, post-herpetic neuralgia, painful polyneuropathy, and phantom limb pain.[14] Opioids have been shown to be ineffective in chronic lumbar root pain. When opioids are being considered for neuropathic pain, it is important to set reasonable expectations of benefit and side effects of chronic therapy so that patients can make an informed decision.[14]

How do I manage patients with chronic pain in the hospital?

The hospitalist is often presented with management of chronic pain conditions as dictated by the patient's providers outside the hospital. Because there is an increased risk of aberrant medication-taking behavior (AMTB), such as opioid abuse and diversion, in this population, attention should be paid to opioid use and outcomes. Although the risk for AMTB is high, physicians are poor at identifying these behaviors and correctly selecting behaviors associated with addiction.[15] A stratification of worrisome behaviors into those more and less concerning for addiction has been proposed.[16] This stratification recognizes that some behaviors concerning for addiction may be the result of inadequate pain control (**Fig. 1**).

The Pain Assessment and Documentation Tool (PADT)[17] is a validated tool created by an expert panel incorporating a catalog of aberrant behaviors and side effects in addition to patients' reported function and pain control. The PADT is intended to be used as an objective record of response to opioid therapy for clinical settings in which there is some risk for negative externalities. An approximation of the tool might be useful for the monitoring of opioid therapy in hospitalized patients.

It is not uncommon for a patient with chronic pain to be admitted with a worsening of that pain or another painful diagnosis. In these scenarios, an additional challenge is posed by hyperalgesia or the experience of normal tactile or visceral stimuli experienced as pain or an increase sensitivity to pain. Hyperalgesia may be induced by damaged tissues or nerves, the circumstance of being sick, or from constant hyperstimulation of opioid receptors as a result of chronic opioid use. In the clinical scenario of acute on chronic pain it is important to undertake a thorough investigation of the cause of pain instead of attributing the presentation to progression of opioid tolerance, given that development of tolerance is rare after establishment of a stable dose. A frank conversation with regard to expectations for the degree of pain relief with opioids can be useful. Some patients retain the expectation that their pain level can be treated to a level of zero pain, a wildly unrealistic therapeutic goal.

Table 1
Medications for neuropathic pain

Medication/Class (1st/2nd/3rd Line[a])	Strong Evidence in Conditions Listed	Notes[b]
Topical lidocaine (1st line)	Localized peripheral neuropathy	Can be used with other 1st-line medications or alone when efficacious
TCAs (nortriptyline, desipramine) (1st line)	Diabetic peripheral neuropathy Post-herpetic neuralgia Painful polyneuropathy Postmastectomy pain Central poststroke pain	Serotonin syndrome Onset over several days to weeks
SSNRIs (duloxetine, venlafaxine) (1st line)	Diabetic peripheral neuropathy Painful polyneuropathy	Serotonin syndrome Onset over several days to weeks
Gabapentin (1st line)	Spinal cord injury pain Neuropathic cancer pain Guillain-Barré syndrome Painful polyneuropathy Post-herpetic neuralgia	Starting with lower doses then titrating up minimizes sedation Relative contraindication in renal disease (recommended dose limit of 100 mg) Onset is rapid but requires titration over weeks
Pregabalin (1st/2nd line)	Central poststroke pain Spinal cord injury pain	Closely related but more potent than gabapentin Low risk for abuse Also carries relative contraindication in renal failure
Opioids[c] (2nd line)	Acute neuropathic pain Neuropathic cancer pain Severe exacerbations of pain Established efficacy for several chronic conditions	Rapid onset for acute pain Targets neuropathic cancer pain well Rapid onset, at least as efficacious as 1st-line agents; however, opioids should not be used unless first line alternatives are exhausted because of risk for negative externalities
Tramadol (2nd line)	Diabetic peripheral neuropathy Post-herpetic neuralgia Painful polyneuropathy Postmastectomy pain	Weak opioid activity Serotonin and norepinephrine reuptake inhibition Lower risk for abuse than opioids
Third-line agents include other antiepileptics, SSRIs, and capsaicin	Evidence lacking	Lower quality of evidence for efficacy Often used as an adjunct to 1st- or 2nd-line agents

Abbreviations: SSNRIs, selective serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

[a] For chronic neuropathic pain, first line agents can be used alone then paired with other first line agents (eg, TCA with gabapentin or pregabalin). When ineffective in combination, a trial of a different first-line agent is recommended before switching to opioids for chronic neuropathic pain.

[b] Medications directed at pain should be initiated in conjunction with treatment directed at the underlying disease when that disease can be identified.

[c] For severe acute neuropathic pain that limits function, the use of an opioid is reasonable as a bridge while titrating other agents.

Data from O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med 2009;122(10A):11.

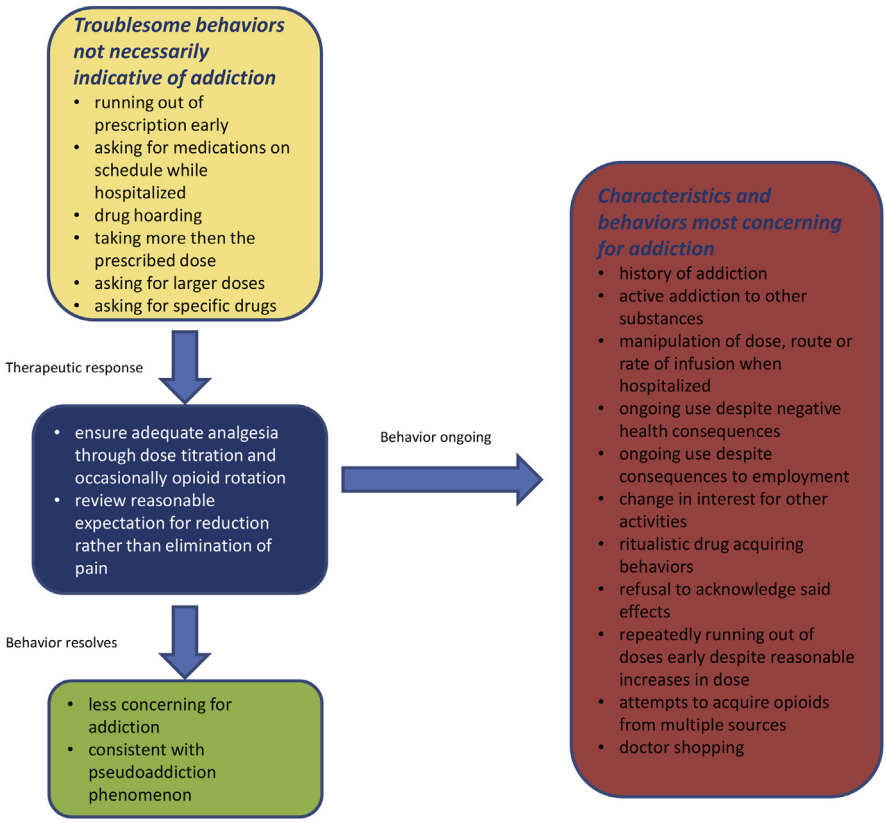

Fig. 1. Aberrant behaviors.

PHYSICIANS' ATTITUDES AND CONCERNS REGARDING OPIOID THERAPY

How should the epidemic of prescription opioid abuse affect my practice?

An epidemic of opioid abuse is widely recognized and, as the primary prescribers of opioids, physicians deserve a greater share of responsibility than previously thought.[18] Pressure for increased use of opioids has been the result of campaigns to address inadequate pain control in clinical settings where benefit far outweighs risk for negative externalities (eg, cancer pain and acute pain), supported in large part by lobbying from the pharmaceutical industry (effecting massive profits in the current era). In addition, fragmentation of care and displacement of the primary care physician has made "doctor shopping" a viable option for those patients who encounter resistance but are still motivated to obtain prescription opioids. Fortunately, hospital medicine is largely spared the difficult and controversial decisions surrounding opioid administration for chronic noncancer-related pain.

In a recent editorial in the *Journal of the American Medical Association*, Caleb Alexander suggests that attempts to curb the widely recognized epidemic of prescription opioid abuse "may not succeed until there is a broader clinical shift from such widespread use of these medicines."[19] In addition, he suggests that the trend toward increase in nonmedical use of opioids is the result of an increase in the use of opioids as prescribed by doctors.

In the midst of an important discussion of the social implications of widespread use of opioids, they remain integral for the treatment of severe acute pain. Reasonable efforts to limit the use of opioids should be made, including use of the lowest effective dose and a thorough workup to elucidate an underlying cause of pain to promptly optimize disease-directed treatment, with subsequent tapering of opioids when possible. In addition, a careful approach to prescribing opioids at the time of discharge, including avoidance of long-acting opioids, should help to minimize the risk for negative externalities. In the case of acute exacerbation of chronic pain, opioids may facilitate a return to function in the short term in hopes that other therapies can help with pain on a more long-term basis. In addition to efforts at limiting the need for opioid therapy, a discussion regarding the risks and benefits of opioid use, including setting reasonable expectations for the degree of pain relief and setting expectations for cessation, can make the transition to management outside of the hospital smoother.

Are opioids safe for use in hospitalized patients?

Opioid safety is well established when used according to best practices in hospitalized patients. The question of safety is largely one of knowledge and implementation of basic principles of opioid use, including knowledge concerning opioid initiation, titration, and rotation. Considering the efficacy of opioids in appropriate clinical settings and the likelihood that patients with acute pain and cancer pain will require hospitalization, it is incumbent on the hospitalist to develop a command of these principles and to understand the appropriate settings for their use.

Am I putting my patient at risk for addiction by using opioids to treat their pain?

The risk of opioid addiction after exposure to opioids in the setting of acute pain is likely to be low.[20] Safeguards including monitoring for the lowest effective dose, close follow-up after discharge when pain medications are prescribed for acute pain, and avoidance of long-acting pain medications should further limit the risk for addiction. Although patients treated with opioids for chronic pain demonstrate low rates of addictive behavior,[21] it is difficult to ignore the correlation between the current epidemic and increased the use of opioids for chronic pain. Viewing opioid use through a public health lens demands consideration of diversion, and suggests that dose and duration of exposure should be minimized as allowed by clinical circumstances.

SIDE EFFECTS OF OPIOIDS

What are the most common side effects of opioids?

Anticipation and treatment of the side effects of opioids should be incorporated in the daily plan for patients requiring opioids for pain. Of importance is that side effects are idiosyncratic, and an individual patient's side-effect profile to a particular agent is unpredictable. The most common side effects are constipation, nausea, vomiting, sedation, respiratory depress, pruritus, and myoclonus. In addition, euphoria can be experienced independent of analgesia, is central to the cycle of addiction, and can be viewed as a side effect. Opioids can contribute to delirium and an increased risk for falls in the elderly, although untreated pain may be a stronger risk factor for falls and delirium. Management in this population demands careful monitoring, including using the lowest effective doses of opioids and tapering as tolerated. In the setting of sympathetic surge from acute pain increasing blood pressure, opioids can result in a lowering of blood pressure.

Whereas most of these side effects occur at a range of frequencies and in a manner idiosyncratic for an individual patient, constipation is nearly inevitable. Relative to other side effects and even analgesic effects, constipation is immune to tolerance.[22] Respiratory depression is the cause of death in most cases of fatal opioid overdose, and is almost always preceded by sedation. Pruritus is less common than either of these effects and is mediated in part by histamine release by mast cells. Myoclonus occurs most often in the setting of renal disease, owing to accumulation of toxic metabolites. Delirium is often multifactorial and has a higher frequency when opioids are used in the setting of other illnesses such as dehydration, baseline cognitive impairment, or renal impairment.

How do I monitor and manage side effects?

As side effects occur with such regularity, hospitalists caring for patients on opioids should anticipate, screen, guard against, and treat these symptoms. Up to 85% of patients taking opioids report adverse events, most frequently constipation and sedation.[23] It should be noted that before treatment of a symptom such as sedation, delirium, or nausea as a side effect of opioid therapy, a broader differential of possible causes should be entertained and addressed.[22]

Respiratory depression occurs in a dose-dependent manner, and patients develop tolerance to this effect over days to weeks when on a relatively stable dose. Opioid receptor agonists such as naloxone result in increased breathing rate in the setting of respiratory depression with opioids.[24] Because of this effect, they are the foundation of treatment for overdose. In addition to reversal of respiratory depression, opioid receptor antagonists can reverse sedation, other side effects, and analgesia. With the potential to induce an acute withdrawal state, naloxone should be used with caution and only in the setting of respiratory arrest, respiratory depression, or sparingly as an aid in diagnosing opioid intoxication in the setting of sedation. One must bear in mind that some degree of sedation should be tolerated to avoid induction of the intense dysphoria, pain, seizure, and ventricular dysrhythmia associated with rapid opioid withdrawal.[25,26] A cautious approach for a patient with respiratory depression (4–8 respirations per minute) is a dilution of 0.4 mg naloxone into 10 mL normal saline solution (naloxone added to 9 mL normal saline) delivered at a rate of 0.02 mg (0.5 mL of solution) every 2 minutes while monitoring eye activity, vocalization, and respiratory rate. Some patients will require more than 0.4 mg naloxone, keeping in mind that the therapeutic goal when using naloxone is not alert mental status but an increase of respiratory rate to greater than 8 respirations per minute. Because the duration of activity of naloxone is relatively brief in comparison with most opioids, a continuous intravenous infusion may be necessary for the duration of the effect of the opioid that is causing respiratory depression. A practical starting rate after the effective dose has been established is an hourly rate of two-thirds the initial dose rate along with a bolus of one-half the initial effective dose available every 15 minutes as needed to maintain the target respiratory rate. In the case of fewer than 4 respirations per minute (deemed respiratory arrest), an initial dose of 0.4 mg repeated every 4 minutes up to 4 doses, along with resuscitation efforts to ensure adequate respiration, is appropriate.

The risk for opioid-induced delirium is greatest in patients with renal failure, baseline cognitive impairment, and polypharmacy, particularly those with other psychoactive medications.[22] Although great effort should be made to avoid delirium in the elderly (the age group at greatest risk), withholding opioids for pain has the opposite effect. With prudent administration, opioids have been shown to decrease delirium in an elderly population hospitalized for hip fracture.[27] Treatment of opioid-induced delirium

is not different from that for other causes of delirium, and centers on removal of contributory factors including treatment of infection, metabolic derangement, polypharmacy, and dehydration, in addition to environmental factors such as noise, and tethering and restoring sensory assistive devices such as hearing aids and eyeglasses. When medications are needed, haloperidol may be appropriate depending on the clinical setting.

Patients generally develop resistance to sedation over several days, although some patients with advanced cancer on large daily doses of opioids experience significant persistent sedation. Small trials have supported the use of methylphenidate, modafinil, and donepezil to improve subjective and functional outcomes in this population.[28–30] Nausea and vomiting occur in approximately one-fifth of patients started on opioids, and can be treated with standard pharmacologic therapies. Myoclonus, most commonly associated with meperidine, occurs from accumulation of toxic metabolites and can also occur with other opioids. When clinically significant, treatments include benzodiazepines, muscle relaxants, and opioid rotation. Occasionally opioids can lead to histamine release from mast cells, causing pruritus, which can be treated with diphenhydramine or other antihistamines. Constipation is common, persistent, and difficult to treat, leading to the recommendation that treatment should be initiated prophylactically at the time opioids are initiated for pain.

SPECIAL CONSIDERATIONS

How can I use opioids safely for my elderly patients? Are there special considerations for chronic pain in this population?

Pain among the elderly is common, occurring in 25% to 50% when living in the community and 45% to 80% among those in nursing homes.[31] For those requiring hospitalization, well over half will have clinically significant pain. This population is even more challenging because of the increased prevalence of organ dysfunction, limited physiologic reserve to deal with additional toxicities such as delirium and constipation, and sometimes cognitive deficits, making assessment more challenging.

Opioids hold a few advantages over nonopioid analgesics in the elderly population. Because renal function deteriorates over time, the elderly have a disproportionate risk for kidney injury with NSAID use. For this reason, NSAIDs should be used rarely and only with great caution in this population. Acetaminophen represents a safe first option, but its use is limited to 3 g or less for frail older adults without liver disease and 2 g for those with risk for or known liver disease. For moderate to severe pain, opioids are often necessary. Selection of an initial opioid is similar across the elderly population, with the caveat that older patients often require lower doses. Dose finding should follow the pattern outlined in the next section, with the exception that starting dose should be conservative. A good rule of thumb is to start with half the dose one would initiate in a younger patient; this makes prompt follow-up and repeat assessment of pain levels all the more important.

Constipation and delirium can occur in this high-risk population and, for reasons similar to those making treatment more challenging, are difficult in the elderly population. Prophylaxis for constipation along with monitoring for the need for more aggressive treatment should be adequate in most cases. As noted earlier, a prospective cohort study of hip-fracture patients demonstrated that delirium was much more likely to develop among those with baseline cognitive deficits and that inadequate analgesia was a stronger risk factor than opioid exposure for delirium.[27]

What is the best practice for opioids in patients with liver disease?

Liver disease affects metabolism of many medications, including opioids, with changes including diminished first-pass metabolism leading to increased bioavailability of oral formulations. In sum, these effects lead to an increased risk for adverse events.[32,33] In the case of codeine, efficacy for pain depends on metabolism to morphine, which can be impaired, thereby decreasing the efficacy of codeine in this population. Owing to its metabolism outside the liver, fentanyl seems to be the best of the opioids in patients with liver disease.[33] One limitation of fentanyl is that there are fewer formulations for administration. Because it is a highly lipophilic medication, there is less control over the nonintravenous forms. Of note, the extremely long-acting nature of fentanyl patches makes it very dangerous in opioid-naïve patients.

What is the best practice for opioid treatment in patients with kidney disease?

Data to guide the management of pain in the setting of major organ dysfunction based on clinical outcomes are lacking. As a rule of thumb, experts recommend "relatively lower starting doses and more cautious dose escalation."[34] Patients with impaired renal function have been shown to have more accumulation of morphine metabolites[35,36] and have an increased risk for adverse events resulting from accumulation of metabolites. There are increasing data showing that at high, persistent doses, hydromorphone may have similar effects. The key is to go slowly and monitor carefully for benefit and burden.

INITIATION OF THERAPY AND OPIOID ROTATION

How do I choose an agent when initiating opioid therapy for pain?

Initial selection should take into account the patient's history with opioids, including previous exposure and efficacy of agents along with the side-effect profile experienced by the patient. A new agent should also take into account underlying medical conditions (see previous section). Finally, a dose should take into account the severity of pain and typical differences in metabolism, particularly among Asian patients, who may have a greater sensitivity to opioid antagonists. Patients should be monitored at an interval commensurate with expected time of onset for efficacy, then periodically for side effects, based on the half-life of the opioid.

The WHO frames the pain management of patients with cancer with a ladder approach as a guideline rather than a rule. An approximation of this approach can be useful in the setting of acute pain or exacerbation of acute pain for the opioid-tolerant patient. The first rung would include nonopioid analgesics such as acetaminophen and NSAIDs for nociceptive pain and gabapentin or pregabalin for neuropathic pain (probably to separate neuropathic pain altogether). A second rung includes weak opioids, specifically codeine, hydrocodone, or tramadol. A final rung consists of the strong opioids, with the advantage that there is typically less of a ceiling effect derived from side effects: treatment can be titrated up to achieve pain control. Agents include oxycodone (when separated from acetaminophen or aspirin), morphine, hydromorphone, and fentanyl, among others. Patients with neuropathic pain should start with a first-line agent such as gabapentin or pregabalin. Because these medications often require a slow titration in dose to reach maximum efficacy, they may fall short for the treatment of acute neuropathic pain. In cases where pain causes functional incapacity, opioids have been shown to be effective and can be considered as a bridge for acute neuropathic pain.

Clinicians should take into account the agents available at their institution, the route of delivery, any comorbidities, the degree of pain, and whether the side-effect profile might limit the use of weak opioids.

What do I need to know about opioid rotation?

Opioid rotation is an essential skill for the management of hospitalized patients (**Box 1**). Because of the controversial nature of opioid therapy for chronic pain and out of respect for the primary care provider, it is unwise to undertake rotation of opioids for the chronic pain condition for which treatment was started as an outpatient. It is entirely possible that a temporary change would be required for an acute pain, in which case the patient's baseline tolerance and history of chronic exposure to opioids should inform doses, and this patient will likely require doses larger than would a patient who was previously opioid-naïve. Inadequate analgesia despite titration, intolerable side effects, a change in available routes of administration, new-onset organ dysfunction, and/or lack of availability of an agent in a particular hospital call for consideration of opioid rotation in hospitalized patients. Although opioid rotation may lead to decreased harm or improved benefit, any trial of opioid rotation should be undertaken with the knowledge that it may not improve patient-centered outcomes. The Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation has proposed a guideline for safe opioid rotation.[37] A multiple-step process is proposed, starting with consideration of the patient's unique clinical circumstances including restrictions on the route of administration, underlying organ dysfunction, and history of success and failure with candidate agents. After choosing an agent and a route, an equianalgesic dosing table is used for calculating a test dose (**Table 2**).[38] To ensure a safe test dose with the new opioid, the equianalgesic dose should be reduced by 25% to 50% to account for anticipated lesser tolerance to

Box 1
Opioid rotation

Steps for Safe Opioid Rotation

1. Choose an agent based on clinical and patient-centered characteristics (considering available routes of administration and comorbidities such as chronic kidney disease)
2. Calculate dose based on equianalgesic dose table[a] (simplified version in **Table 2**)
3. Reduce equianalgesic dose by 25% to 50% to determine test dose (reduction accounts for incomplete cross-tolerance and should be based on clinical judgment with greater reduction for characteristics such as larger baseline dose, advanced age, or frailty)
4. Administer test dose under monitoring for side effects such as respiratory depression
5. Follow up with the patient after administration of test dose to assess efficacy. Follow up at an appropriate time interval (roughly 5–10 minutes after administration of intravenous doses, 30–40 minutes after administration of oral doses[b])
6. Adjust the next dose based on efficacy of the test dose and goals such as pain reduction and improvement in function
7. Add a rescue dose of the new opioid to be administered as needed for breakthrough pain. Start with roughly 10% of anticipated 24-hour cumulative dose

[a] Recommend expert consultation for transition to methadone.
[b] The clinical effects of opioids are idiosyncratic for an individual patient; therefore, any change must be monitored closely to anticipate, prevent, and treat overdose and undertreatment.

Table 2
Equianalgesic dose table

Opioid	IV[a] (mg)	PO[b] (mg)	Ratio IV to PO
Morphine	10	30	1:3
Hydrocodone		30	
Oxycodone		20	
Hydromorphone	1.5	7.5	1:5
Codeine	130	200	1:1.5
Fentanyl[c]	0.2 (200 μg)		

Abbreviations: IV, intravenous; PO, by mouth.
[a] Translate 1:1 for IV: subcutaneous or intramuscular doses.
[b] Translate 1:1 for PO: rectal doses.
[c] Note that duration of effect for IV fentanyl is 1 to 2 hours versus approximately 4 hours for other IV agents.

the effects of the new opioid (known as incomplete cross-tolerance). The amount of dose reduction should be based on clinical judgment, with larger reductions for larger baseline doses, advanced age, and frailty. Owing to the idiosyncratic nature of opioid metabolism, it is not possible to predict accurately how much of a given agent will be required to achieve adequate analgesia. Similarly, the side-effect profile is difficult to predict. For this reason it is important to assess the patient's response to the test dose.

TOLERANCE, WITHDRAWAL, DEPENDENCE, HYPERALGESIA, AND ADDICTION

What is opioid addiction and how does it affect my practice?

Though uncommon in patients who receive opioids for acute pain and cancer pain, opioid addiction is a growing societal concern in an era of black-market abundance and opioid use for chronic pain. Addiction is a complicated biopsychosocial phenomenon characterized not only by dependence and tolerance but by preoccupation with acquiring the drug of abuse and an intense desire for the drug, in addition to behaviors to undermine safeguards against abuse. A working definition for the diagnosis of addiction proposed by Portenoy[39] includes behaviors such as those concerning for addiction as listed in **Fig. 1**, along with "an intense desire for the drug and overwhelming concern about its continued availability (psychological dependence)."[39] A genetic role for addiction has been proposed, with supporting evidence including a greater prevalence of single-nucleotide polymorphisms identified in addicts in comparison with a nonaddict population.[40] Tolerance and dependence occur at the molecular level and result in a predictable withdrawal syndrome when the opioid is not ingested. Although it is possible for patients with painful medical conditions to develop physiologic dependence, it is uncommon for these patients to develop psychological dependence.[20]

Is my sickle cell patient addicted to opioids?

The principle that patients with cancer requiring opioids are unlikely to develop addiction is widely known. The same can be said of sickle cell patients, with studies showing rates of behaviors related to addiction observed with prevalence similar to that of the general population. Fear of opioid addiction in this population is common among

treating physicians, and can lead to inadequate treatment of pain.[41] Although the hospital may select for a population more likely to display AMTB, addiction among those hospitalized with pain crisis is still low.

How do potent opioids differ from weak opioids?

Weak opioids have dose limitations resulting from rapid accrual of side effects relative to analgesia above recommended doses. Codeine is a weak opioid limited by nausea and constipation at doses above those recommended. Strong opioids, on the other hand, can be titrated up as the clinical scenario dictates, without disproportionate accumulation of side effects. Strong opioids include morphine, hydromorphone, fentanyl, and oxycodone when not combined with acetaminophen or aspirin.[12]

How does pseudoaddiction differ from addiction, and dependence differ from tolerance?

Addiction is a phenomenon characterized by compulsive use of opioids, and preoccupation with attaining opioids (opioid-seeking behavior) despite the consequences. Tolerance, psychological dependence, and physiologic dependence are hallmarks of addiction but do not themselves define addiction. Physiologic dependence occurs at the molecular level and results in a predictable withdrawal syndrome when the opioid is not ingested. Although it is possible for patients with painful medical conditions to develop physiologic dependence, it is uncommon for these patients to develop psychological dependence.[20] Pseudoaddiction is a long-standing and more recently described phenomenon whereby a patient displays drug-seeking behaviors normally encountered in addiction. In contrast to opioid addiction, however, the impetus for their behavior is inadequately treated pain.[42]

How does pseudoaddiction affect my practice?

Hospitalists should recognize that patients with physiologic pain stimuli often act in a manner typical of patients with addiction. Patients develop pseudoaddiction because of inadequate frequency or doses of opioids to treat the pain they are experiencing. This situation leads to behaviors that mirror pain medication–seeking behaviors such as requests for more pain medication, asking for rescue doses on schedule, and requesting a change to another medication known to them by name because of its history of efficacy. In an effort to convince providers that they are in pain, patients with pseudoaddicton will moan, cry, grimace, and hold affected body parts. Because of concerns about medication-seeking behavior and widespread fear of inducing tolerance and addiction, hospitalists often can fail to recognize pseudoaddiction for what it is: inadequately treated pain.[42]

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